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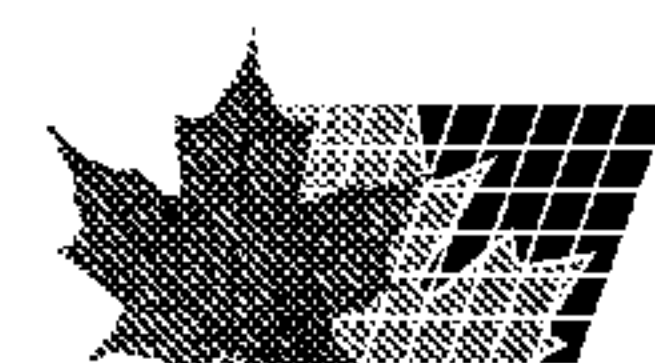
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(57) **Abrégé/Abstract:**

The present invention is directed to compositions of matter useful for the diagnosis and treatment of inflammatory bowel diseases in mammals and to methods of using those compositions of matter for the same.



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(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF INFLAMMATORY BOWEL DISORDERS

(57) Abstract: The present invention is directed to compositions of matter useful for the diagnosis and treatment of inflammatory bowel diseases in mammals and to methods of using those compositions of matter for the same.

COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF INFLAMMATORY BOWEL DISORDERS

1. Field of the Invention

The present invention is directed to compositions of matter useful for the diagnosis and treatment of inflammatory bowel disorders ("IBD") in mammals and to methods of using those compositions of matter for the same.

2. Background of the Invention

The term inflammatory bowel disorder ("IBD") describes a group of chronic inflammatory disorders of unknown causes in which the intestine (bowel) becomes inflamed, often causing recurring cramps or diarrhea. The prevalence of IBD in the US is estimated to be about 200 per 100,000 population. Patients with IBD can be divided into two major groups, those with ulcerative colitis ("UC") and those with Crohn's disease ("CD").

In patients with UC, there is an inflammatory reaction primarily involving the colonic mucosa. The inflammation is typically uniform and continuous with no intervening areas of normal mucosa. Surface mucosal cells as well as crypt epithelium and submucosa are involved in an inflammatory reaction with neutrophil infiltration. Ultimately, this situation typically progresses to epithelial damage with loss of epithelial cells resulting in multiple ulcerations, fibrosis, dysplasia and longitudinal retraction of the colon.

CD differs from UC in that the inflammation extends through all layers of the intestinal wall and involves mesentery as well as lymph nodes. CD may affect any part of the alimentary canal from mouth to anus. The disease is often discontinuous, i.e., severely diseased segments of bowel are separated from apparently disease-free areas. In CD, the bowel wall also thickens which can lead to obstructions. In addition, fistulas and fissures are not uncommon.

Clinically, IBD is characterized by diverse manifestations often resulting in a chronic, unpredictable course. Bloody diarrhea and abdominal pain are often accompanied by fever and weight loss. Anemia is not uncommon, as is severe fatigue. Joint manifestations ranging from arthralgia to acute arthritis as well as abnormalities in liver function are commonly associated with IBD. Patients with IBD also have an increased risk of colon carcinomas compared to the general population. During acute "attacks" of IBD, work and other normal activity are usually impossible, and often a patient is hospitalized.

Although the cause of IBD remains unknown, several factors such as genetic, infectious and immunologic susceptibility have been implicated. IBD is much more common in Caucasians, especially those of Jewish descent. The chronic inflammatory nature of the condition has prompted an intense search for a possible infectious cause. Although agents have been found which stimulate acute inflammation, none has been found to cause the chronic inflammation associated with IBD. The hypothesis that IBD is an autoimmune disease is supported by the previously mentioned extraintestinal manifestation of IBD as joint arthritis, and the known positive response to IBD by

treatment with therapeutic agents such as adrenal glucocorticoids, cyclosporine and azathioprine, which are known to suppress immune response. In addition, the GI tract, more than any other organ of the body, is continuously exposed to potential antigenic substances such as proteins from food, bacterial byproducts (LPS), etc.

Once the diagnosis has been made, typically by endoscopy, the goals of therapy are to induce and maintain a remission. The least toxic agents which patients are typically treated with are the aminosalicylates. Sulfasalazine (Azulfidine), typically administered four times a day, consists of an active molecule of aminosalicylate (5-ASA) which is linked by an azo bond to a sulfapyridine. Anaerobic bacteria in the colon split the azo bond to release active 5-ASA. However, at least 20% of patients cannot tolerate sulfapyridine because it is associated with significant side-effects such as reversible sperm abnormalities, dyspepsia or allergic reactions to the sulpha component. These side effects are reduced in patients taking olsalazine. However, neither sulfasalazine nor olsalazine are effective for the treatment of small bowel inflammation. Other formulations of 5-ASA have been developed which are released in the small intestine (e.g. mesalamine and asacol). Normally it takes 6-8 weeks for 5-ASA therapy to show full efficacy. Patients who do not respond to 5-ASA therapy, or who have a more severe disease, are prescribed corticosteroids. However, this is a short term therapy and cannot be used as a maintenance therapy. Clinical remission is achieved with corticosteroids within 2-4 weeks, however the side effects are significant and include a Cushing goldface, facial hair, severe mood swings and sleeplessness. The response to sulfasalazine and 5-aminosalicylate preparations is poor in Crohn's disease, fair to mild in early ulcerative colitis and poor in severe ulcerative colitis. If these agents fail, powerful immunosuppressive agents such as cyclosporine, prednisone, 6-mercaptopurine or azathioprine (converted in the liver to 6-mercaptopurine) are typically tried. For Crohn's disease patients, the use of corticosteroids and other immunosuppressives must be carefully monitored because of the high risk of intra-abdominal sepsis originating in the fistulas and abscesses common in this disease. Approximately 25% of IBD patients will require surgery (colectomy) during the course of the disease.

Further, the risk of colon cancer is elevated ($\geq 32\times$) in patients with severe ulcerative colitis, particularly if the disease has existed for several years. About 20-25% of patients with IBD eventually require surgery for removal of the colon because of massive bleeding, chronic debilitating illness, perforation of the colon, or risk of cancer. Surgery is also sometimes performed when other forms of medical treatment fail or when the side effects of steroids or other medications threaten the patient's health. As surgery is invasive and drastically life altering, it is not a highly desirable treatment regimen, and is typically the treatment of last resort.

In addition to pharmaceutical medicine and surgery, nonconventional treatments for IBD such as nutritional therapy have also been attempted. For example, Flexical[®], a semi-elemental formula, has been shown to be as effective as the steroid prednisolone. Sanderson *et al.*, *Arch. Dis. Child.* 51:123-7 (1987). However, semi-elemental formulas are relatively expensive and are typically unpalatable - thus their use has been restricted. Nutritional therapy incorporating whole proteins has also been attempted to alleviate the symptoms of IBD. Giafer *et al.*, *Lancet* 335: 816-9 (1990). U.S.P. 5,461,033 describes the use of acidic casein isolated from bovine milk and TGF- β 2. Beattie *et al.*, *Aliment. Pharmacol. Ther.* 8: 1-6 (1994) describes the use of casein in infant formula in children with IBD. U.S.P. 5,952,295 describes the use of casein in an enteric formulation for the treatment of IBD. However, while nutritional therapy is non-toxic, it is only a palliative treatment and does not treat the underlying cause of the disease.

Despite these advances in mammalian IBD therapy, however, there is a great need for additional diagnostic and therapeutic agents capable of detecting and treating IBD in a mammal. Accordingly, it is an objective of the present invention to identify polypeptides that are overexpressed on cells from IBD tissue as compared to on normal cells, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the diagnostic detection and therapeutic treatment of IBD in mammals.

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3. Summary of the Invention

The present invention provides compositions and methods for the diagnosis and treatment of IBD in mammals. The present invention is based on the identification of compounds (*i.e.*, proteins) that test positive in various assays that test modulation (*e.g.*, promotion or inhibition) of certain biological activities. Such compounds are herein referred to as PRO polypeptides. Accordingly, the compounds are believed to be useful drugs and/or drug components for the diagnosis and/or treatment (including prevention and amelioration) of disorders where such effects are desired. In addition, the compositions and methods of the invention provide for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of IBD-related disorders, for monitoring the efficacy of compounds in clinical trials and for identifying subjects who may be predisposed to such IBD-related disorders.

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In one embodiment, the present invention provides a composition comprising a PRO polypeptide, an agonist or antagonist thereof, or an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide, agonist, antagonist or antibody. In another aspect, the composition comprises a further active ingredient. Preferably, the composition is sterile. The PRO polypeptide, agonist, antagonist or antibody may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve extended storage stability. Preserved liquid pharmaceutical formulations might contain multiple doses of PRO polypeptide, agonist, antagonist or antibody, and might, therefore, be suitable for repeated use. In a preferred embodiment, where the composition comprises an antibody, the antibody is a monoclonal antibody, an antibody fragment, a human antibody, a humanized antibody or a single-chain antibody. Antibodies of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which it binds. For diagnostic purposes, the antibodies of the present invention may be detectably labeled.

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In a further embodiment, the present invention provides a method for preparing such a composition useful for the treatment of an IBD comprising admixing a therapeutically effective amount of a PRO polypeptide, agonist, antagonist or antibody with a pharmaceutically acceptable carrier.

In a still further aspect, the present invention provides an article of manufacture comprising:

(a) a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;

(b) a container containing said composition; and

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(c) a label affixed to said container, or a package insert included in said container referring to the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of an IBD, wherein the agonist or antagonist may be an antibody which binds to the PRO polypeptide. The composition may comprise a therapeutically effective

amount of the PRO polypeptide or the agonist or antagonist thereof.

In another embodiment, the present invention provides a method for identifying an agonist of a PRO polypeptide comprising:

(a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

5 (b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the present invention provides a method for identifying an agonist of a PRO polypeptide comprising:

10 (a) contacting cells and a test compound to be screened under conditions suitable for the stimulation of cell proliferation by a PRO polypeptide; and

(b) measuring the proliferation of said cells to determine if the test compound is an effective agonist, wherein the stimulation of cell proliferation is indicative of said test compound being an effective agonist.

15 In another embodiment, the invention provides a method for identifying a compound that inhibits the activity of a PRO polypeptide comprising contacting a test compound with a PRO polypeptide under conditions and for a time sufficient to allow the test compound and polypeptide to interact and determining whether the activity of the PRO polypeptide is inhibited. In a specific preferred aspect, either the test compound or the PRO polypeptide is immobilized on a solid support. In another preferred aspect, the non-immobilized component carries a detectable label. In a preferred aspect, this method comprises the steps of:

20 (a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another preferred aspect, this process comprises the steps of:

25 (a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the stimulation of cell proliferation by a PRO polypeptide; and

(b) measuring the proliferation of the cells to determine if the test compound is an effective antagonist.

30 In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO polypeptide in cells that normally expresses the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO polypeptide; and

(b) determining the inhibition of expression of said polypeptide.

35 In a still further embodiment, the invention provides a compound that inhibits the expression of a PRO polypeptide, such as a compound that is identified by the methods set forth above.

Another aspect of the present invention is directed to an agonist or an antagonist of a PRO polypeptide which may optionally be identified by the methods described above.

One type of antagonist of a PRO polypeptide that inhibits one or more of the functions or activities of the

PRO polypeptide is an antibody. Hence, in another aspect, the invention provides an isolated antibody that binds a PRO polypeptide. In a preferred aspect, the antibody is a monoclonal antibody, which preferably has non-human complementarity-determining-region (CDR) residues and human framework-region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a single-chain antibody, a human antibody or a humanized antibody. Preferably, the antibody specifically binds to the polypeptide. Antibodies of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which it binds. For diagnostic purposes, the antibodies of the present invention may be detectably labeled.

In a still further aspect, the present invention provides a method for diagnosing a disease or susceptibility to a disease which is related to a mutation in a PRO polypeptide-encoding nucleic acid sequence comprising determining the presence or absence of said mutation in the PRO polypeptide nucleic acid sequence, wherein the presence or absence of said mutation is indicative of the presence of said disease or susceptibility to said disease.

In a still further aspect, the invention provides a method of diagnosing an IBD in a mammal which comprises analyzing the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells (*e.g.*, colon cells) obtained from said mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample is indicative of the presence of an IBD in said mammal. The expression of a gene encoding a PRO polypeptide may optionally be accomplished by measuring the level of mRNA or the polypeptide in the test sample as compared to the control sample.

In a still further aspect, the present invention provides a method of diagnosing an IBD in a mammal which comprises detecting the presence or absence of a PRO polypeptide in a test sample of tissue cells (*e.g.*, colon cells) obtained from said mammal, wherein the presence or absence of said PRO polypeptide in said test sample is indicative of the presence of an IBD in said mammal.

In a still further embodiment, the invention provides a method of diagnosing an IBD in a mammal comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells (*e.g.*, colon cells) obtained from the mammal, and (b) detecting the formation of a complex between the antibody and the PRO polypeptide in the test sample, wherein the formation of said complex is indicative of the presence of a, IBD in the mammal. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger or smaller quantity of complexes formed in the test sample indicates the presence of an IBD in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry or other techniques known in the art. The test sample is usually obtained from an individual suspected to have an IBD.

In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a sample suspected of containing the PRO polypeptide to an anti-PRO antibody and determining binding of said antibody to a component of said sample. In a specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably

detectably labeled and/or bound to a solid support.

In further aspects, the invention provides an IBD diagnostic kit comprising an anti-PRO antibody and a carrier in suitable packaging. Preferably, such kit further comprises instructions for using said antibody to detect the presence of the PRO polypeptide. Preferably, the carrier is a buffer, for example. Preferably, the IBD is Crohn's disease or ulcerative colitis.

5 In yet another embodiment, the present invention provides a method for treating an IBD in a mammal comprising administering to the mammal an effective amount of a PRO polypeptide. Preferably, the disorder is Crohn's disease or ulcerative colitis. Preferably, the mammal is human, preferably one who is at risk of developing an IBD.

10 In another preferred embodiment, the PRO polypeptide is administered in combination with a chemotherapeutic agent, a growth inhibitory agent or a cytotoxic agent.

In a further embodiment, the invention provides a method for treating an IBD in a mammal comprising administering to the mammal an effective amount of a PRO polypeptide agonist, antagonist or anti-PRO antibody. Preferably, the IBD is Crohn's disease or ulcerative colitis. Also preferred is where the mammal is human, and where an effective amount of a chemotherapeutic agent, a growth inhibitory agent or a cytotoxic agent is
15 administered in conjunction with the agonist, antagonist or anti-PRO antibody.

Yet another embodiment of the present invention is directed to a method of therapeutically treating a PRO polypeptide-expressing cell in a mammal with an IBD, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody that binds to the PRO polypeptide, thereby resulting in the effective therapeutic treatment of the IBD. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric
20 antibody, human antibody, humanized antibody or single-chain antibody. Antibodies employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

25 In still further embodiments, the invention provides a method for treating an IBD in a mammal that suffers therefrom comprising administering to the mammal a nucleic acid molecule that codes for either (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide or (c) an antagonist of a PRO polypeptide, wherein said agonist or antagonist may be an anti-PRO antibody. In a preferred embodiment, the mammal is human. In another preferred embodiment, the gene is administered via *ex vivo* gene therapy. In a further preferred embodiment, the gene is
30 comprised within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral, or retroviral vector.

In yet another aspect, the invention provides a recombinant retroviral particle comprising a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide, or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein the retroviral vector is in association with retroviral structural proteins. Preferably, the
35 signal sequence is from a mammal, such as from a native PRO polypeptide.

In a still further embodiment, the invention supplies an *ex vivo* producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c)

an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce recombinant retroviral particles.

In other embodiments of the present invention, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

5 In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with
10 or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA
15 molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

20 In a further aspect, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

25 Another aspect of the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

30 In other aspects, the present invention is directed to isolated nucleic acid molecules which hybridize to (a) a nucleotide sequence encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, a PRO polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide amino acid sequence as disclosed herein, or (b) the complement
35 of the nucleotide sequence of (a). In this regard, an embodiment of the present invention is directed to fragments of a full-length PRO polypeptide coding sequence, or the complement thereof, as disclosed herein, that may find use as, for example, hybridization probes useful as, for example, diagnostic probes, antisense oligonucleotide probes, or for encoding fragments of a full-length PRO polypeptide that may optionally encode a polypeptide comprising

a binding site for an anti-PRO polypeptide antibody. Such nucleic acid fragments are usually at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such novel fragments of PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides an isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention provides an isolated PRO polypeptide comprising an amino acid sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention provides an isolated PRO polypeptide comprising an amino acid sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and that is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect of the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate

encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention provides agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

5 In a further embodiment, the invention provides a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention provides a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

10 Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

15 In additional embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli*, yeast, or Baculovirus-infected insect cells. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

20 In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

25 In yet another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, human antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

30 Further embodiments of the present invention will be evident to the skilled artisan upon a reading of the present specification.

4. Brief Description of the Drawings

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) designated herein as "DNA32279".

35 Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) designated herein as "DNA33085".

Figure 4 shows the amino acid sequence (SEQ ID NO:4) derived from the coding sequence of SEQ ID

NO:3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) designated herein as "DNA33457".

Figure 6 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) designated herein as "DNA33461".

5 Figure 8 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) designated herein as "DNA33785".

Figure 10 shows the amino acid sequence (SEQ ID NO:10) derived from the coding sequence of SEQ ID NO:9 shown in Figure 9.

10 Figure 11 shows a nucleotide sequence (SEQ ID NO:11) designated herein as "DNA36725".

Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) designated herein as "DNA40576".

15 Figure 14A-B shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) designated herein as "DNA51786".

Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

Figure 17 shows a nucleotide sequence (SEQ ID NO:17) designated herein as "DNA52594".

20 Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ ID NO:17 shown in Figure 17.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) designated herein as "DNA59776".

Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

25 Figure 21 shows a nucleotide sequence (SEQ ID NO:21) designated herein as "DNA62377".

Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) designated herein as "DNA64882".

30 Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) designated herein as "DNA69553".

Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

Figure 27 shows a nucleotide sequence (SEQ ID NO:27) designated herein as "DNA77509".

35 Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 27.

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) designated herein as "DNA77512".

Figure 30 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID

NO:29 shown in Figure 29.

Figure 31 shows a nucleotide sequence (SEQ ID NO:31) designated herein as "DNA81752".

Figure 32 shows the amino acid sequence (SEQ ID NO:32) derived from the coding sequence of SEQ ID NO:31 shown in Figure 31.

Figure 33 shows a nucleotide sequence (SEQ ID NO:33) designated herein as "DNA82305".

5 Figure 34 shows the amino acid sequence (SEQ ID NO:34) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) designated herein as "DNA82352".

Figure 36 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

10 Figure 37 shows a nucleotide sequence (SEQ ID NO:37) designated herein as "DNA87994".

Figure 38 shows the amino acid sequence (SEQ ID NO:38) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

Figure 39A-B shows a nucleotide sequence (SEQ ID NO:39) designated herein as "DNA88417".

15 Figure 40A-B shows the amino acid sequence (SEQ ID NO:40) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39A-B.

Figure 41 shows a nucleotide sequence (SEQ ID NO:41) designated herein as "DNA88432".

Figure 42A-B shows the amino acid sequence (SEQ ID NO:42) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

Figure 43 shows a nucleotide sequence (SEQ ID NO:43) designated herein as "DNA92247".

20 Figure 44 shows the amino acid sequence (SEQ ID NO:44) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) designated herein as "DNA95930".

Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

25 Figure 47 shows a nucleotide sequence (SEQ ID NO:47) designated herein as "DNA99331".

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) designated herein as "DNA101222".

30 Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) designated herein as "DNA102850".

Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) designated herein as "DNA105792".

35 Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) designated herein as "DNA107429".

Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ ID

NO:55 shown in Figure 55.

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) designated herein as "DNA145582".

Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

Figure 59 shows a nucleotide sequence (SEQ ID NO:59) designated herein as "DNA165608".

5 Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ ID NO:59 shown in Figure 59.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) designated herein as "DNA166819".

Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figure 61.

10 Figure 63 shows a nucleotide sequence (SEQ ID NO:63) designated herein as "DNA168061".

Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) designated herein as "DNA171372".

15 Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) designated herein as "DNA188175".

Figure 68 shows the amino acid sequence (SEQ ID NO:68) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) designated herein as "DNA188182".

20 Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) designated herein as "DNA188200".

Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

25 Figure 73 shows a nucleotide sequence (SEQ ID NO:73) designated herein as "DNA188203".

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

Figure 75 shows a nucleotide sequence (SEQ ID NO:75) designated herein as "DNA188205".

30 Figure 76 shows the amino acid sequence (SEQ ID NO:76) derived from the coding sequence of SEQ ID NO:75 shown in Figure 75.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) designated herein as "DNA188244".

Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) designated herein as "DNA188270".

35 Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ ID NO:79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) designated herein as "DNA188277".

Figure 82 shows the amino acid sequence (SEQ ID NO:82) derived from the coding sequence of SEQ ID

NO:81 shown in Figure 81.

Figure 83 shows a nucleotide sequence (SEQ ID NO:83) designated herein as "DNA188278".

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID NO:83 shown in Figure 83.

Figure 85 shows a nucleotide sequence (SEQ ID NO:85) designated herein as "DNA188287".

5 Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:85 shown in Figure 85.

Figure 87A-B shows a nucleotide sequence (SEQ ID NO:87) designated herein as "DNA188302".

Figure 88A-B shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87A-B.

10 Figure 89 shows a nucleotide sequence (SEQ ID NO:89) designated herein as "DNA188332".

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

Figure 91 shows a nucleotide sequence (SEQ ID NO:91) designated herein as "DNA188339".

15 Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) designated herein as "DNA188340".

Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) designated herein as "DNA188355".

20 Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

Figure 97 shows a nucleotide sequence (SEQ ID NO:97) designated herein as "DNA188425".

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

25 Figure 99 shows a nucleotide sequence (SEQ ID NO:99) designated herein as "DNA188448".

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

Figure 101 shows a nucleotide sequence (SEQ ID NO:101) designated herein as "DNA194566".

30 Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) designated herein as "DNA199788".

Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:103 shown in Figure 103.

Figure 105 shows a nucleotide sequence (SEQ ID NO:105) designated herein as "DNA200227".

35 Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

Figure 107 shows a nucleotide sequence (SEQ ID NO:107) designated herein as "DNA27865".

Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ

ID NO:107 shown in Figure 107.

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) designated herein as "DNA33094".

Figure 110 shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:110 shown in Figure 110.

Figure 111 shows a nucleotide sequence (SEQ ID NO:111) designated herein as "DNA45416".

5 Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:111 shown in Figure 111.

Figure 113 shows a nucleotide sequence (SEQ ID NO:113) designated herein as "DNA48328".

Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figure 113.

10 Figure 115 shows a nucleotide sequence (SEQ ID NO:115) designated herein as "DNA50960".

Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

Figure 117 shows a nucleotide sequence (SEQ ID NO:117) designated herein as "DNA80896".

15 Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:117 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO:119) designated herein as "DNA82319".

Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:119 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:121) designated herein as "DNA82352".

20 Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:121 shown in Figure 121.

Figure 123 shows a nucleotide sequence (SEQ ID NO:123) designated herein as "DNA82363".

Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 123.

25 Figure 125 shows a nucleotide sequence (SEQ ID NO:125) designated herein as "DNA82368".

Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

Figure 127 shows a nucleotide sequence (SEQ ID NO:127) designated herein as "DNA83103".

30 Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) designated herein as "DNA83500".

Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

Figure 131 shows a nucleotide sequence (SEQ ID NO:131) designated herein as "DNA88002".

35 Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 131.

Figure 133 shows a nucleotide sequence (SEQ ID NO:133) designated herein as "DNA92282".

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ

ID NO:133 shown in Figure 133.

Figure 135 shows a nucleotide sequence (SEQ ID NO:135) designated herein as "DNA96934".

Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

Figure 137 shows a nucleotide sequence (SEQ ID NO:137) designated herein as "DNA96943".

5 Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) designated herein as "DNA97005".

Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

10 Figure 141 shows a nucleotide sequence (SEQ ID NO:141) designated herein as "DNA98553".

Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:141 shown in Figure 141.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) designated herein as "DNA102845".

15 Figure 144 shows the amino acid sequence (SEQ ID NO:144) derived from the coding sequence of SEQ ID NO:143 shown in Figure 143.

Figure 145 shows a nucleotide sequence (SEQ ID NO:145) designated herein as "DNA108715".

Figure 146 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:145 shown in Figure 145.

Figure 147 shows a nucleotide sequence (SEQ ID NO:147) designated herein as "DNA108735".

20 Figure 148 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:147 shown in Figure 147.

Figure 149 shows a nucleotide sequence (SEQ ID NO:149) designated herein as "DNA164455".

Figure 150 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:149 shown in Figure 149.

25 Figure 151 shows a nucleotide sequence (SEQ ID NO:151) designated herein as "DNA188178".

Figure 152 shows the amino acid sequence (SEQ ID NO:152) derived from the coding sequence of SEQ ID NO:151 shown in Figure 151.

Figure 153 shows a nucleotide sequence (SEQ ID NO:153) designated herein as "DNA188271".

30 Figure 154 shows the amino acid sequence (SEQ ID NO:154) derived from the coding sequence of SEQ ID NO:153 shown in Figure 153.

Figure 155 shows a nucleotide sequence (SEQ ID NO:155) designated herein as "DNA188338".

Figure 156 shows the amino acid sequence (SEQ ID NO:156) derived from the coding sequence of SEQ ID NO:155 shown in Figure 155.

Figure 157 shows a nucleotide sequence (SEQ ID NO:157) designated herein as "DNA188342".

35 Figure 158 shows the amino acid sequence (SEQ ID NO:158) derived from the coding sequence of SEQ ID NO:157 shown in Figure 157.

Figure 159 shows a nucleotide sequence (SEQ ID NO:159) designated herein as "DNA188427".

Figure 160A-B shows the amino acid sequence (SEQ ID NO:160) derived from the coding sequence of

SEQ ID NO:159 shown in Figure 159.

Figure 161 shows a nucleotide sequence (SEQ ID NO:161) designated herein as "DNA195011".

Figure 162 shows the amino acid sequence (SEQ ID NO:162) derived from the coding sequence of SEQ ID NO:161 shown in Figure 161.

5. DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

5.1. Definitions

The term "inflammatory bowel disorder" or "IBD" as used herein, refers to any chronic disorder in which any portion of the intestine (bowel) becomes inflamed and/or ulcerated. Examples of IBD include, but are not limited to, Crohn's Disease and ulcerative colitis.

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (*i.e.*, PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In certain embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons (if indicated) are shown in bold font and underlined in the figures. Nucleic acid residues indicated as "N" in the accompanying figures are any nucleic acid residue. However, while the PRO polypeptides disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane

domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein may be shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means a PRO polypeptide, preferably an active PRO polypeptide, as defined herein having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length PRO polypeptide). Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the – or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full

length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X," "Y" and "Z" each represent different hypothetical amino acid residues. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes a PRO polypeptide, preferably an active PRO polypeptide, as defined herein and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length PRO polypeptide). Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence

lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence

identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA", wherein "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides. Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are
 5 obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode a PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of
 15 N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" PRO polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding
 25 nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example,
 30 include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably
 35 linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading

phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide or anti-PRO antibody fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

"Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other

than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

"Biological activity" in the context of a molecule that antagonizes a PRO polypeptide that can be identified by the screening assays disclosed herein (*e.g.*, an organic or inorganic small molecule, peptide, etc.) is used to refer to the ability of such molecules to bind or complex with the PRO polypeptide identified herein, or otherwise interfere with the interaction of the PRO polypeptide with other cellular proteins or otherwise inhibits the transcription or translation of the PRO polypeptide.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

"Treating" or "treatment" or "alleviation" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. The disorder may result from any cause.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time.

"Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of the treatment of, alleviating the symptoms of or diagnosis of a cancer refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

The term "PRO polypeptide receptor" as used herein refers to a cellular receptor for a PRO polypeptide as well as variants thereof that retain the ability to bind a PRO polypeptide.

An "effective amount" of a polypeptide or antibody disclosed herein or an agonist or antagonist thereof is an amount sufficient to carry out a specifically stated purpose. An "effective amount" may be determined empirically and in a routine manner, in relation to the stated purpose.

The term "therapeutically effective amount" of an active agent such as a PRO polypeptide or agonist or antagonist thereto or an anti-PRO antibody, refers to an amount effective in the treatment of an IBD in a mammal and can be determined empirically.

A "growth inhibitory amount" of an anti-PRO antibody or PRO polypeptide is an amount capable of inhibiting the growth of a cell either *in vitro* or *in vivo*, and may be determined empirically and in a routine manner.

A "cytotoxic amount" of an anti-PRO antibody or PRO polypeptide is an amount capable of causing the destruction of a cell either *in vitro* or *in vivo*, and may be determined empirically and in a routine manner.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody compositions with polypepitopic specificity, polyclonal antibodies, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below) as long as they exhibit the desired biological or immunological activity. The term "immunoglobulin" (Ig) is used interchangeable with antibody herein.

An "isolated antibody" is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to a H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the α and γ chains and four C_H domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain (C_H1). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, e.g., Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α , δ , ϵ , γ , and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

The term "variable" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and define specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3)

in the V_L , and around about 1-35 (H1), 50-65 (H2) and 95-102 (H3) in the V_H ; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (e.g. residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L , and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the V_H ; Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)).

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier "monoclonal" is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology first described by Kohler et al., Nature, 256:495 (1975), or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, e.g., U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991), for example.

The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Patent No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey, Ape etc), and human constant region sequences.

An "intact" antibody is one which comprises an antigen-binding site as well as a C_L and at least heavy chain constant domains, C_{H1} , C_{H2} and C_{H3} . The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (see U.S. Patent No. 5,641,870, Example 2; Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_{H1}). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large F(ab')₂ fragment which roughly corresponds to

two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C_H1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, *infra*.

The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993).

"Humanized" forms of non-human (*e.g.*, rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones

et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

A "species-dependent antibody," e.g., a mammalian anti-human IgE antibody, is an antibody which has a stronger binding affinity for an antigen from a first mammalian species than it has for a homologue of that antigen from a second mammalian species. Normally, the species-dependent antibody "bind specifically" to a human antigen (i.e., has a binding affinity (Kd) value of no more than about 1×10^{-7} M, preferably no more than about 1×10^{-8} and most preferably no more than about 1×10^{-9} M) but has a binding affinity for a homologue of the antigen from a second non-human mammalian species which is at least about 50 fold, or at least about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The species-dependent antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody.

An antibody "which binds" an antigen of interest is one that binds the antigen with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting a cell expressing the antigen, and does not significantly cross-react with other proteins. In such embodiments, the extent of binding of the antibody to a "non-target" protein will be less than about 10% of the binding of the antibody to its particular target protein as determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA). An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

An "antibody that inhibits the growth of cells expressing a PRO polypeptide" or a "growth inhibitory" antibody is one which binds to and results in measurable growth inhibition of cells expressing or overexpressing the appropriate PRO polypeptide. Preferred growth inhibitory anti-PRO antibodies inhibit growth of PRO-expressing cells by greater than 20%, preferably from about 20% to about 50%, and even more preferably, by greater than 50% (e.g., from about 50% to about 100%) as compared to the appropriate control, the control typically being cells not treated with the antibody being tested. Growth inhibition can be measured at an antibody concentration of about 0.1 to 30 μ g/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the cells to the antibody.

An antibody which "induces apoptosis" is one which induces programmed cell death as determined by binding of annexin V, fragmentation of DNA, cell shrinkage, dilation of endoplasmic reticulum, cell fragmentation, and/or formation of membrane vesicles (called apoptotic bodies). The cell is usually one which overexpresses a PRO polypeptide. Preferably the cell is a tumor cell, e.g., a prostate, breast, ovarian, stomach, endometrial, lung, kidney, colon, bladder cell. Various methods are available for evaluating the cellular events associated with apoptosis. For example, phosphatidyl serine (PS) translocation can be measured by annexin binding; DNA fragmentation can be evaluated through DNA laddering; and nuclear/chromatin condensation along with DNA fragmentation can be evaluated by any increase in hypodiploid cells. Preferably, the antibody which induces apoptosis is one which results in about 2 to 50 fold, preferably about 5 to 50 fold, and most preferably about 10 to 50 fold, induction of annexin binding relative to untreated cell in an annexin binding assay.

Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype.

Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

“Antibody-dependent cell-mediated cytotoxicity” or “ADCC” refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies “arm” the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express Fc γ RIII only, whereas monocytes express Fc γ RI, Fc γ RII and Fc γ RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, Annu. Rev. Immunol. 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an in vitro ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in a animal model such as that disclosed in Clynes et al. (USA) 95:652-656 (1998).

“Fc receptor” or “FcR” describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc γ RI, Fc γ RII and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc γ RII receptors include Fc γ RIIA (an “activating receptor”) and Fc γ RIIB (an “inhibiting receptor”), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc γ RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc γ RIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (see review M. in Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term “FcR” herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)).

“Human effector cells” are leukocytes which express one or more FcRs and perform effector functions. Preferably, the cells express at least Fc γ RIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells may be isolated from a native source, e.g., from blood.

“Complement dependent cytotoxicity” or “CDC” refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996), may be performed.

The terms “cancer” and “cancerous” refer to or describe the physiological condition in mammals that is

typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, multiple myeloma and B-cell lymphoma, brain, as well as head and neck cancer, and associated metastases.

"Tumor", as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

An antibody which "induces cell death" is one which causes a viable cell to become nonviable. The cell is one which expresses a PRO polypeptide, preferably a cell that overexpresses a PRO polypeptide as compared to a normal cell of the same tissue type. Cell death *in vitro* may be determined in the absence of complement and immune effector cells to distinguish cell death induced by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Thus, the assay for cell death may be performed using heat inactivated serum (i.e., in the absence of complement) and in the absence of immune effector cells. To determine whether the antibody is able to induce cell death, loss of membrane integrity as evaluated by uptake of propidium iodide (PI), trypan blue (see Moore et al. Cytotechnology 17:1-11 (1995)) or 7AAD can be assessed relative to untreated cells. Preferred cell death-inducing antibodies are those which induce PI uptake in the PI uptake assay in BT474 cells.

A "PRO-expressing cell" is a cell which expresses an endogenous or transfected PRO polypeptide on the cell surface. A "PRO-expressing IBD" is an IBD comprising cells that have a PRO polypeptide present on the cell surface. A "PRO-expressing IBD" produces sufficient levels of PRO polypeptide on the surface of cells thereof, such that an anti-PRO antibody can bind thereto and have a therapeutic effect with respect to the IBD. A, IBD which "overexpresses" a PRO polypeptide is one which has significantly higher levels of PRO polypeptide at the cell surface thereof, compared to a non-IBD cell of the same tissue type. Such overexpression may be caused by gene amplification or by increased transcription or translation. PRO polypeptide overexpression may be determined in a diagnostic or prognostic assay by evaluating increased levels of the PRO protein present on the surface of a cell (e.g., via an immunohistochemistry assay using anti-PRO antibodies prepared against an isolated PRO polypeptide which may be prepared using recombinant DNA technology from an isolated nucleic acid encoding the PRO polypeptide; FACS analysis, etc.). Alternatively, or additionally, one may measure levels of PRO polypeptide-encoding nucleic acid or mRNA in the cell, e.g., via fluorescent *in situ* hybridization using a nucleic acid based probe corresponding to a PRO-encoding nucleic acid or the complement thereof; (FISH; see WO98/45479 published October, 1998), Southern blotting, Northern blotting, or polymerase chain reaction (PCR) techniques, such as real time quantitative PCR (RT-PCR). One may also study PRO polypeptide overexpression by measuring shed antigen in a biological fluid such as serum, e.g, using antibody-based assays (see also, e.g., U.S. Patent No. 4,933,294 issued

June 12, 1990; WO91/05264 published April 18, 1991; U.S. Patent 5,401,638 issued March 28, 1995; and Sias et al., J. Immunol. Methods 132:73-80 (1990)). Aside from the above assays, various *in vivo* assays are available to the skilled practitioner. For example, one may expose cells within the body of the patient to an antibody which is optionally labeled with a detectable label, e.g., a radioactive isotope, and binding of the antibody to cells in the patient can be evaluated, e.g., by external scanning for radioactivity or by analyzing a biopsy taken from a patient previously exposed to the antibody.

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g., At^{211} , I^{131} , I^{125} , Y^{90} , Re^{186} , Re^{188} , Sm^{153} , Bi^{212} , P^{32} and radioactive isotopes of Lu), chemotherapeutic agents e.g. methotrexate, adriamycin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents, enzymes and fragments thereof such as nucleolytic enzymes, antibiotics, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof, and the various antitumor or anticancer agents disclosed below. Other cytotoxic agents are described below. A tumoricidal agent causes destruction of tumor cells.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell either *in vitro* or *in vivo*. Thus, the growth inhibitory agent may be one which significantly reduces the percentage of PRO-expressing cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb). Paclitaxel and

docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

“Doxorubicin” is an anthracycline antibiotic. The full chemical name of doxorubicin is (8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione.

5 The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH),
10 and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon - α , - β , and - γ ; colony stimulating factors
15 (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- α or TNF- β ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

20 The term “package insert” is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

Table 1

```

/*
*
* C-C increased from 12 to 15
* Z is average of EQ
5  * B is average of ND
* match with stop is _M; stop-stop = 0; J (joker) match = 0
*/
#define _M      -8      /* value of a match with a stop */

10 int      _day[26][26] = {
/*      A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */      { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
/* B */      { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
/* C */      {-2, -4, 15, -5, -5, -4, -3, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
15 /* D */      { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
/* E */      { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
/* F */      {-4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
/* G */      { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
/* H */      {-1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
20 /* I */      {-1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
/* J */      { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */      {-1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
/* L */      {-2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
/* M */      {-1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
25 /* N */      { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
/* O */      {_M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, 0, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */      { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
/* Q */      { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
/* R */      {-2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, -3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
30 /* S */      { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
/* T */      { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
/* U */      { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */      { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
/* W */      {-6, -5, -8, -7, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
35 /* X */      { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */      {-3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
/* Z */      { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};

40

45

50

55

```


Table 1 (cont')

```

/*
*/
#include <stdio.h>
#include <ctype.h>

5  #define MAXJMP      16      /* max jumps in a diag */
   #define MAXGAP      24      /* don't continue to penalize gaps larger than this */
   #define JMPS        1024    /* max jmps in an path */
   #define MX           4      /* save if there's at least MX-1 bases since last jmp */

10  #define DMAT         3      /* value of matching bases */
   #define DMIS         0      /* penalty for mismatched bases */
   #define DINS0        8      /* penalty for a gap */
   #define DINS1        1      /* penalty per base */
15  #define PINS0        8      /* penalty for a gap */
   #define PINS1        4      /* penalty per residue */

   struct jmp {
20       short          n[MAXJMP]; /* size of jmp (neg for dely) */
       unsigned short x[MAXJMP]; /* base no. of jmp in seq x */
   }; /* limits seq to 2^16 -1 */

   struct diag {
25       int            score;      /* score at last jmp */
       long            offset;     /* offset of prev block */
       short           ijmp;       /* current jmp index */
       struct jmp      jp;         /* list of jmps */
   };

30  struct path {
       int             spc;        /* number of leading spaces */
       short           n[JMPS]; /* size of jmp (gap) */
       int             x[JMPS]; /* loc of jmp (last elem before gap) */
   };

35  char          *ofile;          /* output file name */
   char          *namex[2];       /* seq names: getseqs( ) */
   char          *prog;           /* prog name for err msgs */
   char          *seqx[2];        /* seqs: getseqs( ) */
40  int           dmax;            /* best diag: nw( ) */
   int           dmax0;           /* final diag */
   int           dna;             /* set if dna: main( ) */
   int           endgaps;         /* set if penalizing end gaps */
   int           gapx, gapy;      /* total gaps in seqs */
45  int           len0, len1;      /* seq lens */
   int           ngapx, ngapy;    /* total size of gaps */
   int           smax;            /* max score: nw( ) */
   int           *xbm;            /* bitmap for matching */
   long          offset;          /* current offset in jmp file */
50  struct        diag            *dx; /* holds diagonals */
   struct        path            pp[2]; /* holds path for seqs */

   char          *calloc( ), *malloc( ), *index( ), *strcpy( );
   char          *getseq( ), *g_calloc( );

55

60

```


Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
* where file1 and file2 are two dna or two protein sequences.
5 * The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
10 * Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
15 #include "nw.h"
#include "day.h"

static _dbval[26] = {
    1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
20 };

static _pbval[26] = {
    1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
25 1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
    1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)                                main
30     int      ac;
    char      *av[];
{
    prog = av[0];
    if (ac != 3) {
35         fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';', '>' or '<' are ignored\n");
        fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
40     }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
45     xbm = (dna)? _dbval : _pbval;

    endgaps = 0;                                /* 1 to penalize endgaps */
    ofile = "align.out";                        /* output file */

50     nw( );                                /* fill in the matrix, get the possible jumps */
    readjumps( );                            /* get the actual jumps */
    print( );                                /* print stats, alignment */

55     cleanup(0);                            /* unlink any tmp files */
}

```


Table 1 (cont')

```

/* do the alignment, return best score: main( )
* dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
* pro: PAM 250 values
* When scores are equal, we prefer mismatches to any gap, prefer
5  * a new gap to extending an ongoing gap, and prefer a gap in seqx
  * to a gap in seq y.
  */
nw( )
{
10  char      *px, *py;      /* seqs and ptrs */
   int      *ndely, *dely;  /* keep track of dely */
   int      ndelx, delx;    /* keep track of delx */
   int      *tmp;          /* for swapping row0, row1 */
   int      mis;           /* score for each type */
15  int      ins0, ins1;    /* insertion penalties */
   register id;            /* diagonal index */
   register ij;            /* jmp index */
   register *col0, *col1;  /* score for curr, last row */
   register xx, yy;        /* index into seqs */
20
   dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

   ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
   dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
25  col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
   col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
   ins0 = (dna)? DINS0 : PINS0;
   ins1 = (dna)? DINS1 : PINS1;

30  smax = -10000;
   if (endgaps) {
       for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
           col0[yy] = dely[yy] = col0[yy-1] - ins1;
           ndely[yy] = yy;
35       }
       col0[0] = 0;      /* Waterman Bull Math Biol 84 */
   }
   else
40     for (yy = 1; yy <= len1; yy++)
        dely[yy] = -ins0;

   /* fill in match matrix
   */
45  for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
       /* initialize first entry in col
       */
       if (endgaps) {
           if (xx == 1)
50             col1[0] = delx = -(ins0+ins1);
           else
               col1[0] = delx = col0[0] - ins1;
           ndelx = xx;
       }
       else {
55         col1[0] = 0;
           delx = -ins0;
           ndelx = 0;
       }
   }
60

```


Table 1 (cont')

...nw

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++){
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongong del
     * ignore MAXGAP if weighting endgaps
     */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
     * favor new del over ongong del
     */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
     * mis over any del and delx over dely
     */

```


Table 1 (cont')

...nw

```

id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
    col1[yy] = mis;
5  else if (delx >= dely[yy]) {
    col1[yy] = delx;
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
10    && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
15        }
    }
    dx[id].jp.n[ij] = ndelx;
    dx[id].jp.x[ij] = xx;
    dx[id].score = delx;
20 }
    else {
        col1[yy] = dely[yy];
        ij = dx[id].ijmp;
25 if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
            dx[id].ijmp++;
            if (++ij >= MAXJMP) {
                writejumps(id);
                ij = dx[id].ijmp = 0;
                dx[id].offset = offset;
                offset += sizeof(struct jmp) + sizeof(offset);
30            }
        }
        dx[id].jp.n[ij] = -ndely[yy];
        dx[id].jp.x[ij] = xx;
        dx[id].score = dely[yy];
35 }
    if (xx == len0 && yy < len1) {
        /* last col
        */
        if (endgaps)
            col1[yy] -= ins0+ins1*(len1-yy);
        if (col1[yy] > smax) {
45            smax = col1[yy];
            dmax = id;
        }
    }
}
50 if (endgaps && xx < len0)
    col1[yy-1] -= ins0+ins1*(len0-xx);
    if (col1[yy-1] > smax) {
        smax = col1[yy-1];
        dmax = id;
55 }
    tmp = col0; col0 = col1; col1 = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
60 (void) free((char *)col0);
(void) free((char *)col1);
    }

```


Table 1 (cont')

```

/*
*
* print() -- only routine visible outside this module
*
5  * static:
* getmat() -- trace back best path, count matches: print()
* pr_align() -- print alignment of described in array p[]: print()
* dumpblock() -- dump a block of lines with numbers, stars: pr_align()
10 * nums() -- put out a number line: dumpblock()
* putline() -- put out a line (name, [num], seq, [num]): dumpblock()
* stars() -- put a line of stars: dumpblock()
* stripname() -- strip any path and prefix from a seqname
*/

15 #include "nw.h"

#define SPC      3
#define P_LINE   256    /* maximum output line */
#define P_SPC    3      /* space between name or num and seq */

20 extern  _day[26][26];
int      olen;          /* set output line length */
FILE     *fx;           /* output file */

25 print()               print
{
    int      lx, ly, firstgap, lastgap;    /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
30         fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
35     olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) {          /* leading gap in x */
40         pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) {     /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
45         lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) {        /* trailing gap in x */
        lastgap = len0 - dmax0 - 1;
50         lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) {   /* trailing gap in y */
        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
55     getmat(lx, ly, firstgap, lastgap);
    pr_align();
}

60

```


Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
static
5 getmat(lx, ly, firstgap, lastgap)                                getmat
    int    lx, ly;                                /* "core" (minus endgaps) */
    int    firstgap, lastgap;                      /* leading trailing overlap */
{
    int    nm, i0, i1, siz0, siz1;
10    char    outx[32];
    double    pct;
    register    n0, n1;
    register char    *p0, *p1;

15    /* get total matches, score
    */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
20    n0 = pp[1].spc + 1;
    n1 = pp[0].spc + 1;

    nm = 0;
    while ( *p0 && *p1 ) {
25        if (siz0) {
            p1++;
            n1++;
            siz0--;
        }
30        else if (siz1) {
            p0++;
            n0++;
            siz1--;
        }
35        else {
            if (xbm[*p0-'A']&xbm[*p1-'A'])
                nm++;
            if (n0++ == pp[0].x[i0])
                siz0 = pp[0].n[i0++];
40            if (n1++ == pp[1].x[i1])
                siz1 = pp[1].n[i1++];
            p0++;
            p1++;
        }
45    }

    /* pct homology:
    * if penalizing endgaps, base is the shorter seq
    * else, knock off overhangs and take shorter core
50    */
    if (endgaps)
        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
55    pct = 100.*((double)nm)/((double)lx);
    fprintf(fx, "\n");
    fprintf(fx, "<%d match%s in an overlap of %d: %.2f percent similarity\n",
        nm, (nm == 1)? "" : "es", lx, pct);
60

```


Table 1 (cont')

```

fprintf(fx, "<gaps in first sequence: %d", gapx);
if (gapx) {
    (void) sprintf(outx, " (%d %s%s)",
        ngapx, (dna)? "base":"residue", (ngapx == 1)? "" : "s");
    fprintf(fx, "%s", outx);

    fprintf(fx, ", gaps in second sequence: %d", gapy);
    if (gapy) {
        (void) sprintf(outx, " (%d %s%s)",
            ngapy, (dna)? "base":"residue", (ngapy == 1)? "" : "s");
        fprintf(fx, "%s", outx);
    }
    if (dna)
        fprintf(fx,
            "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
            smax, DMAT, DMIS, DINS0, DINS1);
    else
        fprintf(fx,
            "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
            smax, PINS0, PINS1);
    if (endgaps)
        fprintf(fx,
            "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
            firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
            lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
    else
        fprintf(fx, "<endgaps not penalized\n");
}

static nm;          /* matches in core -- for checking */
static lmax;        /* lengths of stripped file names */
static ij[2];       /* jmp index for a path */
static nc[2];       /* number at start of current line */
static ni[2];       /* current elem number -- for gapping */
static siz[2];
static char *ps[2];  /* ptr to current element */
static char *po[2];  /* ptr to next output char slot */
static char out[2][P_LINE]; /* output line */
static char star[P_LINE]; /* set by stars() */

/*
 * print alignment of described in struct path pp[]
 */
static
pr_align( )
{
    int nn;          /* char count */
    int more;
    register i;

    for (i = 0, lmax = 0; i < 2; i++) {
        nn = stripname(nameex[i]);
        if (nn > lmax)
            lmax = nn;

        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
        ps[i] = seqx[i];
        po[i] = out[i];
    }
}

```

...getmat

pr_align

Table 1 (cont')

...pr_align

```

for (nn = nm = 0, more = 1; more; ) {
    for (i = more = 0; i < 2; i++) {
        /*
5         * do we have more of this sequence?
        */
        if (!*ps[i])
            continue;

        more++;

10        if (pp[i].spc) { /* leading space */
            *po[i]++ = ' ';
            pp[i].spc--;
        }
        else if (siz[i]) { /* in a gap */
            *po[i]++ = '-';
            siz[i]--;
        }
        else { /* we're putting a seq element
20             */
            *po[i] = *ps[i];
            if (islower(*ps[i]))
                *ps[i] = toupper(*ps[i]);

            po[i]++;
            ps[i]++;

            /*
25             * are we at next gap for this seq?
            */
            if (ni[i] == pp[i].x[ij[i]]) {
                /*
                * we need to merge all gaps
                * at this location
                */
30                siz[i] = pp[i].n[ij[i]++];
                while (ni[i] == pp[i].x[ij[i]])
                    siz[i] += pp[i].n[ij[i]++];
            }
            ni[i]++;
        }
    }
    if (++nn == olen || !more && nn) {
        dumpblock( );
        for (i = 0; i < 2; i++)
45            po[i] = out[i];
        nn = 0;
    }
}

50 /*
   * dump a block of lines, including numbers, stars: pr_align( )
   */
static
55 dumpblock( )
{
    register i;

    for (i = 0; i < 2; i++)
60     *po[i]-- = '\0';

```

dumpblock

Table 1 (cont')

...dumpblock

```

5      (void) putc('\n', fx);
      for (i = 0; i < 2; i++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' '))
              if (i == 0)
                  nums(i);
              if (i == 0 && *out[1])
                  stars( );
10         putline(i);
              if (i == 0 && *out[1])
                  fprintf(fx, star);
              if (i == 1)
                  nums(i);
15     }
    }
}

/*
20  * put out a number line: dumpblock( )
   */
static
nums(ix)
25  {
    int      ix;      /* index in out[] holding seq line */

    char      nline[P_LINE];
    register  i, j;
    register char *pn, *px, *py;

30     for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
        *pn = ' ';
    for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
        if (*py == ' ' || *py == '-')
            *pn = ' ';
35         else {
            if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                j = (i < 0)? -i : i;
                for (px = pn; j; j /= 10, px--)
                    *px = j%10 + '0';
40                 if (i < 0)
                    *px = '-';

                }
            else
                *pn = ' ';
45             i++;
        }
    }
    *pn = '\0';
    nc[ix] = i;
50     for (pn = nline; *pn; pn++)
        (void) putc(*pn, fx);
    (void) putc('\n', fx);
}

55  /*
   * put out a line (name, [num], seq, [num]): dumpblock( )
   */
static
putline(ix)
60  {
    int      ix;

```

nums

putline

Table 1 (cont')

...putline

```

5      int          i;
      register char *px;

      for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
          (void) putc(*px, fx);
      for (; i < lmax+P_SPC; i++)
          (void) putc(' ', fx);

10     /* these count from 1:
       * ni[] is current element (from 1)
       * nc[] is number at start of current line
       */
15     for (px = out[ix]; *px; px++)
          (void) putc(*px&0x7F, fx);
      (void) putc('\n', fx);
  }

20  /*
   * put a line of stars (seqs always in out[0], out[1]): dumpblock( )
   */
25  static
  stars( )
  {
      int          i;
      register char *p0, *p1, cx, *px;

30     if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
        !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
          return;
      px = star;
      for (i = lmax+P_SPC; i; i--)
35         *px++ = ' ';

      for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++){
          if (isalpha(*p0) && isalpha(*p1)) {
40             if (xbm[*p0-'A']&xbm[*p1-'A'])
                cx = '*';
                nm++;
            }
            else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
45                 cx = '.';
            else
                cx = ' ';

            }
            else
50                 cx = ' ';
            *px++ = cx;
        }
        *px++ = '\n';
        *px = '\0';
55     }

```

stars

Table 1 (cont')

```
/*
 * strip path or prefix from pn, return len: pr_align( )
 */
static
5 stripname(pn)                                stripname
    char    *pn;    /* file name (may be path) */
{
    register char    *px, *py;
10     py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;
15     if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}
20
25
30
35
40
45
50
55
60
```


Table 1 (cont')

```

/*
 * cleanup( ) -- cleanup any tmp file
 * getseq( ) -- read in seq, set dna, len, maxlen
 * g_calloc( ) -- calloc( ) with error checkin
5  * readjumps( ) -- get the good jumps, from tmp file if necessary
 * writejumps( ) -- write a filled array of jumps to a tmp file: nw( )
 */
#include "nw.h"
#include <sys/file.h>
10 char      *jname = "/tmp/homgXXXXXX";          /* tmp file for jumps */
FILE      *fj;

int      cleanup( );                          /* cleanup tmp file */
15 long     lseek( );

/*
 * remove any tmp file if we blow
 */
20 cleanup(i)                                     cleanup
    int      i;
{
    if (fj)
        (void) unlink(jname);
25     exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
30 char      *
getseq(file, len)                                     getseq
35     char      *file;      /* file name */
    int      *len;      /* seq len */
{
    char      line[1024], *pseq;
    register char      *px, *py;
40     int      natgc, tlen;
    FILE      *fp;

    if ((fp = fopen(file, "r")) == 0) {
        fprintf(stderr, "%s: can't read %s\n", prog, file);
45         exit(1);
    }
    tlen = natgc = 0;
    while (fgets(line, 1024, fp)) {
        if (*line == ';' || *line == '<' || *line == '>')
50             continue;
        for (px = line; *px != '\n'; px++)
            if (isupper(*px) || islower(*px))
                tlen++;
    }
55     if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
        fprintf(stderr, "%s: malloc( ) failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
    pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
60

```


Table 1 (cont')

...getseq

```

py = pseq + 4;
*len = tlen;
rewind(fp);
5
while (fgets(line, 1024, fp)) {
    if (*line == ';' || *line == '<' || *line == '>')
        continue;
    for (px = line; *px != '\n'; px++){
10        if (isupper(*px))
            *py++ = *px;
        else if (islower(*px))
            *py++ = toupper(*px);
        if (index("ATGCU",*(py-1)))
15            natgc++;
    }
}
*py++ = '\0';
*py = '\0';
20 (void) fclose(fp);
dna = natgc > (tlen/3);
return(pseq+4);
}

25 char *
g_alloc(msg, nx, sz)
    char *msg;          /* program, calling routine */
    int nx, sz;          /* number and size of elements */
{
30     char *px, *calloc( );

    if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
        if (*msg) {
35             fprintf(stderr, "%s: g_alloc( ) failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
}

40 /*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main( )
 */
readjmps( )
45 {
    int fd = -1;
    int siz, i0, i1;
    register i, j, xx;

50     if (fj) {
        (void) fclose(fj);
        if ((fd = open(jname, O_RDONLY, 0)) < 0) {
            fprintf(stderr, "%s: can't open( ) %s\n", prog, jname);
            cleanup(1);
55         }
    }
    for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
        while (1) {
60             for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                ;

```

g_alloc

readjmps

Table 1 (cont')

...readjumps

```

5      if (j < 0 && dx[dmax].offset && fj) {
          (void) lseek(fd, dx[dmax].offset, 0);
          (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
          (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
          dx[dmax].ijmp = MAXJMP-1;
      }
      else
          break;
10     }
    if (i >= JMPS) {
        fprintf(stderr, "%s: too many gaps in alignment\n", prog);
        cleanup(1);
    }
15     if (j >= 0) {
        siz = dx[dmax].jp.n[j];
        xx = dx[dmax].jp.x[j];
        dmax += siz;
        if (siz < 0) { /* gap in second seq */
20             pp[1].n[i1] = -siz;
            xx += siz;
            /* id = xx - yy + len1 - 1
             */
            pp[1].x[i1] = xx - dmax + len1 - 1;
25             gapy++;
            ngapy -= siz;
        /* ignore MAXGAP when doing endgaps */
            siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
            i1++;
30         }
        else if (siz > 0) { /* gap in first seq */
            pp[0].n[i0] = siz;
            pp[0].x[i0] = xx;
            gapx++;
            ngapx += siz;
35         /* ignore MAXGAP when doing endgaps */
            siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
            i0++;
        }
40     }
    else
        break;
}

45 /* reverse the order of jumps
   */
    for (j = 0, i0--; j < i0; j++, i0--) {
        i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
        i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
50     }
    for (j = 0, i1--; j < i1; j++, i1--) {
        i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
        i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
55     }
    if (fd >= 0)
        (void) close(fd);
    if (fj) {
        (void) unlink(jname);
        fj = 0;
60     offset = 0;
    }

```


Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw( )
 */
5 writejumps(ix)                                     writejumps
    int    ix;
    {
        char    *mktemp( );
10         if (!fj) {
            if (mktemp(jname) < 0) {
                fprintf(stderr, "%s: can't mktemp( ) %s\n", prog, jname);
                cleanup(1);
            }
15         if ((fj = fopen(jname, "w")) == 0) {
            . fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
20         (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
        (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
    }
25
30
35
40
45
50
55

```


Table 2

PRO	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXXYYYYYYY	(Length = 12 amino acids)

% amino acid sequence identity =

- 5 (the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
5 divided by 15 = 33.3%

Table 3

10 PRO	XXXXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXXYYYYYYYZZYZ	(Length = 15 amino acids)

% amino acid sequence identity =

- 15 (the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
5 divided by 10 = 50%

Table 4

PRO-DNA	NNNNNNNNNNNNNNNN	(Length = 14 nucleotides)
20 Comparison DNA	NNNNNNLLLLLLLLLLL	(Length = 16 nucleotides)

% nucleic acid sequence identity =

- (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =
25 6 divided by 14 = 42.9%

Table 5

PRO-DNA	NNNNNNNNNNNNNN	(Length = 12 nucleotides)
30 Comparison DNA	NNNNLLLLVV	(Length = 9 nucleotides)

% nucleic acid sequence identity =

- (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =
35 4 divided by 12 = 33.3%

5.2. Compositions and Methods of the Invention

5.2.1. Anti-PRO Antibodies

In one embodiment, the present invention provides anti-PRO antibodies which may find use herein as therapeutic and/or diagnostic agents. Exemplary antibodies include polyclonal, monoclonal, human, humanized, bispecific, and heteroconjugate antibodies.

5.2.1.1. Polyclonal Antibodies

Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen (especially when synthetic peptides are used) to a protein that is immunogenic in the species to be immunized. For example, the antigen can be conjugated to keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor, using a bifunctional or derivatizing agent, e.g., maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl_2 , or $\text{R}^1\text{N}=\text{C}=\text{NR}$, where R and R^1 are different alkyl groups.

Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later, the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

5.2.1.2. Monoclonal Antibodies

Monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., Nature, 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as described above to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. After immunization, lymphocytes are isolated and then fused with a myeloma cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)).

The hybridoma cells thus prepared are seeded and grown in a suitable culture medium which medium preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells (also referred to as fusion partner). For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the selective culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Preferred fusion partner myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a selective medium that selects against the unfused parental cells. Preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 and derivatives e.g., X63-Ag8-653 cells available from the American Type Culture Collection, Manassas, Virginia, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); and Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis described in Munson et al., Anal. Biochem., 107:220 (1980).

Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal e.g., by i.p. injection of the cells into mice.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such as, for example, affinity chromatography (e.g., using protein A or protein G-Sepharose) or ion-exchange chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, etc.

DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., Curr. Opinion in Immunol., 5:256-262 (1993) and Plückthun, Immunol. Revs. 130:151-188 (1992).

In a further embodiment, monoclonal antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., Nature, 348:552-554 (1990). Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., Bio/Technology, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse et al., Nuc. Acids. Res. 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to

traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The DNA that encodes the antibody may be modified to produce chimeric or fusion antibody polypeptides, for example, by substituting human heavy chain and light chain constant domain (C_H and C_L) sequences for the homologous murine sequences (U.S. Patent No. 4,816,567; and Morrison, et al., Proc. Natl Acad. Sci. USA, 81:6851 (1984)), or by fusing the immunoglobulin coding sequence with all or part of the coding sequence for a non-immunoglobulin polypeptide (heterologous polypeptide). The non-immunoglobulin polypeptide sequences can substitute for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

5.2.1.3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeven et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity and HAMA response (human anti-mouse antibody) when the antibody is

intended for human therapeutic use. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable domain sequences. The human V domain sequence which is closest to that of the rodent is identified and the human framework region (FR) within it accepted for the humanized antibody (Sims et al., J. Immunol. 151:2296 (1993); Chothia et al., J. Mol. Biol., 196:901 (1987)). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., Proc. Natl. Acad. Sci. USA, 89:4285 (1992); Presta et al., J. Immunol. 151:2623 (1993)).

It is further important that antibodies be humanized with retention of high binding affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

Various forms of a humanized anti-PRO antibody are contemplated. For example, the humanized antibody may be an antibody fragment, such as a Fab, which is optionally conjugated with one or more cytotoxic agent(s) in order to generate an immunoconjugate. Alternatively, the humanized antibody may be an intact antibody, such as an intact IgG1 antibody.

As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array into such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits et al., Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggemann et al., Year in Immuno. 7:33 (1993); U.S. Patent Nos. 5,545,806, 5,569,825, 5,591,669 (all of GenPharm); 5,545,807; and WO 97/17852.

Alternatively, phage display technology (McCafferty et al., Nature 348:552-553 [1990]) can be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a

single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B-cell. Phage display can be performed in a variety of formats, reviewed in, e.g., Johnson, Kevin S. and Chiswell, David J., Current Opinion in Structural Biology 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson et al., Nature, 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol. 222:581-597 (1991), or Griffith et al., EMBO J. 12:725-734 (1993). See, also, U.S. Patent Nos. 5,565,332 and 5,573,905.

As discussed above, human antibodies may also be generated by *in vitro* activated B cells (see U.S. Patents 5,567,610 and 5,229,275).

5.2.1.4. Antibody fragments

In certain circumstances there are advantages of using antibody fragments, rather than whole antibodies. The smaller size of the fragments allows for rapid clearance, and may lead to improved access to solid tumors.

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto et al., Journal of Biochemical and Biophysical Methods 24:107-117 (1992); and Brennan et al., Science, 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')₂ fragments (Carter et al., Bio/Technology 10:163-167 (1992)). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')₂ fragment with increased *in vivo* half-life comprising a salvage receptor binding epitope residues are described in U.S. Patent No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; U.S. Patent No. 5,571,894; and U.S. Patent No. 5,587,458. Fv and sFv are the only species with intact combining sites that are devoid of constant regions; thus, they are suitable for reduced nonspecific binding during *in vivo* use. sFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an sFv. See Antibody Engineering, ed. Borrebaeck, *supra*. The antibody fragment may also be a "linear antibody", e.g., as described in U.S. Patent 5,641,870 for example. Such linear antibody fragments may be monospecific or bispecific.

5.2.1.5. Bispecific Antibodies

Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of a PRO protein as described herein. Other such antibodies may combine a PRO binding site with a binding site for another protein. Alternatively, an anti-PRO arm

may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD3), or Fc receptors for IgG (Fc γ R), such as Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIII (CD16), so as to focus and localize cellular defense mechanisms to the PRO-expressing cell. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express PRO. These antibodies possess a PRO-binding arm and an arm which binds the cytotoxic agent (e.g., saporin, anti-interferon- α , vinca alkaloid, ricin A chain, methotrexate or radioactive isotope hapten). Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g., F(ab')₂ bispecific antibodies).

WO 96/16673 describes a bispecific anti-ErbB2/anti-Fc γ RIII antibody and U.S. Patent No. 5,837,234 discloses a bispecific anti-ErbB2/anti-Fc γ RI antibody. A bispecific anti-ErbB2/Fc α antibody is shown in WO98/02463. U.S. Patent No. 5,821,337 teaches a bispecific anti-ErbB2/anti-CD3 antibody.

Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., Nature 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., EMBO J. 10:3655-3659 (1991).

According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. Preferably, the fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. It is preferred to have the first heavy-chain constant region (C_H1) containing the site necessary for light chain bonding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three polypeptide chains into a single expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant affect on the yield of the desired chain combination.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology 121:210 (1986).

According to another approach described in U.S. Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C_H3 domain. In this method, one

or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g., tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g., alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

5 Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S.
10 Patent No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent, sodium arsenite, to stabilize
15 vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

20 Recent progress has facilitated the direct recovery of Fab'-SH fragments from *E. coli*, which can be chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175: 217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well
25 as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets. Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region
30 to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al. Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a V_H connected to a V_L by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary
35 V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber et al., J. Immunol., 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., J. Immunol. 147:60 (1991).

5.2.1.6. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies
 5 are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target
 immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO
 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known
 methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins
 may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable
 10 reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example,
 in U.S. Patent No. 4,676,980.

5.2.1.7. Multivalent Antibodies

A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell
 15 expressing an antigen to which the antibodies bind. The antibodies of the present invention can be multivalent
 antibodies (which are other than of the IgM class) with three or more antigen binding sites (e.g. tetravalent
 antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide
 chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen
 binding sites. The preferred dimerization domain comprises (or consists of) an Fc region or a hinge region. In this
 20 scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc
 region. The preferred multivalent antibody herein comprises (or consists of) three to about eight, but preferably four,
 antigen binding sites. The multivalent antibody comprises at least one polypeptide chain (and preferably two
 polypeptide chains), wherein the polypeptide chain(s) comprise two or more variable domains. For instance, the
 polypeptide chain(s) may comprise VD1-(X1)_n-VD2-(X2)_n-Fc, wherein VD1 is a first variable domain, VD2 is a
 25 second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or
 polypeptide, and n is 0 or 1. For instance, the polypeptide chain(s) may comprise: VH-CH1-flexible linker-VH-CH1-
 Fc region chain; or VH-CH1-VH-CH1-Fc region chain. The multivalent antibody herein preferably further comprises
 at least two (and preferably four) light chain variable domain polypeptides. The multivalent antibody herein may,
 for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain
 30 variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further
 comprise a CL domain.

5.2.1.8. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, e.g., so as to
 35 enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC)
 of the antibody. This may be achieved by introducing one or more amino acid substitutions in an Fc region of the
 antibody. Alternatively or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing

interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp Med. 176:1191-1195 (1992) and Shopes, B. J. Immunol. 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff et al., Cancer Research 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design 3:219-230 (1989). To increase the serum half life of the antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment) as described in U.S. Patent 5,739,277, for example. As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (e.g., IgG₁, IgG₂, IgG₃, or IgG₄) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

5.2.1.9. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, a growth inhibitory agent, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ²¹²Bi, ¹³¹I, ¹³¹In, ⁹⁰Y, and ¹⁸⁶Re. Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

Conjugates of an antibody and one or more small molecule toxins, such as maytansinoids, a calicheamicin, a trichothene, and CC1065, and the derivatives of these toxins that have toxin activity, are also contemplated herein.

5.2.1.9.1. Maytansine and Maytansinoids

In one preferred embodiment, an anti-PRO antibody (full length or fragments) of the invention is conjugated to one or more maytansinoid molecules.

Maytansinoids are mitototic inhibitors which act by inhibiting tubulin polymerization. Maytansine was first isolated from the east African shrub *Maytenus serrata* (U.S. Patent No. 3,896,111). Subsequently, it was discovered that certain microbes also produce maytansinoids, such as maytansinol and C-3 maytansinol esters (U.S. Patent No. 4,151,042). Synthetic maytansinol and derivatives and analogues thereof are disclosed, for example, in U.S. Patent Nos. 4,137,230; 4,248,870; 4,256,746; 4,260,608; 4,265,814; 4,294,757; 4,307,016; 4,308,268; 4,308,269; 4,309,428; 5 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,364,866; 4,424,219; 4,450,254; 4,362,663; and 4,371,533, the disclosures of which are hereby expressly incorporated by reference.

5.2.1.9.2. Maytansinoid-antibody conjugates

In an attempt to improve their therapeutic index, maytansine and maytansinoids have been conjugated to 10 antibodies specifically binding to tumor cell antigens. Immunoconjugates containing maytansinoids and their therapeutic use are disclosed, for example, in U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP 0 425 235 B1, the disclosures of which are hereby expressly incorporated by reference. Liu et al., Proc. Natl. Acad. Sci. USA 93:8618-8623 (1996) described immunoconjugates comprising a maytansinoid designated DM1 linked to the monoclonal antibody C242 directed against human colorectal cancer. The conjugate was found to be highly 15 cytotoxic towards cultured colon cancer cells, and showed antitumor activity in an *in vivo* tumor growth assay. Chari et al., Cancer Research 52:127-131 (1992) describe immunoconjugates in which a maytansinoid was conjugated via a disulfide linker to the murine antibody A7 binding to an antigen on human colon cancer cell lines, or to another murine monoclonal antibody TA.1 that binds the HER-2/*neu* oncogene. The cytotoxicity of the TA.1-maytansinoid conjugate was tested *in vitro* on the human breast cancer cell line SK-BR-3, which expresses 3×10^5 HER-2 surface 20 antigens per cell. The drug conjugate achieved a degree of cytotoxicity similar to the free maytansinoid drug, which could be increased by increasing the number of maytansinoid molecules per antibody molecule. The A7-maytansinoid conjugate showed low systemic cytotoxicity in mice.

5.2.1.9.3. Anti-PRO polypeptide antibody-maytansinoid conjugates

25 Anti-PRO antibody-maytansinoid conjugates are prepared by chemically linking an anti-PRO antibody to a maytansinoid molecule without significantly diminishing the biological activity of either the antibody or the maytansinoid molecule. An average of 3-4 maytansinoid molecules conjugated per antibody molecule has shown efficacy in enhancing cytotoxicity of target cells without negatively affecting the function or solubility of the antibody, although even one molecule of toxin/antibody would be expected to enhance cytotoxicity over the use of 30 naked antibody. Maytansinoids are well known in the art and can be synthesized by known techniques or isolated from natural sources. Suitable maytansinoids are disclosed, for example, in U.S. Patent No. 5,208,020 and in the other patents and nonpatent publications referred to hereinabove. Preferred maytansinoids are maytansinol and maytansinol analogues modified in the aromatic ring or at other positions of the maytansinol molecule, such as various maytansinol esters.

35 There are many linking groups known in the art for making antibody-maytansinoid conjugates, including, for example, those disclosed in U.S. Patent No. 5,208,020 or EP Patent 0 425 235 B1, and Chari et al., Cancer Research 52:127-131 (1992). The linking groups include disulfide groups, thioether groups, acid labile groups,

photolabile groups, peptidase labile groups, or esterase labile groups, as disclosed in the above-identified patents, disulfide and thioether groups being preferred.

Conjugates of the antibody and maytansinoid may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimide HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutarelddehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). Particularly preferred coupling agents include N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP) (Carlsson et al., Biochem. J. 173:723-737 [1978]) and N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) to provide for a disulfide linkage.

The linker may be attached to the maytansinoid molecule at various positions, depending on the type of the link. For example, an ester linkage may be formed by reaction with a hydroxyl group using conventional coupling techniques. The reaction may occur at the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with a hydroxyl group, and the C-20 position having a hydroxyl group. In a preferred embodiment, the linkage is formed at the C-3 position of maytansinol or a maytansinol analogue.

5.2.1.9.4. Calicheamicin

Another immunoconjugate of interest comprises an anti-PRO antibody conjugated to one or more calicheamicin molecules. The calicheamicin family of antibiotics are capable of producing double-stranded DNA breaks at sub-picomolar concentrations. For the preparation of conjugates of the calicheamicin family, see U.S. patents 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, 5,877,296 (all to American Cyanamid Company). Structural analogues of calicheamicin which may be used include, but are not limited to α_1^I , α_2^I , α_3^I , N-acetyl- γ_1^I , PSAG and θ^I (Hinman et al., Cancer Research 53:3336-3342 (1993), Lode et al., Cancer Research 58:2925-2928 (1998) and the aforementioned U.S. patents to American Cyanamid). Another anti-tumor drug that the antibody can be conjugated is QFA which is an antifolate. Both calicheamicin and QFA have intracellular sites of action and do not readily cross the plasma membrane. Therefore, cellular uptake of these agents through antibody mediated internalization greatly enhances their cytotoxic effects.

5.2.1.9.5. Other Cytotoxic Agents

Other anti-tumor agents that can be conjugated to the anti-PRO antibodies of the invention include BCNU, streptozocin, vincristine and 5-fluorouracil, the family of agents known collectively LL-E33288 complex described in U.S. patents 5,053,394, 5,770,710, as well as esperamicins (U.S. patent 5,877,296).

Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, WO 93/21232

published October 28, 1993.

The present invention further contemplates an immunoconjugate formed between an antibody and a compound with nucleolytic activity (e.g., a ribonuclease or a DNA endonuclease such as a deoxyribonuclease; DNase).

For selective destruction of the tumor, the antibody may comprise a highly radioactive atom. A variety of radioactive isotopes are available for the production of radioconjugated anti-PRO antibodies. Examples include At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu. When the conjugate is used for diagnosis, it may comprise a radioactive atom for scintigraphic studies, for example tc^{99m} or I¹²³, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

The radio- or other labels may be incorporated in the conjugate in known ways. For example, the peptide may be biosynthesized or may be synthesized by chemical amino acid synthesis using suitable amino acid precursors involving, for example, fluorine-19 in place of hydrogen. Labels such as tc^{99m} or I¹²³, Re¹⁸⁶, Re¹⁸⁸ and In¹¹¹ can be attached via a cysteine residue in the peptide. Yttrium-90 can be attached via a lysine residue. The IODOGEN method (Fraker et al (1978) Biochem. Biophys. Res. Commun. 80: 49-57 can be used to incorporate iodine-123. "Monoclonal Antibodies in Immunoscintigraphy" (Chatal, CRC Press 1989) describes other methods in detail.

Conjugates of the antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimide HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science* 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of the cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., *Cancer Research* 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

Alternatively, a fusion protein comprising the anti-PRO antibody and cytotoxic agent may be made, e.g., by recombinant techniques or peptide synthesis. The length of DNA may comprise respective regions encoding the two portions of the conjugate either adjacent one another or separated by a region encoding a linker peptide which does not destroy the desired properties of the conjugate.

In yet another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pre-targeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) which is conjugated to a cytotoxic agent (e.g., a radionucleotide).

5.2.1.10. Immunoliposomes

The anti-PRO antibodies disclosed herein may also be formulated as immunoliposomes. A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030 (1980); U.S. Pat. Nos. 4,485,045 and 4,544,545; and WO97/38731 published October 23, 1997. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem. 257:286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon et al., J. National Cancer Inst. 81(19):1484 (1989).

5.2.1.11. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed below, can be administered for the treatment of various disorders as noted above and below in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. *See, e.g.,* Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations

include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRONDEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

5.2.2. Screening for Antibodies With the Desired Properties

Techniques for generating antibodies have been described above. One may further select antibodies with certain biological characteristics, as desired.

The growth inhibitory effects of an anti-PRO antibody of the invention may be assessed by methods known in the art, *e.g.*, using cells which express a PRO polypeptide either endogenously or following transfection with the PRO gene. For example, appropriate tumor cell lines and PRO-transfected cells may be treated with an anti-PRO monoclonal antibody of the invention at various concentrations for a few days (*e.g.*, 2-7 days) and stained with crystal violet or MTT or analyzed by some other colorimetric assay. Another method of measuring proliferation would be by comparing ³H-thymidine uptake by the cells treated in the presence or absence an anti-PRO antibody of the invention. After antibody treatment, the cells are harvested and the amount of radioactivity incorporated into the DNA quantitated in a scintillation counter. Appropriate positive controls include treatment of a selected cell line with a growth inhibitory antibody known to inhibit growth of that cell line. Growth inhibition of tumor cells *in vivo* can be determined in various ways known in the art. Preferably, the tumor cell is one that overexpresses a PRO polypeptide. Preferably, the anti-PRO antibody will inhibit cell proliferation of a PRO-expressing tumor cell *in vitro* or *in vivo* by about 25-100% compared to the untreated tumor cell, more preferably, by about 30-100%, and even more preferably by about 50-100% or 70-100%, at an antibody concentration of about 0.5 to 30 μ g/ml. Growth inhibition can be measured at an antibody concentration of about 0.5 to 30 μ g/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the antibody. The antibody is growth inhibitory *in vivo* if administration of the anti-PRO antibody at about 1 μ g/kg to about 100 mg/kg body weight results in reduction in tumor size or reduction of tumor cell proliferation within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

To select for antibodies which induce cell death, loss of membrane integrity as indicated by, *e.g.*, propidium iodide (PI), trypan blue or 7AAD uptake may be assessed relative to control. A PI uptake assay can be performed

in the absence of complement and immune effector cells. PRO polypeptide-expressing tumor cells are incubated with medium alone or medium containing of the appropriate monoclonal antibody at e.g, about 10 μ g/ml . The cells are incubated for a 3 day time period. Following each treatment, cells are washed and aliquoted into 35 mm strainer-capped 12 x 75 tubes (1ml per tube, 3 tubes per treatment group) for removal of cell clumps. Tubes then receive PI (10 μ g/ml). Samples may be analyzed using a FACSCAN® flow cytometer and FACSCONVERT® CellQuest software (Becton Dickinson). Those antibodies which induce statistically significant levels of cell death as determined by PI uptake may be selected as cell death-inducing antibodies.

To screen for antibodies which bind to an epitope on a PRO polypeptide bound by an antibody of interest, a routine cross-blocking assay such as that described in Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. This assay can be used to determine if a test antibody binds the same site or epitope as an anti-PRO antibody of the invention. Alternatively, or additionally, epitope mapping can be performed by methods known in the art . For example, the antibody sequence can be mutagenized such as by alanine scanning, to identify contact residues. The mutant antibody is initially tested for binding with polyclonal antibody to ensure proper folding. In a different method, peptides corresponding to different regions of a PRO polypeptide can be used in competition assays with the test antibodies or with a test antibody and an antibody with a characterized or known epitope.

5.2.3. Antibody Dependent Enzyme Mediated Prodrug Therapy (ADEPT)

The antibodies of the present invention may also be used in ADEPT by conjugating the antibody to a prodrug-activating enzyme which converts a prodrug (e.g., a peptidyl chemotherapeutic agent, see WO81/01145) to an active anti-cancer drug. See, for example, WO 88/07378 and U.S. Patent No. 4,975,278.

The enzyme component of the immunoconjugate useful for ADEPT includes any enzyme capable of acting on a prodrug in such a way so as to covert it into its more active, cytotoxic form.

Enzymes that are useful in the method of this invention include, but are not limited to, alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratia protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypeptidases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as β -galactosidase and neuraminidase useful for converting glycosylated prodrugs into free drugs; β -lactamase useful for converting drugs derivatized with β -lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes", can be used to convert the prodrugs of the invention into free active drugs (see, e.g., Massey, Nature 328:457-458 (1987)). Antibody-abzyme conjugates can be prepared as described herein for delivery of the abzyme to a tumor cell population.

The enzymes of this invention can be covalently bound to the anti-PRO antibodies by techniques well known in the art such as the use of the heterobifunctional crosslinking reagents discussed above. Alternatively,

fusion proteins comprising at least the antigen binding region of an antibody of the invention linked to at least a functionally active portion of an enzyme of the invention can be constructed using recombinant DNA techniques well known in the art (see, e.g., Neuberger et al., Nature 312:604-608 (1984)).

5.2.4. Full-Length PRO Polypeptides

5 The present invention also provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs (partial and full-length) encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below.

As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual
10 nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, in some cases, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

5.2.5. Anti-PRO Antibody and PRO Polypeptide Variants

In addition to the anti-PRO antibodies and full-length native sequence PRO polypeptides described herein, it is contemplated that anti-PRO antibody and PRO polypeptide variants can be prepared. Anti-PRO antibody and PRO polypeptide variants can be prepared by introducing appropriate nucleotide changes into the encoding DNA,
20 and/or by synthesis of the desired antibody or polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the anti-PRO antibody or PRO polypeptide, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the anti-PRO antibodies and PRO polypeptides described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding
25 the antibody or polypeptide that results in a change in the amino acid sequence as compared with the native sequence antibody or polypeptide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the anti-PRO antibody or PRO polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the anti-PRO antibody or PRO polypeptide with that of homologous known
30 protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation
35 allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

Anti-PRO antibody and PRO polypeptide fragments are provided herein. Such fragments may be truncated

at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native antibody or protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the anti-PRO antibody or PRO polypeptide.

5 Anti-PRO antibody and PRO polypeptide fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating antibody or polypeptide fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired antibody or polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the 10 PCR. Preferably, anti-PRO antibody and PRO polypeptide fragments share at least one biological and/or immunological activity with the native anti-PRO antibody or PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid 15 classes, are introduced and the products screened.

Table 6

	Original Residue	Exemplary Substitutions	Preferred Substitutions
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
10	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe; norleucine	leu
15	Leu (L)	norleucine; ile; val; met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
20	Ser (S)	thr	thr
	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe; ala; norleucine	leu

Substantial modifications in function or immunological identity of the anti-PRO antibody or PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., *Nucl. Acids Res.*, 13:4331 (1986); Zoller et al., *Nucl. Acids Res.*, 10:6487 (1987)], cassette mutagenesis [Wells et al., *Gene*, 34:315 (1985)], restriction selection mutagenesis [Wells et al., *Philos. Trans. R. Soc. London SerA*, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the anti-PRO antibody or PRO polypeptide

variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244:1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

Any cysteine residue not involved in maintaining the proper conformation of the anti-PRO antibody or PRO polypeptide also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the anti-PRO antibody or PRO polypeptide to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (e.g., 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and human PRO polypeptide. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Nucleic acid molecules encoding amino acid sequence variants of the anti-PRO antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-PSCA antibody.

5.2.6. Modifications of Anti-PRO Antibodies and PRO Polypeptides

Covalent modifications of anti-PRO antibodies and PRO polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of an anti-PRO antibody or PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the

N- or C- terminal residues of the anti-PRO antibody or PRO polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking anti-PRO antibody or PRO polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparagyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the anti-PRO antibody or PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the antibody or polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence anti-PRO antibody or PRO polypeptide (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence anti-PRO antibody or PRO polypeptide. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Glycosylation of antibodies and other polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the anti-PRO antibody or PRO polypeptide is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original anti-PRO antibody or PRO polypeptide (for O-linked glycosylation sites). The anti-PRO antibody or PRO polypeptide amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the anti-PRO antibody or PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the anti-PRO antibody or PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the anti-PRO antibody or PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of anti-PRO antibody or PRO polypeptide comprises linking the antibody or polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. The antibody or polypeptide also may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules), or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Oslo, A., Ed., (1980).

The anti-PRO antibody or PRO polypeptide of the present invention may also be modified in a way to form chimeric molecules comprising an anti-PRO antibody or PRO polypeptide fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the anti-PRO antibody or PRO polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the anti-PRO antibody or PRO polypeptide. The presence of such epitope-tagged forms of the anti-PRO antibody or PRO polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the anti-PRO antibody or PRO polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an α -tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the anti-PRO antibody or PRO polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of an anti-PRO antibody or PRO polypeptide in place of at least one variable region within an Ig

molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH₂ and CH₃, or the hinge, CH₁, CH₂ and CH₃ regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

5.2.7. Preparation of Anti-PRO Antibodies and PRO Polypeptides

5 The description below relates primarily to production of anti-PRO antibodies and PRO polypeptides by culturing cells transformed or transfected with a vector containing anti-PRO antibody- and PRO polypeptide-encoding nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare anti-PRO antibodies and PRO polypeptides. For instance, the appropriate amino acid sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g.,
10 Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the anti-PRO antibody or PRO polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to
15 produce the desired anti-PRO antibody or PRO polypeptide.

5.2.7.1. Isolation of DNA Encoding Anti-PRO Antibody or PRO Polypeptide

DNA encoding anti-PRO antibody or PRO polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the anti-PRO antibody or PRO polypeptide mRNA and to express it at a detectable
20 level. Accordingly, human anti-PRO antibody or PRO polypeptide DNA can be conveniently obtained from a cDNA library prepared from human tissue. The anti-PRO antibody- or PRO polypeptide-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected
25 probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding anti-PRO antibody or PRO polypeptide is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

Techniques for screening a cDNA library are well known in the art. The oligonucleotide sequences selected
30 as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

35 Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the

full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

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5.2.7.2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for anti-PRO antibody or PRO polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host

cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan^r*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan^r*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

Full length antibody, antibody fragments, and antibody fusion proteins can be produced in bacteria, in particular when glycosylation and Fc effector function are not needed, such as when the therapeutic antibody is conjugated to a cytotoxic agent (e.g., a toxin) and the immunoconjugate by itself shows effectiveness in tumor cell destruction. Full length antibodies have greater half life in circulation. Production in *E. coli* is faster and more cost efficient. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. 5,648,237 (Carter et al.), U.S. 5,789,199 (Joly et al.), and U.S. 5,840,523 (Simmons et al.) which describes translation initiation region (TIR) and signal sequences for optimizing expression and secretion, these patents incorporated herein by reference. After expression, the antibody is isolated from the *E. coli* cell paste in a soluble fraction and can be purified through, e.g., a protein A or G column depending on the isotype. Final purification can be carried out similar to the process for purifying antibody expressed e.g., in CHO cells.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for anti-PRO antibody- or PRO polypeptide-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, *Nature*, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., *Bio/Technology*, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., *J. Bacteriol.*, 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906; Van den Berg et al., *Bio/Technology*, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., *J. Basic Microbiol.*, 28:265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., *Proc. Natl. Acad. Sci. USA*, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., *Biochem. Biophys. Res. Commun.*, 112:284-289 [1983]; Tilburn et al., *Gene*, 26:205-221 [1983]; Yelton et al., *Proc. Natl. Acad. Sci. USA*, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, *EMBO J.*, 4:475-479 [1985]). Methylophilic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, *The Biochemistry of Methylophilic Yeasts*, 269 (1982).

Suitable host cells for the expression of glycosylated anti-PRO antibody or PRO polypeptide are derived

from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells, such as cell cultures of cotton, corn, potato, soybean, petunia, tomato, and tobacco. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for transfection of *Spodoptera frugiperda* cells.

However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary cells/-DHFR (CHO, Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); mouse sertoli cells (TM4, Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

Host cells are transformed with the above-described expression or cloning vectors for anti-PRO antibody or PRO polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

5.2.7.3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding anti-PRO antibody or PRO polypeptide may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the anti-PRO antibody- or PRO polypeptide-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the

alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as

5 signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning

10 vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

15 An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the anti-PRO antibody- or PRO polypeptide-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al.,

20 Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the anti-PRO antibody- or PRO polypeptide-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of

25 potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the *tac* promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding

30 anti-PRO antibody or PRO polypeptide.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate

35 isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription

controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

Anti-PRO antibody or PRO polypeptide transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the anti-PRO antibody or PRO polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the anti-PRO antibody or PRO polypeptide coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding anti-PRO antibody or PRO polypeptide.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of anti-PRO antibody or PRO polypeptide in recombinant vertebrate cell culture are described in Gething et al., *Nature*, 293:620-625 (1981); Mantei et al., *Nature*, 281:40-46 (1979); EP 117,060; and EP 117,058.

5.2.7.4. Culturing the Host Cells

The host cells used to produce the anti-PRO antibody or PRO polypeptide of this invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., *Meth. Enz.* 58:44 (1979), Barnes et al., *Anal. Biochem.* 102:255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Patent Re. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as GENTAMYCIN™ drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and

glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

5.2.7.5. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

5.2.7.6. Purification of Anti-PRO Antibody and PRO Polypeptide

Forms of anti-PRO antibody and PRO polypeptide may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of anti-PRO antibody and PRO polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify anti-PRO antibody and PRO polypeptide from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the anti-PRO antibody and PRO polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular anti-PRO antibody or PRO polypeptide produced.

When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris,

either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Carter et al., Bio/Technology 10:163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human $\gamma 1$, $\gamma 2$ or $\gamma 4$ heavy chains (Lindmark et al., J. Immunol. Meth. 62:1-13 (1983)). Protein G is recommended for all mouse isotypes and for human $\gamma 3$ (Guss et al., EMBO J. 5:1567-1575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrene-divinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_H3 domain, the Bakerbond ABXTM resin (J. T. Baker, Phillipsburg, NJ) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSETM chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5-4.5, preferably performed at low salt concentrations (e.g., from about 0-0.25M salt).

5.2.8. Pharmaceutical Formulations

Therapeutic formulations of the anti-PRO antibodies and/or PRO polypeptides used in accordance with the present invention are prepared for storage by mixing an antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as acetate, Tris, phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine;

monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; tonicifiers such as trehalose and sodium chloride; sugars such as sucrose, mannitol, trehalose or sorbitol; surfactant such as polysorbate; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG). The antibody preferably comprises the antibody at a concentration of between 5-200 mg/ml, preferably between 10-100 mg/ml.

The formulations herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, in addition to an anti-PRO antibody, it may be desirable to include in the one formulation, an additional antibody, e.g., a second anti-PRO antibody which binds a different epitope on the PRO polypeptide, or an antibody to some other target such as a growth factor that affects the growth of the particular disorder. Alternatively, or additionally, the composition may further comprise a chemotherapeutic agent, cytotoxic agent, cytokine, growth inhibitory agent, anti-hormonal agent, and/or cardioprotectant. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT® (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

5.2.9. Diagnosis and Treatment with Anti-PRO Antibodies and PRO Polypeptides

In one embodiment, PRO polypeptide overexpression may be analyzed by immunohistochemistry (IHC). Paraffin embedded tissue sections from a tissue biopsy (e.g., colon tissue from a patient with an IBD) may be subjected to the IHC assay and accorded a PRO protein staining intensity criteria as follows:

Score 0 - no staining is observed or membrane staining is observed in less than 10% of tissue cells.

Score 1+ - a faint/barely perceptible membrane staining is detected in more than 10% of the tissue cells.

The cells are only stained in part of their membrane.

Score 2+ - a weak to moderate complete membrane staining is observed in more than 10% of the tissue cells.

Score 3+ - a moderate to strong complete membrane staining is observed in more than 10% of the tissue cells.

Those tissues (*e.g.*, colon tissue from a patient with an IBD) with 0 or 1+ scores for PRO polypeptide expression may be characterized as not overexpressing PRO, whereas those tissues with 2+ or 3+ scores may be characterized as overexpressing PRO.

5 Alternatively, or additionally, FISH assays such as the INFORM® (sold by Ventana, Arizona) or PATHVISION® (Vysis, Illinois) may be carried out on formalin-fixed, paraffin-embedded tissue to determine the extent (if any) of PRO overexpression in the tissue (*e.g.*, colon tissue from a patient with an IBD).

10 PRO overexpression or amplification may be evaluated using an *in vivo* diagnostic assay, *e.g.*, by administering a molecule (such as an antibody) which binds the molecule to be detected and is tagged with a detectable label (*e.g.*, a radioactive isotope or a fluorescent label) and externally scanning the patient for localization of the label.

15 As described above, the anti-PRO antibodies of the invention have various non-therapeutic applications. The anti-PRO antibodies of the present invention can be useful for diagnosis and staging of PRO polypeptide-expressing disorders (*e.g.*, in radioimaging). The antibodies are also useful for purification or immunoprecipitation of PRO polypeptide from cells, for detection and quantitation of PRO polypeptide *in vitro*, *e.g.*, in an ELISA or a Western blot, to kill and eliminate PRO-expressing cells from a population of mixed cells as a step in the purification of other cells.

20 Where the disorder is a cancer, current treatment involves one or a combination of the following therapies: surgery to remove the cancerous tissue, radiation therapy, and chemotherapy. Anti-PRO antibody therapy may be especially desirable in elderly patients who do not tolerate the toxicity and side effects of chemotherapy well and in metastatic disease where radiation therapy has limited usefulness. The tumor targeting anti-PRO antibodies of the invention are useful to alleviate PRO-expressing cancers upon initial diagnosis of the disease or during relapse. For therapeutic applications, the anti-PRO antibody can be used alone, or in combination therapy with, *e.g.*, hormones, antiangiogens, or radiolabelled compounds, or with surgery, cryotherapy, and/or radiotherapy. Anti-PRO antibody treatment can be administered in conjunction with other forms of conventional therapy, either consecutively with, pre- or post-conventional therapy. Chemotherapeutic drugs such as TAXOTERE® (docetaxel), TAXOL® (paclitaxel), estramustine and mitoxantrone are used in treating cancer, in particular, in good risk patients. In the present method of the invention for treating or alleviating cancer, the cancer patient can be administered anti-PRO antibody in conjunction with treatment with the one or more of the preceding chemotherapeutic agents. In particular, combination therapy with paclitaxel and modified derivatives (see, *e.g.*, EP0600517) is contemplated. The anti-PRO antibody will be administered with a therapeutically effective dose of the chemotherapeutic agent. In another embodiment, the anti-PRO antibody is administered in conjunction with chemotherapy to enhance the activity and efficacy of the chemotherapeutic agent, *e.g.*, paclitaxel. The Physicians' Desk Reference (PDR) discloses dosages of these agents that have been used in treatment of various cancers. The dosing regimen and dosages of these aforementioned chemotherapeutic drugs that are therapeutically effective will depend on the particular cancer being treated, the extent of the disease and other factors familiar to the physician of skill in the art and can be determined by the physician.

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In one particular embodiment, an immunoconjugate comprising the anti-PRO antibody conjugated with a cytotoxic agent is administered to the patient. Preferably, the immunoconjugate bound to the PRO protein is internalized by the cell, resulting in increased therapeutic efficacy of the immunoconjugate in killing the cancer cell to which it binds. In a preferred embodiment, the cytotoxic agent targets or interferes with the nucleic acid in the cancer cell. Examples of such cytotoxic agents are described above and include maytansinoids, calicheamicins, ribonucleases and DNA endonucleases.

The anti-PRO antibodies or immunoconjugates are administered to a human patient, in accord with known methods, such as intravenous administration, e.g., as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous or subcutaneous administration of the antibody is preferred.

Other therapeutic regimens may be combined with the administration of the anti-PRO antibody. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Preferably such combined therapy results in a synergistic therapeutic effect.

It may also be desirable to combine administration of the anti-PRO antibody or antibodies, with administration of an antibody directed against another antigen associated with the particular disorder.

In another embodiment, the antibody therapeutic treatment method of the present invention involves the combined administration of an anti-PRO antibody (or antibodies) and one or more chemotherapeutic agents or growth inhibitory agents, including co-administration of cocktails of different chemotherapeutic agents. Chemotherapeutic agents include estramustine phosphate, prednimustine, cisplatin, 5-fluorouracil, melphalan, cyclophosphamide, hydroxyurea and hydroxyureataxanes (such as paclitaxel and doxorubicin) and/or anthracycline antibiotics. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy Service Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992).

The antibody may be combined with an anti-hormonal compound; e.g., an anti-estrogen compound such as tamoxifen; an anti-progesterone such as onapristone (see, EP 616 812); or an anti-androgen such as flutamide, in dosages known for such molecules. Where the disorder to be treated is androgen independent, the patient may previously have been subjected to anti-androgen therapy and, after the disorder becomes androgen independent, the anti-PRO antibody (and optionally other agents as described herein) may be administered to the patient.

Sometimes, it may be beneficial to also co-administer a cardioprotectant (to prevent or reduce myocardial dysfunction associated with the therapy) or one or more cytokines to the patient. In addition to the above therapeutic regimes, the patient may be subjected to surgical removal of tissue cells and/or radiation therapy, before, simultaneously with, or post antibody therapy. Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the agent and anti-PRO antibody.

For the prevention or treatment of disease, the dosage and mode of administration will be chosen by the physician according to known criteria. The appropriate dosage of antibody will depend on the type of disease to be

treated, as defined above, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments. Preferably, the antibody is administered by intravenous infusion or by subcutaneous injections. Depending on the type and severity of the disease, about 1 μ g/kg to about 50 mg/kg body weight (e.g., about 0.1-
5 15mg/kg/dose) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A dosing regimen can comprise administering an initial loading dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg/kg of the anti-PRO antibody. However, other dosage regimens may be useful. A typical daily dosage might range from about μ g/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days
10 or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. The progress of this therapy can be readily monitored by conventional methods and assays and based on criteria known to the physician or other persons of skill in the art.

Aside from administration of the antibody protein to the patient, the present application contemplates administration of the antibody by gene therapy. Such administration of nucleic acid encoding the antibody is
15 encompassed by the expression "administering a therapeutically effective amount of an antibody". See, for example, WO96/07321 published March 14, 1996 concerning the use of gene therapy to generate intracellular antibodies.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells; *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient, usually at the site where the antibody is required. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is
20 introduced into these isolated cells and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes which are implanted into the patient (see, e.g., U.S. Patent Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro*
25 include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. A commonly used vector for *ex vivo* delivery of the gene is a retroviral vector.

The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral vectors (such as adenovirus, Herpes simplex I virus, or adeno-associated virus) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are DOTMA, DOPE and DC-Chol, for example). For review of the currently known
30 gene marking and gene therapy protocols see Anderson et al., Science 256:808-813 (1992). See also WO 93/25673 and the references cited therein.

The anti-PRO antibodies of the invention can be in the different forms encompassed by the definition of "antibody" herein. Thus, the antibodies include full length or intact antibody, antibody fragments, native sequence antibody or amino acid variants, humanized, chimeric or fusion antibodies, immunoconjugates, and functional
35 fragments thereof. In fusion antibodies an antibody sequence is fused to a heterologous polypeptide sequence. The antibodies can be modified in the Fc region to provide desired effector functions. As discussed in more detail in the sections herein, with the appropriate Fc regions, the naked antibody bound on the cell surface can induce cytotoxicity,

e.g., via antibody-dependent cellular cytotoxicity (ADCC) or by recruiting complement in complement dependent cytotoxicity, or some other mechanism. Alternatively, where it is desirable to eliminate or reduce effector function, so as to minimize side effects or therapeutic complications, certain other Fc regions may be used.

In one embodiment, the antibody competes for binding or bind substantially to, the same epitope as the antibodies of the invention. Antibodies having the biological characteristics of the present anti-PRO antibodies of the invention are also contemplated.

Methods of producing the above antibodies are described in detail herein.

The present anti-PRO antibodies are useful for treating a PRO-expressing disorder (e.g., an IBD) or alleviating one or more symptoms of the disorder in a mammal. Such an IBD includes, but is not limited to, Crohn's disease and ulcerative colitis. The antibody is able to bind to at least a portion of the cells that express the PRO polypeptide in the mammal. In a preferred embodiment, the antibody is effective to destroy or kill PRO-expressing cells or inhibit the growth of such cells, *in vitro* or *in vivo*, upon binding to PRO polypeptide on the cell. Such an antibody includes a naked anti-PRO antibody (not conjugated to any agent). Naked antibodies that have cytotoxic or cell growth inhibition properties can be further harnessed with a cytotoxic agent to render them even more potent in cell destruction. Cytotoxic properties can be conferred to an anti-PRO antibody by, e.g., conjugating the antibody with a cytotoxic agent, to form an immunoconjugate as described herein. The cytotoxic agent or a growth inhibitory agent is preferably a small molecule. Toxins such as calicheamicin or a maytansinoid and analogs or derivatives thereof, are preferable.

The invention provides a composition comprising an anti-PRO antibody of the invention, and a carrier. For the purposes of treating a disorder (e.g., an IBD), compositions can be administered to the patient in need of such treatment, wherein the composition can comprise one or more anti-PRO antibodies present as an immunoconjugate or as the naked antibody. In a further embodiment, the compositions can comprise these antibodies in combination with other therapeutic agents such as cytotoxic or growth inhibitory agents, including chemotherapeutic agents. The invention also provides formulations comprising an anti-PRO antibody of the invention, and a carrier. In one embodiment, the formulation is a therapeutic formulation comprising a pharmaceutically acceptable carrier.

Another aspect of the invention is isolated nucleic acids encoding the anti-PRO antibodies. Nucleic acids encoding both the H and L chains and especially the hypervariable region residues, chains which encode the native sequence antibody as well as variants, modifications and humanized versions of the antibody, are encompassed.

The invention also provides methods useful for treating a PRO polypeptide-expressing disorder (e.g., an IBD) or alleviating one or more symptoms of the disorder in a mammal, comprising administering a therapeutically effective amount of an anti-PRO antibody to the mammal. The antibody therapeutic compositions can be administered short term (acute) or chronic, or intermittent as directed by physician. Also provided are methods of inhibiting the growth of, and killing a PRO polypeptide-expressing cell.

The invention also provides kits and articles of manufacture comprising at least one anti-PRO antibody. Kits containing anti-PRO antibodies find use e.g., for PRO cell killing assays, for purification or immunoprecipitation of PRO polypeptide from cells. For example, for isolation and purification of PRO, the kit can contain an anti-PRO antibody coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies for detection and quantitation of an IBD *in vitro*, e.g., in an ELISA or a Western blot. Such antibody

useful for detection may be provided with a label such as a fluorescent or radiolabel.

5.2.10. Articles of Manufacture and Kits

Another embodiment of the invention is an article of manufacture containing materials useful for the treatment of PRO expressing disorders (*e.g.*, an IBD). The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the cancer condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-PRO antibody of the invention. The label or package insert indicates that the composition is used for treating a specific disorder (*e.g.*, an IBD such as Crohn's disease or ulcerative colitis). The label or package insert will further comprise instructions for administering the antibody composition to the IBD patient. Additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

Kits are also provided that are useful for various purposes, *e.g.*, for PRO-expressing cell killing assays, for purification or immunoprecipitation of PRO polypeptide from cells. For isolation and purification of PRO polypeptide, the kit can contain an anti-PRO antibody coupled to beads (*e.g.*, sepharose beads). Kits can be provided which contain the antibodies for detection and quantitation of PRO polypeptide *in vitro*, *e.g.*, in an ELISA or a Western blot. As with the article of manufacture, the kit comprises a container and a label or package insert on or associated with the container. The container holds a composition comprising at least one anti-PRO antibody of the invention. Additional containers may be included that contain, *e.g.*, diluents and buffers, control antibodies. The label or package insert may provide a description of the composition as well as instructions for the intended *in vitro* or diagnostic use.

5.2.11. Uses of PRO Polypeptides

5.2.11.1. Animal Models using PRO Polypeptides

Recombinant (transgenic) animal models can be engineered by introducing the coding portion of the PRO genes identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, *e.g.*, baboons, chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (U.S. Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (*e.g.*, Van der Putten *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 6148-615 (1985)); gene targeting in embryonic stem cells (Thompson *et al.*, Cell, **56**: 313-321 (1989)); electroporation of embryos (Lo, Mol. Cell. Biol., **3**: 1803-1814 (1983)); and sperm-mediated gene transfer. Lavitrano *et al.*, Cell, **57**: 717-73 (1989). For a review, *see* for example, U.S. Patent No. 4,736,866.

For the purpose of the present invention, transgenic animals include those that carry the transgene only in part of their cells ("mosaic animals"). The transgene can be integrated either as a single transgene, or in concatamers, *e.g.*, head-to-head or head-to-tail tandems. Selective introduction of a transgene into a particular cell type is also possible by following, for example, the technique of Lasko *et al.*, Proc. Natl. Acad. Sci. USA, **89**: 6232-636 (1992). The expression of the transgene in transgenic animals can be monitored by standard techniques. For example, Southern blot analysis or PCR amplification can be used to verify the integration of the transgene. The level of mRNA expression can then be analyzed using techniques such as *in situ* hybridization, Northern blot analysis, PCR, or immunocytochemistry. The animals are further examined for signs of tumor or cancer development.

Alternatively, "knock-out" animals can be constructed that have a defective or altered gene encoding a PRO polypeptide identified herein, as a result of homologous recombination between the endogenous gene encoding the PRO polypeptide and altered genomic DNA encoding the same polypeptide introduced into an embryonic cell of the animal. For example, cDNA encoding a particular PRO polypeptide can be used to clone genomic DNA encoding that polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a particular PRO polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker that can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector. *See, e.g.*, Thomas and Capecchi, Cell, **51**: 503 (1987) for a description of homologous recombination vectors. The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected. *See, e.g.*, Li *et al.*, Cell, **69**: 915 (1992). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse or rat) to form aggregation chimeras. *See, e.g.*, Bradley, in Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, E. J. Robertson, ed. (IRL: Oxford, 1987), pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock-out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized, for instance, by their ability to defend against certain pathological conditions and by their development of pathological conditions due to absence of the PRO polypeptide.

5.2.11.2. Tissue Distribution

The results of the assays described herein can be verified by further studies, such as by determining mRNA expression in various human tissues.

As noted before, gene amplification and/or gene expression in various tissues may be measured by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, Proc. Natl. Acad. Sci. USA, **77**:5201-5205 (1980)), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes.

Gene expression in various tissues, alternatively, may be measured by immunological methods, such as immunohistochemical staining of tissue sections and assay of cell culture or body fluids, to quantitate directly the

expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native-sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope. General techniques for generating antibodies, and special protocols for *in situ* hybridization are provided hereinbelow.

5.2.11.3. Antibody Binding Studies

The results of the assays described herein can be further verified by antibody binding studies, in which the ability of anti-PRO antibodies to inhibit the effect of the PRO polypeptides on cells used in the assays is tested. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies, the preparation of which were described above.

Antibody binding studies may be carried out in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, Monoclonal Antibodies: A Manual of Techniques (CRC Press, Inc., 1987), pp.147-158.

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyte for binding with a limited amount of antibody. The amount of target protein in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies preferably are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte that remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyte is bound by a first antibody that is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. *See, e.g.*, U.S. Pat. No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

For immunohistochemistry, the tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

5.2.11.4. Gene Therapy

Described below are methods and compositions whereby disease symptoms may be ameliorated. Certain diseases are brought about, at least in part, by an excessive level of gene product, or by the presence of a gene product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of such disease symptoms.

Alternatively, certain other diseases are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a gene product's activity. As such, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of such disease

symptoms.

In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement of such a target gene's expression, or the activity of the target gene product, will reinforce the protective effect it exerts. Some disease states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of such disease symptoms.

The PRO polypeptides described herein and polypeptidyl agonists and antagonists may be employed in accordance with the present invention by expression of such polypeptides *in vivo*, which is often referred to as gene therapy.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells: *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient, usually at the sites where the PRO polypeptide is required, *i.e.*, the site of synthesis of the PRO polypeptide, if known, and the site (*e.g.*, wound) where biological activity of the PRO polypeptide is needed. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells, and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes that are implanted into the patient (*see, e.g.*, U.S. Pat. Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or transferred *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, transduction, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. Transduction involves the association of a replication-defective, recombinant viral (preferably retroviral) particle with a cellular receptor, followed by introduction of the nucleic acids contained by the particle into the cell. A commonly used vector for *ex vivo* delivery of the gene is a retrovirus.

The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral or non-viral vectors (such as adenovirus, lentivirus, Herpes simplex I virus, or adeno-associated virus (AAV)) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are, for example, DOTMA, DOPE, and DC-Chol; *see, e.g.*, Tonkinson *et al.*, Cancer Investigation, 14(1): 54-65 (1996)). The most preferred vectors for use in gene therapy are viruses, most preferably adenoviruses, AAV, lentiviruses, or retroviruses. A viral vector such as a retroviral vector includes at least one transcriptional promoter/enhancer or locus-defining element(s), or other elements that control gene expression by other means such as alternate splicing, nuclear RNA export, or post-translational modification of messenger. In addition, a viral vector such as a retroviral vector includes a nucleic acid molecule that, when transcribed in the presence of a gene encoding the PRO polypeptide, is operably linked thereto and acts as a translation initiation sequence. Such vector constructs also include a packaging signal, long terminal repeats (LTRs) or portions thereof, and positive and negative strand primer binding sites appropriate to the virus used (if these are not already present in the viral vector). In addition, such vector typically includes a signal sequence for secretion of the PRO polypeptide from a host cell in which it is placed. Preferably the signal sequence for this purpose is a mammalian signal sequence, most preferably the native signal sequence for the PRO polypeptide. Optionally, the vector construct may also include a signal that directs polyadenylation, as well as one or more restriction sites and a translation termination sequence. By way of example, such vectors will typically

include a 5' LTR, a tRNA binding site, a packaging signal, an origin of second-strand DNA synthesis, and a 3' LTR or a portion thereof. Other vectors can be used that are non-viral, such as cationic lipids, polylysine, and dendrimers.

In some situations, it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell-surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins that bind to a cell-surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, *e.g.*, capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins that undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem., **262**: 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA, **87**: 3410-3414 (1990). For a review of the currently known gene marking and gene therapy protocols, *see*, Anderson *et al.*, Science, **256**: 808-813 (1992). *See also* WO 93/25673 and the references cited therein.

Suitable gene therapy and methods for making retroviral particles and structural proteins can be found in, *e.g.*, U.S. Pat. No. 5,681,746.

5.2.11.5. Use of Gene as a Diagnostic

This invention is also related to the use of the gene encoding the PRO polypeptide as a diagnostic. Detection of a mutated form of the PRO polypeptide will allow a diagnosis, or a susceptibility to a disorder, such as an IBD, since mutations in the PRO polypeptide may cause IBD.

Individuals carrying mutations in the genes encoding a human PRO polypeptide may be detected at the DNA level by a variety of techniques. Nucleic acids for diagnosis may be obtained from a patient's cells, such as from blood, urine, saliva, tissue biopsy, and autopsy material. The genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR (Saiki *et al.*, Nature, **324**: 163-166 (1986)) prior to analysis. RNA or cDNA may also be used for the same purpose. As an example, PCR primers complementary to the nucleic acid encoding the PRO polypeptide can be used to identify and analyze the PRO polypeptide mutations. For example, deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to radiolabeled RNA encoding the PRO polypeptide, or alternatively, radiolabeled antisense DNA sequences encoding the PRO polypeptide. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase A digestion or by differences in melting temperatures.

Genetic testing based on DNA sequence differences may be achieved by detection of alteration in electrophoretic mobility of DNA fragments in gels with or without denaturing agents. Small sequence deletions and insertions can be visualized by high resolution gel electrophoresis. DNA fragments of different sequences may be distinguished on denaturing formamide gradient gels in which the mobilities of different DNA fragments are retarded in the gel at different positions according to their specific melting or partial melting temperatures. *See, e.g.*, Myers *et al.*, Science, **230**: 1242 (1985).

Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method, for example, Cotton *et al.*, Proc. Natl. Acad. Sci. USA, **85**: 4397-4401 (1985).

In addition to more conventional gel-electrophoresis and DNA sequencing, mutations can also be detected by *in situ* analysis.

Thus, the detection of a specific DNA sequence may be achieved by methods such as hybridization, RNase protection, chemical cleavage, direct DNA sequencing, or the use of restriction enzymes, *e.g.*, restriction fragment length polymorphisms (RFLP), and Southern blotting of genomic DNA.

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5.2.11.6. Use to Detect PRO Polypeptide Levels

A competition assay may be employed wherein antibodies specific to the PRO polypeptide are attached to a solid support and the labeled PRO polypeptide and a sample derived from the host are passed over the solid support and the amount of label detected attached to the solid support can be correlated to a quantity of the PRO polypeptide in the sample.

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5.2.11.7. Chromosome Mapping

The sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphisms) are presently available for marking chromosomal location. The mapping of DNAs to chromosomes according to the present invention is an important first step in correlating those sequences with genes associated with disease.

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Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the cDNA. Computer analysis for the 3'- untranslated region is used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the primer will yield an amplified fragment.

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PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular DNA to a particular chromosome. Using the present invention with the same oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes or pools of large genomic clones in an analogous manner. Other mapping strategies that can similarly be used to map to its chromosome include *in situ* hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome-specific cDNA libraries.

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Fluorescence *in situ* hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with cDNA as short as 500 or 600 bases; however, clones larger than 2,000 bp have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. FISH requires use of the clones from which the gene encoding the PRO polypeptide was derived, and the longer the better. For example, 2,000 bp is good, 4,000 bp is better, and more than 4,000 is probably not necessary to get good results a reasonable percentage of the time. For a review of this technique, see, Verma *et al.*, Human Chromosomes: a Manual of Basic Techniques (Pergamon Press, New York, 1988).

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Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence

on the chromosome can be correlated with genetic map data. Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available online through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region is then identified through linkage analysis (coinheritance of physically adjacent genes).

Next, it is necessary to determine the differences in the cDNA or genomic sequence between affected and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the disease.

With current resolution of physical mapping and genetic mapping techniques, a cDNA precisely localized to a chromosomal region associated with the disease could be one of between 50 and 500 potential causative genes. (This assumes 1 megabase mapping resolution and one gene per 20 kb).

5.2.11.8. Screening Assays for Drug Candidates

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptide encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, *e.g.*, on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, *e.g.*, a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, *e.g.*, the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, *e.g.*, by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, *e.g.*, cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-

protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, *Nature (London)*, 340: 245-246 (1989); Chien *et al.*, *Proc. Natl. Acad. Sci. USA*, 88: 9578-9582 (1991)) as disclosed by Chevray and Nathans, *Proc. Natl. Acad. Sci. USA*, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

If the PRO polypeptide has the ability to stimulate the proliferation of endothelial cells in the presence of the co-mitogen ConA, then one example of a screening method takes advantage of this ability. Specifically, in the proliferation assay, human umbilical vein endothelial cells are obtained and cultured in 96-well flat-bottomed culture plates (Costar, Cambridge, MA) and supplemented with a reaction mixture appropriate for facilitating proliferation of the cells, the mixture containing Con-A (Calbiochem, La Jolla, CA). Con-A and the compound to be screened are added and after incubation at 37°C, cultures are pulsed with ^3H -thymidine and harvested onto glass fiber filters (phD; Cambridge Technology, Watertown, MA). Mean ^3H -thymidine incorporation (cpm) of triplicate cultures is determined using a liquid scintillation counter (Beckman Instruments, Irvine, CA). Significant ^3H -thymidine incorporation indicates stimulation of endothelial cell proliferation.

To assay for antagonists, the assay described above is performed; however, in this assay the PRO polypeptide is added along with the compound to be screened and the ability of the compound to inhibit ^3H -thymidine incorporation in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of

the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan *et al.*, Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to the labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with the labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

The compositions useful in the treatment of IBD include, without limitation, antibodies, small organic and inorganic molecules, peptides, phosphopeptides, antisense and ribozyme molecules, triple-helix molecules, etc., that inhibit the expression and/or activity of the target gene product.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with a PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, *e.g.*, an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - *see*, Lee *et al.*, Nucl. Acids Res., 6:3073 (1979); Cooney *et al.*, Science, 241: 456 (1988); Dervan *et al.*, Science, 251:1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. A sequence "complementary" to a portion of an RNA, as referred to herein, means a sequence

having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex helix formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988).

The antisense oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger, *et al.*, 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre, *et al.*, 1987, *Proc. Natl. Acad. Sci. U.S.A.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *BioTechniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an α -anomeric oligonucleotide. An α -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual

β -units, the strands run parallel to each other (Gautier, *et al.*, 1987, *Nucl. Acids Res.* 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue, *et al.*, 1987, *Nucl. Acids Res.* 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue, *et al.*, 1987, *FEBS Lett.* 215:327-330).

Oligonucleotides of the invention may be synthesized by standard methods known in the art, *e.g.*, by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.).

5 As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein, *et al.* (1988, *Nucl. Acids Res.* 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin, *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:7448-7451), *etc.*

10 The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, *e.g.*, between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

15 Antisense or sense RNA or DNA molecules are generally at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that
20 referenced length.

Potential antagonists further include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

25 Additional potential antagonists are ribozymes, which are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details *see, e.g.*, Rossi, *Current Biology*, 4: 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

30 While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy target gene mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions which form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Myers, 1995, *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers, New York, (see especially Figure 4, page 833)
35 and in Haseloff and Gerlach, 1988, *Nature*, 334:585-591, which is incorporated herein by reference in its entirety.

Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the target gene mRNA, *i.e.*, to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one which occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) and which has been extensively described by Thomas Cech and collaborators (Zaug, *et al.*, 1984, *Science*, 224:574-578; Zaug and Cech, 1986, *Science*, 231:470-475; Zaug, *et al.*, 1986, *Nature*, 324:429-433; published International patent application No. WO 88/04300 by University Patents Inc.; Been and Cech, 1986, *Cell*, 47:207-216). The Cech-type ribozymes have an eight base pair active site that hybridizes to a target RNA sequence whereafter cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes that target eight base-pair active site sequences that are present in the target gene.

As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (*e.g.*, for improved stability, targeting, *etc.*) and should be delivered to cells that express the target gene *in vivo*. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous target gene messages and inhibit translation. Because ribozymes, unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details *see, e.g.*, PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

5.2.11.9. Administration Protocols, Schedules, Doses, and Formulations

The molecules herein and agonists and antagonists thereto are pharmaceutically useful as a prophylactic and therapeutic agent for various disorders and diseases as set forth above.

Therapeutic compositions of the PRO polypeptides or agonists or antagonists are prepared for storage by mixing the desired molecule having the appropriate degree of purity with optional pharmaceutically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences, 16th edition, Osol, A. ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates

including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEENTM, PLURONICSTM or polyethylene glycol (PEG).

Additional examples of such carriers include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts, or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, and polyethylene glycol. Carriers for topical or gel-based forms of agonist or antagonist include polysaccharides such as sodium carboxymethylcellulose or methylcellulose, polyvinylpyrrolidone, polyacrylates, polyoxyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wood wax alcohols. For all administrations, conventional depot forms are suitably used. Such forms include, for example, microcapsules, nano-capsules, liposomes, plasters, inhalation forms, nose sprays, sublingual tablets, and sustained-release preparations. The PRO polypeptides or agonists or antagonists will typically be formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml.

PRO polypeptides or agonists or antagonists to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution. PRO polypeptides ordinarily will be stored in lyophilized form or in solution if administered systemically. If in lyophilized form, the PRO polypeptide or agonist or antagonist thereto is typically formulated in combination with other ingredients for reconstitution with an appropriate diluent at the time for use. An example of a liquid formulation of a PRO polypeptide or agonist or antagonist is a sterile, clear, colorless unpreserved solution filled in a single-dose vial for subcutaneous injection. Preserved pharmaceutical compositions suitable for repeated use may contain, for example, depending mainly on the indication and type of polypeptide:

- a) PRO polypeptide or agonist or antagonist thereto;
- b) a buffer capable of maintaining the pH in a range of maximum stability of the polypeptide or other molecule in solution, preferably about 4-8;
- c) a detergent/surfactant primarily to stabilize the polypeptide or molecule against agitation-induced aggregation;
- d) an isotonifier;
- e) a preservative selected from the group of phenol, benzyl alcohol and a benzethonium halide, *e.g.*, chloride; and
- f) water.

If the detergent employed is non-ionic, it may, for example, be polysorbates (*e.g.*, POLYSORBATETM (TWEENTM) 20, 80, etc.) or poloxamers (*e.g.*, POLOXAMERTM 188). The use of non-ionic surfactants permits the formulation to be exposed to shear surface stresses without causing denaturation of the polypeptide. Further, such surfactant-containing formulations may be employed in aerosol devices such as those used in a pulmonary dosing, and needleless jet injector guns (*see, e.g.*, EP 257,956).

An isotonifier may be present to ensure isotonicity of a liquid composition of the PRO polypeptide or agonist or antagonist thereto, and includes polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol, and mannitol. These sugar alcohols can be used alone or in

combination. Alternatively, sodium chloride or other appropriate inorganic salts may be used to render the solutions isotonic.

The buffer may, for example, be an acetate, citrate, succinate, or phosphate buffer depending on the pH desired. The pH of one type of liquid formulation of this invention is buffered in the range of about 4 to 8, preferably about physiological pH.

5 The preservatives phenol, benzyl alcohol and benzethonium halides, *e.g.*, chloride, are known antimicrobial agents that may be employed.

Therapeutic PRO polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle. The formulations are preferably administered as repeated intravenous (i.v.), subcutaneous (s.c.), or intramuscular
10 (i.m.) injections, or as aerosol formulations suitable for intranasal or intrapulmonary delivery (for intrapulmonary delivery *see, e.g.*, EP 257,956).

PRO polypeptides can also be administered in the form of sustained-released preparations. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the protein, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples
15 of sustained-release matrices include polyesters, hydrogels (*e.g.*, poly(2-hydroxyethyl-methacrylate) as described by Langer *et al.*, J. Biomed. Mater. Res., 15: 167-277 (1981) and Langer, Chem. Tech., 12: 98-105 (1982) or poly(vinylalcohol)), polylactides (U.S. Patent No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, Biopolymers, 22: 547-556 (1983)), non-degradable ethylene-vinyl acetate (Langer *et al.*, *supra*), degradable lactic acid-glycolic acid copolymers such as the Lupron Depot™ (injectable microspheres
20 composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated proteins remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a
25 loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for protein stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

30 Sustained-release PRO polypeptide compositions also include liposomally entrapped PRO polypeptides. Liposomes containing the PRO polypeptide are prepared by methods known *per se*: DE 3,218,121; Epstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688-3692 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese patent application 83-118008; U.S. Patent Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily the liposomes are of the small (about 200-800
35 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. % cholesterol, the selected proportion being adjusted for the optimal therapy.

The therapeutically effective dose of a PRO polypeptide or agonist or antagonist thereto will, of course, vary depending on such factors as the pathological condition to be treated (including prevention), the method of

administration, the type of compound being used for treatment, any co-therapy involved, the patient's age, weight, general medical condition, medical history, etc., and its determination is well within the skill of a practicing physician. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the maximal therapeutic effect. If the PRO polypeptide has a narrow host range, for the treatment of human patients formulations comprising human PRO polypeptide, more preferably native-sequence human PRO polypeptide, are preferred. The clinician will administer the PRO polypeptide until a dosage is reached that achieves the desired effect for treatment of the condition in question.

With the above guidelines, the effective dose generally is within the range of from about 0.001 to about 1.0 mg/kg, more preferably about 0.01-1.0 mg/kg, most preferably about 0.01-0.1 mg/kg.

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

The route of PRO polypeptide or antagonist or agonist administration is in accord with known methods, *e.g.*, by injection or infusion by intravenous, intramuscular, intracerebral, intraperitoneal, intracerebrospinal, subcutaneous, intraocular, intraarticular, intrasynovial, intrathecal, oral, topical, or inhalation routes, or by sustained-release systems as noted below. The PRO polypeptide or agonist or antagonists thereof also are suitably administered by intratumoral, peritumoral, intralesional, or perilesional routes, to exert local as well as systemic therapeutic effects. The intraperitoneal route is expected to be particularly useful, for example, in the treatment of ovarian tumors.

If a peptide or small molecule is employed as an antagonist or agonist, it is preferably administered orally or non-orally in the form of a liquid or solid to mammals.

Examples of pharmacologically acceptable salts of molecules that form salts and are useful hereunder include alkali metal salts (*e.g.*, sodium salt, potassium salt), alkaline earth metal salts (*e.g.*, calcium salt, magnesium salt), ammonium salts, organic base salts (*e.g.*, pyridine salt, triethylamine salt), inorganic acid salts (*e.g.*, hydrochloride, sulfate, nitrate), and salts of organic acid (*e.g.*, acetate, oxalate, p-toluenesulfonate).

For compositions herein that are useful for bone, cartilage, tendon, or ligament regeneration, the therapeutic method includes administering the composition topically, systemically, or locally as an implant or device. When administered, the therapeutic composition for use is in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage, or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Preferably, for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone

and cartilage and preferably capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

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

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

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

5.2.11.10. Combination Therapies

The effectiveness of the PRO polypeptide or an agonist or antagonist thereof in preventing or treating the disorder in question may be improved by administering the active agent serially or in combination with another agent that is effective for those purposes, either in the same composition or as separate compositions.

For some indications, PRO polypeptides or their agonists or antagonists may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as EGF, PDGF, TGF- α or TGF- β , IGF, FGF, and CTGF.

In addition, PRO polypeptides or their agonists or antagonists used to treat cancer may be combined with cytotoxic, chemotherapeutic, or growth-inhibitory agents as identified above. Also, for cancer treatment, the PRO polypeptide or agonist or antagonist thereof is suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances.

The effective amounts of the therapeutic agents administered in combination with the PRO polypeptide or agonist or antagonist thereof will be at the physician's or veterinarian's discretion. Dosage administration and adjustment is done to achieve maximal management of the conditions to be treated. The dose will additionally depend on such factors as the type of the therapeutic agent to be used and the specific patient being treated. Typically, the amount employed will be the same dose as that used, if the given therapeutic agent is administered without the PRO polypeptide.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

6. EXAMPLES

Commercially available reagents referred to in the Examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following Examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA. Unless otherwise noted, the present invention uses standard procedures of recombinant DNA technology, such as those described hereinabove and in the following textbooks: Sambrook *et al.*, *supra*; Ausubel *et al.*, Current Protocols in Molecular Biology (Green Publishing Associates and Wiley Interscience, N.Y., 1989); Innis *et al.*, PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc.: N.Y., 1990); Harlow *et al.*, Antibodies: A Laboratory Manual (Cold Spring Harbor Press: Cold Spring Harbor, 1988); Gait, Oligonucleotide Synthesis (IRL Press: Oxford, 1984); Freshney, Animal Cell Culture, 1987; Coligan *et al.*, Current Protocols in Immunology, 1991.

6.1. EXAMPLE 1: Deposit and/or Public Availability of Material

The following materials were deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below.

Table 7

<u>Material</u>	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
DNA32279-1131	209259	9/16/97
DNA33085-1110	209087	5/30/97
DNA33461-1199	209367	10/15/97
DNA33785-1143	209417	10/28/97
DNA52594-1270	209679	3/17/1998
DNA59776-1600	203128	8/18/98
DNA62377-1381-1	203552	12/22/98
DNA168061-2897	1600-PTA	3/30/2000
DNA171372-2908	1783-PTA	4/25/2000

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

The following materials are publicly available and accessible as follows:

Table 8

	<u>Material</u>	<u>Accession Number</u>
	DNA32279	NM_006329
20	DNA33085	NM_003841
	DNA33457	NM_003665
	DNA33461	NM_020997
	DNA33785	NM_006072
	DNA36725	NM_002190
25	DNA40576	NM_003266
	DNA51786	NM_000230
	DNA52594	NM_014452
	DNA59776	P_Z65071
	DNA62377	NM_013278
30	DNA64882	NM_002407
	DNA69553	NM_002195
	DNA77509	NM_003212
	DNA77512	NM_006507
	DNA81752	NM_001561
35	DNA82305	NM_002580
	DNA82352	NM_002991
	DNA87994	NM_003225

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	DNA88417	NM_000885
	DNA88432	NM_000888
	DNA92247	NM_004633
	DNA95930	NM_014432
	DNA99331	NM_001511
5	DNA101222	NM_003263
	DNA102850	NM_000577
	DNA105792	NM_002391
	DNA107429	NM_000758
	DNA145582	DNA145582
10	DNA165608	NM_021258
	DNA166819	P_T87432
	DNA168061	P_Z60585
	DNA171372	DNA171372
	DNA188175	NM_003842
15	DNA188182	NM_014143
	DNA188200	HUMTDGF3A
	DNA188203	NM_001330
	DNA188205	NM_005214
	DNA188244	NM_006119
20	DNA188270	NM_000641
	DNA188277	M15329
	DNA188278	NM_000576
	DNA188287	NM_000880
	DNA188302	NM_000245
25	DNA188332	P_V19157
	DNA188339	NM_004158
	DNA188340	AB037599
	DNA188355	NM_004591
	DNA188425	NM_002994
30	DNA188448	NM_005118
	DNA194566	NM_001837
	DNA199788	NM_002990
	DNA200227	NM_003814
	DNA27865	P_AAA54109
35	DNA33094	WIF1
	DNA45416	HS159A1
	DNA48328	WNT4
	DNA50960	BD102846

	DNA80896	D26579
	DNA82319	CCL25
	DNA82352	CCL24
	DNA82363	CXCL9
	DNA82368	BC028217
5	DNA83103	AL353732
	DNA83500	P_AAF4264
	DNA88002	HSU16261
	DNA92282	P_ABL88225
	DNA96934	HSIFD4
10	DNA96943	HSIFNG2
	DNA97005	BC028372
	DNA98553	HSAMAC1
	DNA102845	HSMCP3A
	DNA108715	SCYA4
15	DNA108735	CCL1
	DNA164455	IL1F6
	DNA188178	AF074332
	DNA188271	IL13
	DNA188338	CXCL11
20	DNA188342	AF146761
	DNA188427	MERTK
	DNA195011	HSA251549

6.2. EXAMPLE 2: Use of PRO as a Hybridization Probe

25 The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO (as shown in accompanying figures) or a fragment thereof is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

30 Hybridization and washing of filters containing either library DNAs is performed under the following high-stringency conditions. Hybridization of radiolabeled probe derived from the gene encoding PRO polypeptide to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

35 DNAs having a desired sequence identity with the DNA encoding full-length native sequence can then be identified using standard techniques known in the art.

6.3. EXAMPLE 3: Expression of PRO in *E. coli*

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see, Bolivar *et al.*, Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a poly-His leader (including the first six STII codons, poly-His sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook *et al.*, *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq)). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an OD₆₀₀ of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 ml water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000

rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni²⁺-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the
5 desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding
10 solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A₂₈₀ absorbance are analyzed on SDS
15 polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using
20 a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.4. EXAMPLE 4: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (*see* EP 307,247, published March 15, 1989), is employed as the expression vector.
30 Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook *et al.*, *supra*. The resulting vector is called pRK5-PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and
35 optionally, nutrient components and/or antibiotics. About 10 µg pRK5-PRO DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya *et al.*, *Cell*, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, and a precipitate is allowed to form for 10 minutes at 25°C. The

precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml ³⁵S-cysteine and 200 µCi/ml ³⁵S-methionine.

5 After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of the PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

10 In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Sompayrac *et al.*, Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 µg/ml bovine insulin and 15 0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO₄ or DEAE-dextran. As described above, the cell cultures can be 20 incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ³⁵S-methionine. After determining the presence of a PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO polypeptide can then be concentrated and purified by any selected method.

25 Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-His tag into a Baculovirus expression vector. The poly-His tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as 30 described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni²⁺-chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

35 Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (*e.g.*, extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or as a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel *et al.*, Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used in expression in CHO cells is as described in Lucas *et al.*, Nucl. Acids Res., 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Qiagen), Dosper® or Fugene® (Boehringer Mannheim). The cells are grown as described in Lucas *et al.*, *supra*. Approximately 3×10^7 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into a water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 ml of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 ml of selective media (0.2 μ m filtered PS20 with 5% 0.2 μ m diafiltered fetal bovine serum). The cells are then aliquoted into a 100 ml spinner containing 90 ml of selective media. After 1-2 days, the cells are transferred into a 250 ml spinner filled with 150 ml selective growth medium and incubated at 37°C. After another 2-3 days, 250 ml, 500 ml and 2000 ml spinners are seeded with 3×10^5 cells/ml. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2×10^6 cells/ml. On day 0, the cell number and pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 ml of 500 g/L glucose and 0.6 ml of 10% antifoam (*e.g.*, 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability drops below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate is either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni²⁺-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni²⁺-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which has been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μ l of 1 M Tris buffer, pH 9. The highly purified protein is subsequently

desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.5. EXAMPLE 5: Expression of PRO in Yeast

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.6. EXAMPLE 6: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-His tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO (such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular) is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley *et al.*, Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-His tagged PRO can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert *et al.*, Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25

ml Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 ml, washed with 25 ml of water and equilibrated with 25 ml of loading buffer. The filtered cell extract is loaded
5 onto the column at 0.5 ml per minute. The column is washed to baseline A₂₈₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A₂₈₀ baseline again, the column is developed with a 0 to 500 mM imidazole gradient in the secondary wash buffer. One ml fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-
10 conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₁₀-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Following PCR amplification, the respective coding sequences are subcloned into a baculovirus
15 expression vector (pb.PH.IgG for IgG fusions and pb.PH.His.c for poly-His tagged proteins), and the vector and Baculogold® baculovirus DNA (Pharmingen) are co-transfected into 105 *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711), using Lipofectin (Gibco BRL). pb.PH.IgG and pb.PH.His are modifications of the commercially available baculovirus expression vector pVL1393 (Pharmingen), with modified polylinker regions to include the His or Fc tag sequences. The cells are grown in Hink's TNM-FH medium supplemented with 10%
20 FBS (Hyclone). Cells are incubated for 5 days at 28°C. The supernatant is harvested and subsequently used for the first viral amplification by infecting Sf9 cells in Hink's TNM-FH medium supplemented with 10% FBS at an approximate multiplicity of infection (MOI) of 10. Cells are incubated for 3 days at 28°C. The supernatant is harvested and the expression of the constructs in the baculovirus expression vector is determined by batch binding of 1 ml of supernatant to 25 ml of Ni²⁺-NTA beads (QIAGEN) for histidine tagged proteins or
25 Protein-A Sepharose CL-4B beads (Pharmacia) for IgG tagged proteins followed by SDS-PAGE analysis comparing to a known concentration of protein standard by Coomassie blue staining.

The first viral amplification supernatant is used to infect a spinner culture (500 ml) of Sf9 cells grown in ESF-921 medium (Expression Systems LLC) at an approximate MOI of 0.1. Cells are incubated for 3 days at 28°C. The supernatant is harvested and filtered. Batch binding and SDS-PAGE analysis is repeated, as
30 necessary, until expression of the spinner culture is confirmed.

The conditioned medium from the transfected cells (0.5 to 3 L) is harvested by centrifugation to remove the cells and filtered through 0.22 micron filters. For the poly-His tagged constructs, the protein construct is purified using a Ni²⁺-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni²⁺-NTA column equilibrated in 20
35 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer

containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc containing) constructs of proteins are purified from the conditioned media as follows. The conditioned media is pumped onto a 5 ml Protein A column (Pharmacia) which has been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 ml of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity of the proteins is verified by SDS polyacrylamide gel (PAGE) electrophoresis and N-terminal amino acid sequencing by Edman degradation.

Alternatively, a modified baculovirus procedure may be used incorporating high-5 cells. In this procedure, the DNA encoding the desired sequence is amplified with suitable systems, such as Pfu (Stratagene), or fused upstream (5'-of) of an epitope tag contained with a baculovirus expression vector. Such epitope tags include poly-His tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pIE1-1 (Novagen). The pIE1-1 and pIE1-2 vectors are designed for constitutive expression of recombinant proteins from the baculovirus ie1 promoter in stably-transformed insect cells (1). The plasmids differ only in the orientation of the multiple cloning sites and contain all promoter sequences known to be important for ie1-mediated gene expression in uninfected insect cells as well as the hr5 enhancer element. pIE1-1 and pIE1-2 include the translation initiation site and can be used to produce fusion proteins. Briefly, the desired sequence or the desired portion of the sequence (such as the sequence encoding the extracellular domain of a transmembrane protein) is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector. For example, derivatives of pIE1-1 can include the Fc region of human IgG (pb.PH.IgG) or an 8 histidine (pb.PH.His) tag downstream (3'-of) the desired sequence. Preferably, the vector construct is sequenced for confirmation.

High-5 cells are grown to a confluency of 50% under the conditions of, 27°C, no CO₂, NO pen/strep. For each 150 mm plate, 30 µg of pIE based vector containing the sequence is mixed with 1 ml Ex-Cell medium (Media: Ex-Cell 401 + 1/100 L-Glu JRH Biosciences #14401-78P (note: this media is light sensitive)), and in a separate tube, 100 µl of CellFectin (CellFECTIN (GibcoBRL #10362-010) (vortexed to mix)) is mixed with 1 ml of Ex-Cell medium. The two solutions are combined and allowed to incubate at room temperature for 15 minutes. 8 ml of Ex-Cell media is added to the 2 ml of DNA/CellFECTIN mix and this is layered on high-5 cells that have been washed once with Ex-Cell media. The plate is then incubated in darkness for 1 hour at room temperature. The DNA/CellFECTIN mix is then aspirated, and the cells are washed once with Ex-Cell to remove excess CellFECTIN, 30 ml of fresh Ex-Cell media is added and the cells are incubated for 3 days at 28°C. The supernatant is harvested and the expression of the sequence in the baculovirus expression vector is determined by batch binding of 1 ml of supernatant to 25 ml of Ni²⁺-NTA beads (QIAGEN) for histidine tagged proteins or Protein-A Sepharose CL-4B beads (Pharmacia) for IgG tagged proteins followed by SDS-PAGE analysis comparing to a known concentration of protein standard by Coomassie blue staining.

The conditioned media from the transfected cells (0.5 to 3 L) is harvested by centrifugation to remove the cells and filtered through 0.22 micron filters. For the poly-His tagged constructs, the protein comprising the sequence is purified using a Ni²⁺-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni²⁺-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 48°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is then subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc containing) constructs of proteins are purified from the conditioned media as follows. The conditioned media is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 ml of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity of the sequence is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation and other analytical procedures as desired or necessary.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.7. EXAMPLE 7: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind the PRO polypeptide or an epitope on the PRO polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells

which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

6.8. EXAMPLE 8: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

6.9. EXAMPLE 9: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located

intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

6.10. EXAMPLE 10: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of

homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

5 It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be
10 used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place
15 of or in addition to x-ray crystallography.

6.11. EXAMPLE 11: Quantitative Analysis of PRO mRNA Expression

In this assay, a 5' nuclease assay (for example, TaqMan®) and real-time quantitative PCR (for example, ABI Prism® 7700 Sequence Detection System (Applied Biosystems, Foster City, CA)), were used to find genes
20 that are overexpressed in an IBD as compared to normal non-IBD tissue. The 5' nuclease assay reaction is a fluorescent PCR-based technique which makes use of the 5' exonuclease activity of Taq DNA polymerase enzyme to monitor gene expression in real time. Two oligonucleotide primers (whose sequences are based upon the gene of interest) are used to generate an amplicon typical of a PCR reaction. A third oligonucleotide, or probe, is designed to detect nucleotide sequence located between the two PCR primers. The probe is
25 non-extendible by Taq DNA polymerase enzyme, and is labeled with a reporter fluorescent dye and a quencher fluorescent dye. Any laser-induced emission from the reporter dye is quenched by the quenching dye when the two dyes are located close together as they are on the probe. During the PCR amplification reaction, the Taq DNA polymerase enzyme cleaves the probe in a template-dependent manner. The resultant probe fragments disassociate in solution, and signal from the released reporter dye is free from the quenching effect of the second
30 fluorophore. One molecule of reporter dye is liberated for each new molecule synthesized, and detection of the unquenched reporter dye provides the basis for quantitative interpretation of the data.

The 5' nuclease procedure is run on a real-time quantitative PCR device such as the ABI Prism® 7700 Sequence Detection System. The system consists of a thermocycler, laser, charge-coupled device (CCD) camera and computer. The system amplifies samples in a 96-well format on a thermocycler. During amplification,
35 laser-induced fluorescent signal is collected in real-time through fiber optics cables for all 96 wells, and detected at the CCD. The system includes software for running the instrument and for analyzing the data.

5' nuclease assay data are initially expressed as C_t , or the threshold cycle. This is defined as the cycle at which the reporter signal accumulates above the background level of fluorescence. The ΔC_t value is used as quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when compared to an internal standard (*GAPDH* transcripts). ΔC_t is calculated as $\Delta C_t = C_t^{\text{gene1 in sample1}} - C_t^{\text{GAPDH in sample1}}$. This is to control for differences in mRNA concentration in the different samples. Data from the six normal colon RNA samples were averaged together, and then the ΔC_t calculated using *GAPDH* as the reference.

The $\Delta\Delta C_t$ values are used as quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing IBD colon RNA results to normal colon RNA results. The $\Delta\Delta C_t$ was calculated by subtracting the signal for the normal colon mRNA from the signal for disease mRNA. $\Delta\Delta C_t = \Delta C_t^{\text{disease}} - \Delta C_t^{\text{normal}}$. The fold difference was calculated as $2^{-\Delta\Delta C_t}$. As one C_t unit corresponds to 1 PCR cycle, or approximately a 2-fold relative increase relative to normal, two units corresponds to a 4-fold relative increase, 3 units corresponds to an 8-fold relative increase and so on, one can quantitatively measure the relative fold increase in mRNA expression between two or more different tissues.

Using this technique, the molecules listed below have been identified as being significantly overexpressed (fold difference ≥ 15 in IBD versus normal) or underexpressed (fold difference ≤ 50 in IBD versus normal) in greater than 1/3 of IBD samples as compared to normal non-IBD tissue. In a separate analysis, the raw C_t values were analyzed by a Kruskal-Wallis test with the hypothesis that the genes had common C_t values in the UC, CD and normal groups. The genes were ranked by their Kruskal-Wallis statistic scores, with larger scores indicating differences in expression between the groups. The genes thus identified represent excellent polypeptide targets for the diagnosis and therapy of IBD in mammals.

<u>Molecule</u>	<u>upregulation of expression in:</u>	<u>as compared to:</u>
DNA92247	Ulcerative colitis and Crohn's disease	matched normal colon tissue
DNA188425	Ulcerative colitis and Crohn's disease	matched normal colon tissue
DNA188287	Ulcerative colitis	matched normal colon tissue
DNA188332	Ulcerative colitis and Crohn's disease	matched normal colon tissue
DNA87994	Ulcerative colitis and Crohn's disease	matched normal colon tissue
DNA188278	Ulcerative colitis	matched normal colon tissue
DNA99331	Ulcerative colitis and Crohn's disease	matched normal colon tissue
DNA64882	Ulcerative colitis	matched normal colon tissue
DNA188277	Ulcerative colitis	matched normal colon tissue
DNA188182	Ulcerative colitis and Crohn's disease	matched normal colon tissue
DNA105792	Ulcerative colitis and Crohn's disease	matched normal colon tissue
DNA59776	Ulcerative colitis	matched normal colon tissue
DNA62377	Ulcerative colitis	matched normal colon tissue
DNA188355	Ulcerative colitis and Crohn's disease	matched normal colon tissue
DNA171372	Ulcerative colitis	matched normal colon tissue
DNA188302	Ulcerative colitis and Crohn's disease	matched normal colon tissue

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	DNA88432	Ulcerative colitis and Crohn's disease	matched normal colon tissue
	DNA51786	Ulcerative colitis	matched normal colon tissue
	DNA95930	Ulcerative colitis	matched normal colon tissue
	DNA188205	Ulcerative colitis	matched normal colon tissue
	DNA77509	Ulcerative colitis	matched normal colon tissue
5	DNA40576	Ulcerative colitis	matched normal colon tissue
	DNA33461	Ulcerative colitis and Crohn's disease	matched normal colon tissue
	DNA33085	Ulcerative colitis	matched normal colon tissue
	DNA32279	Ulcerative colitis	matched normal colon tissue
	DNA69553	Ulcerative colitis	matched normal colon tissue
10	DNA188448	Ulcerative colitis	matched normal colon tissue
	DNA102850	Ulcerative colitis	matched normal colon tissue
	DNA194566	Ulcerative colitis and Crohn's disease	matched normal colon tissue
	DNA77512	Ulcerative colitis and Crohn's disease	matched normal colon tissue
	DNA33785	Ulcerative colitis	matched normal colon tissue
15	DNA82352	Ulcerative colitis and Crohn's disease	matched normal colon tissue
	DNA188340	Ulcerative colitis	matched normal colon tissue
	DNA188203	Ulcerative colitis	matched normal colon tissue
	DNA145582	Ulcerative colitis	matched normal colon tissue
	DNA88417	Ulcerative colitis	matched normal colon tissue
20	DNA101222	Ulcerative colitis	matched normal colon tissue
	DNA199788	Ulcerative colitis	matched normal colon tissue
	DNA166819	Ulcerative colitis	matched normal colon tissue
	DNA81752	Ulcerative colitis	matched normal colon tissue
	DNA188270	Ulcerative colitis	matched normal colon tissue
25	DNA82305	Ulcerative colitis	matched normal colon tissue
	DNA107429	Ulcerative colitis	matched normal colon tissue
	DNA168061	Ulcerative colitis	matched normal colon tissue
	DNA33457	Ulcerative colitis	matched normal colon tissue
	DNA36725	Ulcerative colitis	matched normal colon tissue
30	DNA188200	Ulcerative colitis	matched normal colon tissue
	DNA45416	Ulcerative colitis	matched normal colon tissue
	DNA80896	Ulcerative colitis	matched normal colon tissue
	DNA82352	Ulcerative colitis	matched normal colon tissue
	DNA82363	Ulcerative colitis	matched normal colon tissue
35	DNA82368	Ulcerative colitis	matched normal colon tissue
	DNA83103	Ulcerative colitis and Crohn's disease	matched normal colon tissue
	DNA83500	Ulcerative colitis	matched normal colon tissue

	DNA88002	Ulcerative colitis	matched normal colon tissue
	DNA92282	Ulcerative colitis	matched normal colon tissue
	DNA96934	Ulcerative colitis and Crohn's disease	matched normal colon tissue
	DNA96943	Ulcerative colitis	matched normal colon tissue
	DNA97005	Crohn's disease	matched normal colon tissue
5	DNA98553	Ulcerative colitis	matched normal colon tissue
	DNA102845	Ulcerative colitis	matched normal colon tissue
	DNA108735	Ulcerative colitis	matched normal colon tissue
	DNA164455	Ulcerative colitis	matched normal colon tissue
	DNA188178	Ulcerative colitis	matched normal colon tissue
10	DNA188271	Ulcerative colitis	matched normal colon tissue
	DNA188338	Ulcerative colitis	matched normal colon tissue
	DNA188342	Ulcerative colitis	matched normal colon tissue
	DNA188427	Ulcerative colitis	matched normal colon tissue
	DNA195011	Ulcerative colitis and Crohn's disease	matched normal colon tissue
15	DNA188244	Crohn's disease	matched normal colon tissue
	DNA165608	Crohn's disease	matched normal colon tissue
	DNA188339	Crohn's disease	matched normal colon tissue
	DNA188175	Crohn's disease	matched normal colon tissue
20	<u>Molecule</u>	<u>downregulation of expression in:</u>	<u>as compared to:</u>
	DNA51786	Crohn's disease	matched normal colon tissue
	DNA52594	Crohn's disease	matched normal colon tissue
	DNA200227	Ulcerative colitis and Crohn's disease	matched normal colon tissue
	DNA27865	Crohn's disease	matched normal colon tissue
25	DNA33094	Ulcerative colitis	matched normal colon tissue
	DNA48328	Ulcerative colitis	matched normal colon tissue
	DNA50960	Ulcerative colitis	matched normal colon tissue
	DNA82319	Ulcerative colitis	matched normal colon tissue
	DNA97005	Ulcerative colitis	matched normal colon tissue
30	DNA108715	Ulcerative colitis	matched normal colon tissue

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the

claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid having at least 80% nucleic acid sequence identity to:

(a) a nucleotide sequence that encodes the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

(b) a nucleotide sequence that encodes the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

, lacking its associated signal peptide;

(c) a nucleotide sequence that encodes the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), with its associated signal peptide;

(d) a nucleotide sequence that encodes the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18

(SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(e) the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105) ;

(f) the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure

11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17),
 Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID
 NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ
 ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41
 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure
 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55),
 Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID
 NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ
 ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure
 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85),
 Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID
 NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ
 ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107),
 Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ
 ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure
 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID
 NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure
 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID
 NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure
 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID
 NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(g) the full-length coding sequence of the cDNA deposited under any ATCC accession number shown
 in Table 7 or available under any Accession Number shown in Table 8; or

(h) the complement of (a), (b), (c), (d), (e), (f), or (g).

2. An isolated nucleic acid comprising:

(a) a nucleotide sequence that encodes the amino acid sequence shown in Figure 2 (SEQ ID NO:2),
 Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10),
 Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID
 NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ
 ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34
 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure
 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48),
 Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID
 NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ
 ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72
 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure
 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86),

Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

(b) a nucleotide sequence that encodes the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(c) a nucleotide sequence that encodes the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18

(SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), with its associated signal peptide;

(d) a nucleotide sequence that encodes the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID

NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(e) the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(f) the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure

49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55),
 Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID
 NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ
 ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure
 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85),
 5 Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID
 NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ
 ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure
 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID
 NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure
 10 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID
 NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure
 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID
 NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure
 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID
 15 NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(g) the full-length coding sequence of the cDNA deposited under any ATCC accession number shown
 in Table 7 or available under any Accession Number shown in Table 8; or

(h) the complement of (a), (b), (c), (d), (e), (f), or (g).

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3. An isolated nucleic acid that hybridizes to:

(a) a nucleotide sequence that encodes the amino acid sequence shown in Figure 2 (SEQ ID NO:2),
 Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10),
 Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID
 25 NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ
 ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34
 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure
 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48),
 Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID
 30 NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ
 ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72
 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure
 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86),
 Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID
 35 NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102
 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108),
 Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ

ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

(b) a nucleotide sequence that encodes the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(c) a nucleotide sequence that encodes the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ

ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56
 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure
 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70),
 Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID
 NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ
 5 ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94
 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure
 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID
 NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure
 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID
 10 NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure
 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID
 NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure
 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID
 NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure
 15 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), with its associated signal
 peptide;

(d) a nucleotide sequence that encodes the extracellular domain of the polypeptide shown in Figure 2
 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ
 ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18
 20 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure
 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32),
 Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID
 NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ
 ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56
 25 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure
 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70),
 Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID
 NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ
 ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94
 30 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure
 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID
 NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure
 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID
 NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure
 35 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID
 NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure
 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID

NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(e) the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(f) the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure

79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85),
 Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID
 NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ
 ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107),
 Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ
 ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure
 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID
 NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure
 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID
 NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure
 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID
 NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(g) the full-length coding sequence of the cDNA deposited under any ATCC accession number shown
 in Table 7 or available under any Accession Number shown in Table 8; or

(h) the complement of (a), (b), (c), (d), (e), (f), or (g).

4. The nucleic acid of Claim 3, wherein the hybridization occurs under stringent conditions.

5. The nucleic acid of Claim 3 which is at least about 5 nucleotides in length.

6. An expression vector comprising the nucleic acid of Claim 1.

7. The expression vector of Claim 6, wherein said nucleic acid is operably linked to control
 sequences recognized by a host cell transformed with the vector.

8. A host cell comprising the expression vector of Claim 7.

9. The host cell of Claim 8 which is a CHO cell, an *E. coli* cell or a yeast cell.

10. A process for producing a polypeptide comprising culturing the host cell of Claim 8 under
 conditions suitable for expression of said polypeptide and recovering said polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6
 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14
 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure
 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28),

Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66),
 5 Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

(b) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28),
 25 Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure

140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162); lacking its associated signal peptide;

(c) an amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), with its associated signal peptide;

(d) an amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78),

Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(f) an amino acid sequence encoded by the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15),

NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

or

(g) an amino acid sequence encoded by the full-length coding sequence of the cDNA deposited under any ATCC accession number shown in Table 7 or available under any Accession Number shown in Table 8.

12. An isolated polypeptide comprising:

(a) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure

98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

(b) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(c) an amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26

(SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), with its associated signal peptide;

(d) an amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure

138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 1 (SEQ ID NO:1),

5 Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41
10 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure
15 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ
20 ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure
25 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(f) an amino acid sequence encoded by the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID
30 NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID
35 NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75),

Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);
or

(g) an amino acid sequence encoded by the full-length coding sequence of the cDNA deposited under any ATCC accession number shown in Table 7 or available under any Accession Number shown in Table 8.

13. A chimeric polypeptide comprising the polypeptide of Claim 11 fused to a heterologous polypeptide.

14. The chimeric polypeptide of Claim 13, wherein said heterologous polypeptide is an epitope tag sequence or an Fc region of an immunoglobulin.

15. An isolated antibody which binds to a polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104),

NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

(b) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(c) an amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure

34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40),
 Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID
 NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ
 ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64
 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure
 5 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78),
 Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID
 NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ
 ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102
 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108),
 10 Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ
 ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure
 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID
 NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure
 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID
 15 NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure
 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID
 NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), with its associated signal peptide;

(d) an amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID
 NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID
 20 NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ
 ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26
 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure
 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40),
 Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID
 25 NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ
 ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64
 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure
 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78),
 Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID
 30 NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ
 ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102
 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108),
 Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ
 ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure
 35 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID
 NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure
 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID

NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(f) an amino acid sequence encoded by the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83),

NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119),
 5 Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);
 10 or

(g) an amino acid sequence encoded by the full-length coding sequence of the cDNA deposited under any ATCC accession number shown in Table 7 or available under any Accession Number shown in Table 8.

15 16. The antibody of Claim 15 which binds to a polypeptide comprising:

(a) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28),
 20 Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66),
 25 Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure
 30 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure

154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162);

(b) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(c) an amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ

ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), with its associated signal peptide;

(d) an amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162), lacking its associated signal peptide;

(e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ

ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

(f) an amino acid sequence encoded by the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID

NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);
or

5 (g) an amino acid sequence encoded by the full-length coding sequence of the cDNA deposited under any ATCC accession number shown in Table 7 or available under any Accession Number shown in Table 8.

17. The antibody of Claim 15 which is a monoclonal antibody.

18. The antibody of Claim 15 which is an antibody fragment.

10

19. The antibody of Claim 15 which is a chimeric or a humanized antibody.

20. The antibody of Claim 15 which is conjugated to a growth inhibitory agent.

15

21. The antibody of Claim 15 which is conjugated to a cytotoxic agent.

22. The antibody of Claim 21, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

20

23. The antibody of Claim 21, wherein the cytotoxic agent is a toxin.

24. The antibody of Claim 23, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

25

25. The antibody of Claim 23, wherein the toxin is a maytansinoid.

26. The antibody of Claim 15 which is produced in bacteria.

27. The antibody of Claim 15 which is produced in CHO cells.

30

28. The antibody of Claim 15 which induces death of a cell to which it binds.

29. The antibody of Claim 15 which is detectably labeled.

35

30. An isolated nucleic acid comprising a nucleotide sequence that encodes the antibody of Claim

15.

31. An expression vector comprising the nucleic acid of Claim 30 operably linked to control sequences recognized by a host cell transformed with the vector.

32. A host cell comprising the expression vector of Claim 31.

5 33. The host cell of Claim 32 which is a CHO cell, an *E. coli* cell or a yeast cell.

34. A process for producing an antibody comprising culturing the host cell of Claim 32 under conditions suitable for expression of said antibody and recovering said antibody from the cell culture.

10 35. A composition of matter comprising:

- (a) the polypeptide of Claim 11;
- (b) the chimeric polypeptide of Claim 13; or
- (c) the antibody of Claim 15, in combination with a carrier.

15 36. The composition of matter of Claim 35, wherein said carrier is a pharmaceutically acceptable carrier.

37. An article of manufacture:

- (a) a container; and
- 20 (b) the composition of matter of Claim 35 contained within said container.

38. The article of manufacture of Claim 37 further comprising a label affixed to said container, or a package insert included with said container, referring to the use of said composition of matter for the therapeutic treatment of or the diagnostic detection of a cancer.

25

39. A method of killing a cell that expresses a polypeptide having at least 80% amino acid sequence identity to:

- (a) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID

~~Figure 76~~ (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162); or

(b) an amino acid sequence encoded by a nucleotide sequence comprising the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

said method comprising contacting said cell with an antibody that binds to said polypeptide on said cell, thereby killing said cell.

40. The method of Claim 39, wherein said antibody is a monoclonal antibody.

41. The method of Claim 39, wherein said antibody is an antibody fragment.

42. The method of Claim 39, wherein said antibody is a chimeric or a humanized antibody.

43. The method of Claim 39, wherein said antibody is conjugated to a growth inhibitory agent.

44. The method of Claim 39, wherein said antibody is conjugated to a cytotoxic agent.

45. The method of Claim 44, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

46. The method of Claim 44, wherein the cytotoxic agent is a toxin.

47. The method of Claim 46, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

48. The method of Claim 46, wherein the toxin is a maytansinoid.

49. The method of Claim 39, wherein said antibody is produced in bacteria.

50. The method of Claim 39, wherein said antibody is produced in CHO cells.

51. The method of Claim 39, wherein said cell is further exposed to radiation treatment or a chemotherapeutic agent.

52. The method of Claim 39, wherein said cell is selected from the group consisting of an Ulcerative colitis cell and a Crohn's disease cell.

53. The method of Claim 39, wherein said cell overexpresses said polypeptide as compared to a normal cell of the same tissue origin.

54. A method of therapeutically treating a mammal having an IBD comprising cells that express a polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure

22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162); or

(b) an amino acid sequence encoded by a nucleotide sequence comprising the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ

ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

5 said method comprising administering to said mammal a therapeutically effective amount of an antibody that binds to said polypeptide, thereby effectively treating said mammal.

55. The method of Claim 54, wherein said antibody is a monoclonal antibody.

10 56. The method of Claim 54, wherein said antibody is an antibody fragment.

57. The method of Claim 54, wherein said antibody is a chimeric or a humanized antibody.

15 58. The method of Claim 54, wherein said antibody is conjugated to a growth inhibitory agent.

59. The method of Claim 54, wherein said antibody is conjugated to a cytotoxic agent.

20 60. The method of Claim 59, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

61. The method of Claim 59, wherein the cytotoxic agent is a toxin.

25 62. The method of Claim 61, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

63. The method of Claim 61, wherein the toxin is a maytansinoid.

64. The method of Claim 54, wherein said antibody is produced in bacteria.

30 65. The method of Claim 54, wherein said antibody is produced in CHO cells.

66. The method of Claim 54, wherein said IBD is further exposed to radiation treatment or a chemotherapeutic agent.

35 67. The method of Claim 54, wherein said IBD is selected from the group consisting of Ulcerative colitis and Crohn's disease.

68. A method of determining the presence of a polypeptide in a sample suspected of containing said polypeptide, wherein said polypeptide has at least 80% amino acid sequence identity to:

(a) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162); or

(b) an amino acid sequence encoded by a nucleotide sequence comprising the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ

ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

said method comprising exposing said sample to an antibody that binds to said polypeptide and determining binding of said antibody to said polypeptide in said sample.

69. The method of Claim 68, wherein said sample comprises a cell suspected of expressing said polypeptide.

70. The method of Claim 69, wherein said cell is an IBD cell.

71. The method of Claim 68, wherein said antibody is detectably labeled.

72. A method of diagnosing the presence of an IBD in a mammal, said method comprising detecting the level of expression of a gene encoding a polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure

112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160) or Figure 162 (SEQ ID NO:162); or

(b) an amino acid sequence encoded by a nucleotide sequence comprising the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

in a test sample of tissue cells obtained from said mammal and in a control sample of known normal cells of the same tissue origin, wherein a higher or lower level of expression of said polypeptide in the test sample, as compared to the control sample, is indicative of the presence of an IBD in the mammal from which the test sample was obtained.

73. The method of Claim 72, wherein the step detecting the level of expression of a gene encoding said polypeptide comprises employing an oligonucleotide in an *in situ* hybridization or RT-PCR analysis.

75. A method of diagnosing the presence of an IBD in a mammal, said method comprising contacting a test sample of tissue cells obtained from said mammal with an antibody that binds to a polypeptide having at least 80% amino acid sequence identity to:

(b) an amino acid sequence encoded by a nucleotide sequence comprising the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ

ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), or Figure 105 (SEQ ID NO:105) Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161);

and detecting the formation of a complex between said antibody and said polypeptide in the test sample, wherein the formation of a complex is indicative of the presence of an IBD in said mammal.

76. The method of Claim 75, wherein said antibody is detectably labeled.

77. The method of Claim 75, wherein said test sample of tissue cells is obtained from an individual suspected of having an IBD.

78. A method of therapeutically treating a mammal having an IBD comprising administering to said mammal a therapeutically effective amount of a polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence shown in Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), or Figure 106 (SEQ ID NO:106); or

(b) an amino acid sequence encoded by a nucleotide sequence comprising the nucleotide sequence shown in Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), or Figure 105 (SEQ ID NO:105), thereby effectively treating said mammal.

79. The method of Claim 78, wherein said IBD is Crohn's disease.

80. A method of diagnosing the presence of an IBD in a mammal, said method comprising detecting the level of expression of a gene encoding a polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence shown in Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), or Figure 106 (SEQ ID NO:106); or

(b) an amino acid sequence encoded by a nucleotide sequence comprising the nucleotide sequence shown in Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), or Figure 105 (SEQ ID NO:105),

in a test sample of tissue cells obtained from said mammal and in a control sample of known normal cells of the same tissue origin, wherein a lower level of expression of said polypeptide in the test sample, as compared to the control sample, is indicative of the presence of an IBD in the mammal from which the test sample was obtained.

81. The method of Claim 80, wherein the step detecting the level of expression of a gene encoding said polypeptide comprises employing an oligonucleotide in an *in situ* hybridization or RT-PCR analysis.

82. The method of Claim 80, wherein the step detecting the level of expression of a gene encoding said polypeptide comprises employing an antibody in an immunohistochemistry analysis.

83. The method of Claim 80, wherein the IBD is Crohn's disease.

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Figure 1

CTCGCAGCCGAGCGCGGCCGGGGAAGGGCTCTCCTTCCAGCGCCGAGCACTGGGCCCCTGG
CAGACGCCCCAAGATTGTTGTGAGGAGTCTAGCCAGTTGGTGAGCGCTGTAATCTGAACC
AGCTGTGTCCAGACTGAGGCCCATTTGCATTGTTTAACTACTTAGAAAATGAAGTGTT
CATTTTTAACATTCTCTCTCCAATTGGTTTAAATGCTGAATTACTGAAGAGGGCTAAGCAA
AACCAGGTGCTTGCGCTGAGGGCTCTGCAGTGGCTGGGAGGACCCCGCGCTCTCCCCGT
GTCCTCTCCACGACTCGCTCGGCCCTCTGGAATAAAACACCCGCGAGCCCCGAGGGCCC
AGAGGAGGCCGACGTGCCCCGAGCTCCTCCGGGGGTCCCGCCCGCGAGCTTTCTTCTCGCC
TTCGCATCTCCTCCTCGCGCTCTTGGACATGCCAGGAATAAAAAGGATACTCACTGTTA
CCATTCTGGCTCTCTGTCTTCCAAGCCCTGGGAATGCACAGGCACAGTGCACGAATGGCT
TTGACCTGGATCGCCAGTCAGGACAGTGTTTAGATATTGATGAATGCCGAACCATCCCCG
AGGCCTGCCGAGGAGACATGATGTGTGTTAACCAAAATGGCGGGTATTTATGCATTCCCC
GGACAAACCTGTGTATCGAGGGCCCTACTCGAACCCCTACTCGACCCCTACTCAGGTC
CGTACCCAGCAGCTGCCCCACCACTCTCAGCTCCAACTATCCACGATCTCCAGGCCTC
TTATATGCCGCTTTGGATACCAGATGGATGAAAGCAACCAATGTGTGGATGTGGACGAGT
GTGCAACAGATTCCACACAGTGCAACCCACCCAGATCTGCATCAATACTGAAGGCGGGT
ACACCTGCTCCTGCACCGACGGATATTGGCTTCTGGAAGGCCAGTGCTTAGACATTGATG
AATGTCGCTATGGTTACTGCCAGCAGCTCTGTGCGAATGTTCTGGATCCTATTCTTGTA
CATGCAACCTGGTTTTACCCTCAATGAGGATGGAAGGTCTTGCCAAGATGTGAACGAGT
GTGCCACCGAGAACCCCTGCGTGCAACCTGCGTCAACACCTACGGCTCTCTCATCTGCC
GCTGTGACCCAGGATATGAACTTGAGGAAGATGGCGTTCATTGCAGTGATATGGACGAGT
GCAGCTTCTCTGAGTTCTCTGCCAACATGAGTGTGTGAACCAGCCCGGCACATACTTCT
GCTCCTGCCCTCCAGGCTACATCCTGCTGGATGACAACCGAAGCTGCCAAGACATCAACG
AATGTGAGCACAGGAACCACACGTGCAACCTGCAGCAGACGTGCTACAATTTACAAGGGG
GCTTCAAATGCATCGACCCCATCCGCTGTGAGGAGCCTTATCTGAGGATCAGTGATAACC
GCTGTATGTGTCCTGCTGAGAACCCTGGCTGCAGAGACCAGCCCTTTACCATCTTGTACC
GGGACATGGACGTGGTGTGAGGACGCTCCGTTCCCGCTGACATCTTCCAAATGCAAGCCA
CGACCCGCTACCCTGGGGCCTATTACATTTTCCAGATCAAATCTGGGAATGAGGGCAGAG
AATTTTACATGCGGCAAACGGGCCCCATCAGTGCCACCCCTGGTGATGACACGCCCCATCA
AAGGGCCCCGGGAAATCCAGCTGGACTTGGAATGATCACTGTCAACACTGTCATCAACT
TCAGAGGCAGCTCCGTGATCCGACTGCGGATATATGTGTGCGAGTACCCATTCTGAGCCT
CGGGCTGGAGCCTCCGACGCTGCCTCTCATTGGCACCAAGGGACAGGAGAAGAGAGGAAA
TAACAGAGAGAAATGAGAGCGACACAGACGTTAGGCATTTCTGCTGAACGTTTCCCGAA
GAGTCAGCCCCGACTTCCTGACTCTCACCTGTACTATTGCAGACCTGTCACCCTGCAGGA
CTTGCCACCCCCAGTTCTTATGACACAGTTATCAAAAAGTATTATCATTGCTCCCCTGAT
AGAAGATTGTTGGTGAATTTTCAAGGCCTTCAGTTTATTTCCACTATTTTCAAAGAAAAT
AGATTAGGTTTGCGGGGGTCTGAGTCTATGTTCAAAGACTGTGAACAGCTTGCTGTCACT
TCTTCACCTCTTCCACTCCTTCTCTCACTGTGTTACTGCTTTGCAAAGACCCGGGAGCTG
GCGGGGAACCCCTGGGAGTAGCTAGTTTGGTTTTTGGGTACACAGAGAAGGCTATGTAAAC
AAACCACAGCAGGATCGAAGGGTTTTTAGAGAAATGTGTTTCAAACCATGCCTGGTATTT
TCAACCATAAAAGAAGTTTCAGTTGTCTTAAATTTGTATAACGGTTTAAATTCTGTCTTG
TTCATTTTGAGTATTTTAAAAAATATGTCGTAGAATTCCTTCGAAAGGCCTTCAGACAC
ATGCTATGTTCTGTCTTCCCAAACCCAGTCTCCTCTCCATTTTAGCCCAGTGTTTTCTTT
GAGGACCCCTTAATCTTGCTTTCTTTAGAATTTTACCCAATTGGATTGGAATGCAGAGG
TCTCCAAACTGATTAAATATTTGAAGAGA

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Figure 2

MPGIKRILTVTILALCLPSPGNAQAQCTNGFDLDRQSGQCLDIDECRTIPEACRGDMMCV
NQNGGYLCIPRTNPVYRGPYSNPYSTPYSGPYPAAPPLSAPNYPTISRPLICRFGYQMD
ESNQCVDVDECATDSHQCNPTQICINTEGGYTCSCTDGYWLLEGQCLDIDECRYGYCQQL
CANVPGSYSCTCNPGFLLNEDGRSCQDVNECATENPCVQTCVNTYGSLICRCDPGYELEE
DGVHCSDMDECSFSEFLCQHECVNQPGTYFCSCPPGYILLDDNRSCQDINECEHRNHTCN
LQOTCYNLQGGFKCIDPIRCEEPLYLRISDNRCMCPAENPGCRDQPFITILYRDMDVVSGRS
VPADIFQMQAATTRYPGAYYIFQIKSGNEGREFYMRQTGPISATLVMTRPIKGPREIQLDL
EMITVNTVINFRGSSVIRLRIYVSQYPF

Signal sequence.

1-25

Transmembrane domain.

none

N-glycosylation site.

283-286

296-299

N-myristoylation site.

21-26

64-69

149-154

186-191

226-231

242-247

267-272

310-315

Aspartic acid and asparagine hydroxylation site.

144-155

181-192

262-273

Cell attachment sequence.

54-57

EGF-like domain.

131-166

172-205

211-245

251-286

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Figure 3

GCTGTGGGAACCTCTCCACGCGCACGAACTCAGCCAACGATTTCTGATAGATTTTTTGGGA
GTTTGACCAGAGATGCAAGGGGTGAAGGAGCGCTTCCTACCGTTAGGGAACTCTGGGGAC
AGAGCGCCCCGGCCGCTGATGGCCGAGGCAGGGTGCAGACCCAGGACCCAGGACGGCGTC
GGGAACCATACCATGGCCCGGATCCCCAAGACCCTAAAGTTCGTCGTCGTCATCGTCGCG
GTCCTGCTGCCAGTCTTAGCTTACTCTGCCACCACTGCCCCGGCAGGAGGAAGTTCCTCCAG
CAGACAGTGGCCCCACAGCAACAGAGGCACAGCTTCAAGGGGGAGGAGTGTCCAGCAGGA
TCTCATAGATCAGAACATACTGGAGCCTGTAACCCGTCACAGAGGGTGTGGATTACACC
AACGCTTCCAACAATGAACCTTCTTGCTTCCCATGTACAGTTTGTAAATCAGATCAAAAA
CATAAAAGTTCCTGCACCATGACCAGAGACACAGTGTGTGTCAGTGTAAAGAAGGCACCTTC
CGGAATGAAAACCTCCCCAGAGATGTGCCGGAAGTGTAGCAGGTGCCCTAGTGGGGAAGTC
CAAGTCAGTAATTGTACGTCCTGGGATGATATCCAGTGTGTTGAAGAATTTGGTGCCAAT
GCCACTGTGGAAACCCAGCTGCTGAAGAGACAATGAACACCAGCCCCGGGGACTCCTGCC
CCAGCTGCTGAAGAGACAATGAACACCAGCCCAGGGACTCCTGCCCCAGCTGCTGAAGAG
ACAATGACCACCAGCCCCGGGGACTCCTGCCCCAGCTGCTGAAGAGACAATGACCACCAGC
CCGGGGACTCCTGCCCCAGCTGCTGAAGAGACAATGACCACCAGCCCCGGGGACTCCTGCC
TCTTCTCATTACCTCTCATGCACCATCGTAGGGATCATAGTTCTAATTGTGCTTCTGATT
GTGTTTGTGTTGAAAGACTTCAGTGTGGAAGAAATTCCTTCCTTACCTGAAAGGTTTCAGGT
AGGCGCTGGCTGAGGGCGGGGGCGCTGGACACTCTCTGCCCTGCCTCCCTCTGCTGTGT
TCCCACAGACAGAAACGCCTGC

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Figure 4

MQGVKERFLPLGNSGDRAPRPPDGRGRVRPRTQDGVGNHTMARIPKTLKFVVVIVAVLLP
VLAYSATTARQEEVPQQTVAPOQQQRHSFKGEECPAGSHRSEHTGACNPCTEGVDYTNASN
NEPSCFPCTVCKSDQKHKSCTMTRDTVCQCKEGTFRNENSPEMCRKCSRCPSGEVQVSN
CTSWDDIQCVEEFGANATVETPAAEETMNTSPGTPAPAAEETMNTSPGTPAPAAEETMTT
SPGTPAPAAEETMTTSPGTPAPAAEETMTTSPGTPASSHYLSCTIVGIIVLIVLLIVFV

Signal sequence.
none

Transmembrane domain.
none

N-glycosylation site.
38-41
117-120
180-183
196-199

cAMP- and cGMP-dependent protein kinase phosphorylation site.
166-169

N-myristoylation site.
96-101
112-117
154-159
194-199
273-278

TNFR/NGFR cysteine-rich region
109-149
151-189

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Figure 5

CGGACGCGTGGGCCCCCTGGTGGGCCCAGCAAGATGGATCTACTGTGGATCCTGCCCTCCC
TGTGGCTTCTCCTGCTTGGGGGGCCTGCCTGCCTGAAGACCCAGGAACACCCCAGCTGCC
CAGGACCCAGGGAAGTGAAGCCAGCAAAGTTGTCCTCCTGCCAGTTGTCCCGGAGCTC
CAGGAAGTCCTGGGGAGAAGGGAGCCCCAGGTCCTCAAGGGCCACCTGGACCACCAGGCA
AGATGGGCCCCAAGGGTGAGCCAGGCCCCAGAACTGCCGGGAGCTGTTGAGCCAGGGCG
CCACCTTGAGCGGCTGGTACCATCTGTGCCTACCTGAGGGCAGGGCCCTCCCAGTCTTTT
GTGACATGGACACCGAGGGGGGGCGGCTGGCTGGTGTTCAGAGGCGCCAGGATGGTTCTG
TGGATTTCTTCCGCTCTTGGTCCTCCTACAGAGCAGGTTTTTGGGAACCAAGAGTCTGAAT
TCTGGCTGGGAAATGAGAATTTGCACCAGCTTACTCTCCAGGGTAACGGGGAGCTGCGGG
TAGAGCTGGAAGACTTTAATGGTAACCGTACTTTGCCCCACTATGCGACCTTCCGCCTCC
TCGGTGAGGTAGACCACTACCAGCTGGCACTGGGCAAGTTCTCAGAGGGCACTGCAGGGG
ATTCCCTGAGCCTCCACAGTGGGAGGCCCTTTACCACCTATGACGCTGACCACGATTCAA
GCAACAGCAACTGTGCAGTGATTGTCCACGGTGCCTGGTGGTATGCATCCTGTTACCGAT
CAAATCTCAATGGTCGCTATGCAGTGTCTGAGGCTGCCGCCACAAATATGGCATTGACT
GGGCCTCAGGCCGTGGTGTGGGCCACCCCTACCGCAGGGTTCGGATGATGCTTCGATAGG
GCACTCTGGCAGCCAGTGCCCTTATCTCTCCTGTACAGCTTCCGGATCGTCAGCCACCTT
GCCTTTGCCAACCACCTCTGCTTGCTGTCCACATTTAAAAATAAAATCATTTTAGCCCT
TTCA

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Figure 6

MDLLWILPSLWLLLLGGPACLKTQEHPSCPGPRELEASKVVLLPSCPGAPGSPGEKGAPG
PQGPPGPPGKMGPKEGPGPRNCRELLSQGATLSGWYHLCLPEGRALPVFCMDTEGGGWL
VFQRRQDGSVDFFRSWSSYRAGFGNQESEFWLGNENLHQLTLQGNWELRVELEDFNGNRT
FAHYATFRLLGEVDHYQLALGKFSEGTAGDSLHSGRPFTTYDADHDSSNSNCAVIVHG
AWWYASCYRSNLNGRYAVSEAAAHKYGIDWASGRGVGHPYRRVRMMLR

Signal sequence.

1-16

Transmembrane domain.

none

N-glycosylation site.

178-181

Glycosaminoglycan attachment site.

272-275

Tyrosine kinase phosphorylation site.

188-196

N-myristoylation site.

16-21

89-94

144-149

267-272

Fibrinogen beta and gamma chains C-terminal domain signature.

242-254

Fibrinogen beta and gamma chains, C-term

78-256

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Figure 7

TGAGACCCTCCTGCAGCCTTCTCAAGGGACAGCCCCACTCTGCCTCTTGCTCCTCCAGGG
CAGCACCATGCAGCCCCTGTGGCTCTGCTGGGCACTCTGGGTGTTGCCCCCTGGCCAGCCC
CGGGGCCGCCCTGACCGGGGAGCAGCTCCTGGGCAGCCTGCTGCGGCAGCTGCAGCTCAA
AGAGGTGCCCACCCTGGACAGGGCCGACATGGAGGAGCTGGTCATCCCCACCCACGTGAG
GGCCCAGTACGTGGCCCTGCTGCAGCGCAGCCACGGGGACCGCTCCCGCGGAAAGAGGTT
CAGCCAGAGCTTCCGAGAGGTGGCCGGCAGGTTCCCTGGCGTTGGAGGCCAGCACACACCT
GCTGGTGTTTCGGCATGGAGCAGCGGCTGCCGCCAACAGCGAGCTGGTGCAGGCCGTGCT
GCGGCTCTTCCAGGAGCCGGTCCCCAAGGCCGCGCTGCACAGGCACGGGCGGCTGTCCCC
GCGCAGCGCCCCGGGCCCGGGTGACCGTCGAGTGGCTGCGCGTCCGCGACGACGGCTCCAA
CCGCACCTCCCTCATCGACTCCAGGCTGGTGTCCGTCCACGAGAGCGGCTGGAAGGCCTT
CGACGTGACCGAGGCCGTGAACCTTCTGGCAGCAGCTGAGCCGGCCCCGGCAGCCGCTGCT
GCTACAGGTGTTCGGTGCAGAGGGAGCATCTGGGCCCCGCTGGCGTCCGGCGCCCACAAGCT
GGTCCGCTTTGCCTCGCAGGGGGCGCCAGCCGGGCTTGGGGAGCCCCAGCTGGAGCTGCA
CACCTGGACCTTGGGGACTATGGAGCTCAGGGCGACTGTGACCCTGAAGCACCAATGAC
CGAGGGCACC CGCTGCTGCCGCCAGGAGATGTACATTGACCTGCAGGGGATGAAGTGGGC
CGAGAACTGGGTGCTGGAGCCCCCGGGCTTCCTGGCTTATGAGTGTGTGGGCACCTGCCG
GCAGCCCCCGGAGGCCCTGGCCTTCAAGTGGCCGTTTCTGGGGCCTCGACAGTGCATCGC
CTCGGAGACTGACTCGCTGCCCATGATCGTCAGCATCAAGGAGGGAGGCAGGACCAGGCC
CCAGGTGGTCAGCCTGCCCAACATGAGGGTGCAGAAGTGCAGCTGTGCCTCGGATGGTGC
GCTCGTGCCAAGGAGGCTCCAGCCATAGGCGCCTAGTGTAGCCATCGAGGGACTTGACTT
GTGTGTGTTTCTGAAGTGTTTCGAGGGTACCAGGAGAGCTGGCGATGACTGAACTGCTGAT
GGACAAATGCTCTGTGCTCTCTAGTGAGCCCTGAATTTGCTTCCTCTGACAAGTTACCTC
ACCTAATTTTTTGCTTCTCAGGAATGAGAATCTTTGGCCACTGGAGAGCCCTTGCTCAGTT
TTCTCTATTCTTATTATTCACTGCACTATATTCTAAGCACTTACATGTGGAGATACTGTA
ACCTGAGGGCAGAAAGCCANTGTGTCAATTGTTTACTTGTCTGTCACTGGATCTGGGCT
AAAGTCCTCCACCACCACTCTGGACCTAAGACCTGGGGTTAAGTGTGGGTGTGCATCCC
CAATCCAGATAATAAAGACTTTGTAAAACATGAATAAAACACATTTTATTCTAAAA

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Figure 8

MQPLWLCWALWVLPLASPGAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQ
YVALLQRSHGDRSRGKRFSQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRL
FQEPVPKAALHRHGRLSPRSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDV
TEAVNFWQQLSRPRQPPLLLQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTL
DLGDYGAQGDCDPEAPMTEGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQP
PEALAFKWPFLGPRQCIASETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKSCASDGALV
PRRLQP

Signal sequence.

1-18

Transmembrane domain.

none

N-glycosylation site.

158-161

cAMP- and cGMP-dependent protein kinase phosphorylation site.

76-79

N-myristoylation site.

19-24

156-161

225-230

260-265

274-279

Amidation site.

74-77

TGF-beta family signature.

282-297

TGF-beta propeptide.

10-233

Transforming growth factor beta like.

260-354

Figure 9

[illegible]

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Figure 10

MMGLSLASAVLLASLLSLHLGTATRGSDISKTCCEFQYSHKPLPWTWVRSYEFTSNSCSQR
AVIFTTKRGKKVCTHPRKKWVQKYISLLKTPKQL

Signal sequence.
1-23

Transmembrane domain.
none

N-myristoylation site.
3-8
26-31

Amidation site.
68-71

Small cytokines (intecrine/chemokine).
23-88

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Figure 11

GGCACAAACTCATCCATCCCCAGTTGATTGGAAGAAACAACGATGACTCCTGGGAAGACC
TCATTGGTGTCACTGCTACTGCTGCTGAGCCTGGAGGCCATAGTGAAGGCAGGAATCACA
ATCCCACGAAATCCAGGATGCCCAAATTCTGAGGACAAGAAGTTCCCCCGGACTGTGATG
GTCAACCTGAACATCCATAACCGGAATACCAATACCAATCCCAAAGGTCCTCAGATTAC
TACAACCGATCCACCTCACCTTGGAATCTCCACCGCAATGAGGACCCTGAGAGATATCCC
TCTGTGATCTGGGAGGCAAAGTGCCGCCACTTGGGCTGCATCAACGCTGATGGGAACGTG
GACTACCACATGAACTCTGTCCCCATCCAGCAAGAGATCCTGGTCCTGCGCAGGGAGCCT
CCACACTGCCCCAACTCCTTCCGGCTGGAGAAGATACTGGTGTCCGTGGGCTGCACCTGT
GTCACCCCGATTGTCCACCATGTGGCCTAAACACTCCCCAAAGCAGTTAGACTATGGAGA
GCCGACCCAGCCCCCTCAGGAACCCTCATCCTTCAAAGACAGCCTCATTTTCGGACTAACT
CATTAGAGTTCTTAAGGCAGTTTGTCCAATTAAAGCTTCAGAGGTAACACTTGGCCAAGA
TATGAGATCTGAATTACCTTTCCTCTTTCCAAGAAGGAAGGTTTGACTGAGTACCAATT
TGCTTCTTGTTTACTTTTTTAAGGGCTTTAAGTTATTTATGTATTTAATATGCCCTGAGA
TAACTTTGGGGTATAAGATTCCATTTTAATGAATTACCTACTTTATTTTGTGTTGCTTTT
TAAAGAAGATAAGATTCTGGGCTTGGGAATTTTATTATTTAAAAGGTAAAACCTGTATTT
ATTTGAGCTATTTAAGGATCTATTTATGTTTAAAGTATTTAGAAAAAGGTGAAAAAGCACT
ATTATCAGTTCTGCCTAGGTAAATGTAAGATAGAATTAAATGGCAGTGCAAAATTTCTGA
GTCTTTACAACATACGGATATAGTATTTCTCCTCTTTGTTTTTAAAAGTTATAACATGG
CTGAAAAGAAAGATTAAACCTACTTTCATAGTATTAATTTAAATTTTGCAATTTGTTGAG
GTTTTACAAGAGATACAGCAAGTCTAACTCTCGGTTCCATTAAACCCTAATAATAAAATC
CTTCTGTAATAAA

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Figure 12

MTPGKTSLVSLLLLLLSLEAIVKAGITIPRNP GCPNSEDKNFPRTVMVNLNIHNRNTNTNP
KRSSDYYNRSTSPWNLHRNEDPERYP SVIWEAKCRHLGCINADGNVDYHMNSVPIQQEIL
VLRREPPHCPNSFRLEKILVSVGCTCVTPIVHHVA

Signal sequence.

1-19

Transmembrane domain.

none

N-glycosylation site.

68-71

cAMP- and cGMP-dependent protein kinase phosphorylation site.

61-64

Tyrosine kinase phosphorylation site.

78-85

N-myristoylation site.

32-37

98-103

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Figure 13

CACAAAACCAGTGAGGATGATGCCAGAATGATGTCTGCCTCGCGCCTGGCTGGGACTCTG
ATCCCAGCCATGGCCTTCCTCTCCTGCGTGAGACCAGAAAGCTGGGAGCCCTGCGTGGAG
GTGGTTCCTAATATTACTTATCAATGCATGGAGCTGAATTTCTACAAAATCCCCGACAAC
CTCCCCCTTCTCAACCAAGAACCTGGACCTGAGCTTTAATCCCCTGAGGCATTTAGGCAGC
TATAGCTTCTTCAGTTTCCCAGAACTGCAGGTGCTGGATTTATCCAGGTGTGAAATCCAG
ACAATTGAAGATGGGGCATATCAGAGCCTAAGCCACCTCTCTACCTTAATATTGACAGGA
AACCCCATCCAGAGTTTAGCCCTGGGAGCCTTTTCTGGACTATCAAGTTTACAGAAGCTG
GTGGCTGTGGAGACAAATCTAGCATCTCTAGAGAACTTCCCCATTGGACATCTCAAACT
TTGAAAGAACTTAATGTGGCTCACAATCTTATCCAATCTTTCAAATTACCTGAGTATTTT
TCTAATCTGACCAATCTAGAGCACTTGGACCTTTCCAGCAACAAGATTCAAAGTATTTAT
TGCACAGACTTGCGGGTTCTACATCAAATGCCCTACTCAATCTCTCTTTAGACCTGTCC
CTGAACCTTATGAACTTTATCCAACCAGGTGCATTTAAAGAAATTAGGCTTCATAAGCTG
ACTTTAAGAAATAATTTTGATAGTTTAAATGTAATGAAAACCTTGATTTCAAGGTCTGGCT
GGTTTAGAAGTCCATCGTTTGGTTCTGGGAGAATTTAGAAATGAAGGAACTTGGAAGAG
TTTGACAAATCTGCTCTAGAGGGCCTGTGCAATTTGACCATTTGAAGAATTCCGATTAGCA
TACTTAGACTACTACCTCGATGATATTATTGACTTATTTAATTGTTTGACAAATGTTTCT
TCATTTTCCCTGGTGAGTGTGACTATTGAAAGGGTAAAAGACTTTTCTTATAATTTTCGGA
TGGCAACATTTAGAATTAGTTAACTGTAAATTTGGACAGTTTCCCACATTGAAACTCAAA
TCTCTCAAAAGGCTTACTTTCACTTCCAACAAAGGTGGGAATGCTTTTTTCAGAAGTTGAT
CTACCAAGCCTTGAGTTTCTAGATCTCAGTAGAAATGGCTTGAGTTTCAAAGGTTGCTGT
TCTCAAAGTGATTTTGGGACAACCAGCCTAAAGTATTTAGATCTGAGCTTCAATGGTGTT
ATTACCATGAGTTCAAACCTTCTTGGGCTTAGAACAACCTAGAACATCTGGATTTCCAGCAT
TCCAATTTGAAACAAATGAGTGAGTTTTCAGTATTCCTATCACTCAGAAACCTCATTTAC
CTTGACATTTCTCATACTCACACCAGAGTTGCTTTCAATGGCATCTTCAATGGCTTGTCC
AGTCTCGAAGTCTTGAAAATGGCTGGCAATTCCTTCCAGGAAAACCTTCCTTCCAGATATC
TTCACAGAGCTGAGAAAACCTTGACCTTCTGGACCTCTCTCAGTGTCAACTGGAGCAGTTG
TCTCCAACAGCATTTAACTCACTCTCCAGTCTTCAGGTACTAAATATGAGCCACAACAAC
TTCTTTTTCATTGGATACGTTTCTTATAAGTGCTGAACTCCCTCCAGGTTCTTGATTAC
AGTCTCAATCACATAATGACTTCCAAAAAACAGGAACCTACAGCATTTTCCAAGTAGTCTA
GCTTTCTTAAATCTTACTCAGAATGACTTTGCTTGTAATTGTGAACACCAGAGTTTCCTG
CAATGGATCAAGGACCAGAGGCAGCTCTTGGTGGAAGTTGAACGAATGGAATGTGCAACA
CCTTCAGATAAGCAGGGCATGCCTGTGCTGAGTTTGAATATCACCTGTCAGATGAATAAG
ACCATCATTTGGTGTGTCGGTCCCTCAGTGTGCTTGTAGTATCTGTTGTAGCAGTTCTGGTC
TATAAGTTCTATTTTACCTGATGCTTCTTGCTGGCTGCATAAAGTATGGTAGAGGTGAA
AACATCTATGATGCCTTTGTTATCTACTCAAGCCAGGATGAGGACTGGGTAAGGAATGAG
CTAGTAAAGAATTTAGAAGAAGGGGTGCCTCCATTTAGCTCTGCCTTCACTACAGAGAC
TTTATTCCCGGTGTGGCCATTGCTGCCAACATCATCCATGAAGGTTTCCATAAAAGCCGA
AAGGTGATTGTTGTGGTGTCCCAGCACTTCATCCAGAGCCGCTGGTGTATCTTTGAATAT
GAGATTGCTCAGACCTGGCAGTTTCTGAGCAGTCGTGCTGGTATCATCTTCATTGTCCTG
CAGAAGGTGGAGAAGACCCTGCTCAGGCAGCAGGTGGAGCTGTACCGCCTTCTCAGCAGG
AACACTTACCTGGAGTGGGAGGACAGTGTCTGGGGCGGCACATCTTCTGGAGACGACTC
AGAAAAGCCCTGCTGGATGGTAAATCATGGAATCCAGAAGGAACAGTGGGTACAGGATGC
AATTGGCAGGAAGCAACATCTATCTGAAGAGGAAAAATAAAAACCTCCTGAGGCATTTCT
TGCCCAGCTGGGTCCAACAC

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Figure 14A

MMSASRLAGTLIPAMAFSLCVRPESWEPCVEVVPNITYQCMELNFYKIPDNLPFSTKNLD
LSFNPLRHLGSYSFFSFPELQVLDLSRCEIQTIEDGAYQSLSHLSTLILTGNPIQSLALG
AFSGLSSLQKLVAVETNLASLENFPIGHLKTLEKELNVAHNLIQSFKLPEYFSNLTNLEHL
DLSSNKIQSIYCTDLRVLHQMPLLNLSLDLSLNPMNFIQPGAFKEIRLHKLTLRNNFDSL
NVMKTCIQGLAGLEVHRLVLGEFRNEGNLEKFDKSALEGLCNLTIEEFRLAYLDYYLDDI
IDLFNCLTNVSSFSLSVSVTIERVKDFSYNFGWQHLELVNCKFGQFPTLKLKSLKRLTFTS
NKGGNAFSEVDLPSEFLDLSRNGLSFKGCCSQSDFGTTSLKYLDLSFNGVITMSSNFLG
LEQLEHLDFQHSNLKQMSEFSVFLSLRNLIYLDISHTHTRVAFNGIFNGLSSLEVLMAG
NSFQENFLPDIFTTELRLNLTFLDLSQCQLEQLSPTAFNSLSSLQVLNMSHNNFFSLDTFPY
KCLNSLQVLDYSLNHIMTSKKQELQHFPSLAFLNLTQNDFACTCEHQSFLOWIKDQRQL
LVEVERMECATPSDKQGMPVLSLNITCQMNKTIIGVSVLSVLVSVVAVLVYKFYFHLML
LAGCIKYGRGENIYDAFVIYSSQDEDWVRNELVKNLEEGVPPFQLCLHYRDFIPGVAIAA
NIIHEGFHKSRKVIIVVSQHFIQSRWCIFEYEIAQTWQFLSSRAGIIFIVLQKVEKTLRLR
QQVELYRLLSRNTYLEWEDSVLGRHIFWRRLRKALLDGKSWNPEGTVGTGCNWQEATSI

Signal sequence.

1-23

Transmembrane domain.

634-654

N-glycosylation site.

35-38

173-176

205-208

282-285

309-312

497-500

526-529

575-578

624-627

630-633

cAMP- and cGMP-dependent protein kinase phosphorylation site.

354-357

Tyrosine kinase phosphorylation site.

322-328

N-myristoylation site.

96-101

120-125

343-348

364-369

465-470

715-720

825-830

828-833

TIR domain.

676-814

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Figure 14B

Leucine Rich Repeat.

55-78

79-102

103-126

151-175

176-199

374-399

400-422

423-444

472-496

497-520

521-547

Leucine rich repeat C-terminal domain.

579-628

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Figure 15

ATGCATTGGGGAACCTGTGCGGATTCTTGTGGCTTTGGCCCTATCTTTTCTATGTCCAA
GCTGTGCCCATCCAAAAAGTCCAAGATGACACCAAAACCTCATCAAGACAATTGTCACC
AGGATCAATGACATTTACACACGCAGTCAGTCTCCTCCAAACAGAAAGTCACCGGTTTG
GACTTCATTCTGGGCTCCACCCCATCCTGACCTTATCCAAGATGGACCAGACACTGGCA
GTCTACCAACAGATCCTCACCAGTATGCCTTCCAGAAACGTGATCCAAATATCCAACGAC
CTGGAGAACCTCCGGGATCTTCTTCACGTGCTGGCCTTCTCTAAGAGCTGCCACTTGCCC
TGGGCCAGTGGCCTGGAGACCTTGGACAGCCTGGGGGGTGTCTTGAAGCTTCAGGCTAC
TCCACAGAGGTGGTGGCCCTGAGCAGGCTGCAGGGGTCTCTGCAGGACATGCTGTGGCAG
CTGGACCTCAGCCCTGGGTGCGGGGTACCGACAAAACCTCACACATGCCACCGTGCCCA
GCACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCCCTAAACCAAGGACACC
CTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGAC
CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC
CAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCC
CCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACC
CTGCCCCCATCCCGGAAGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAA
GGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC
TACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTC
ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAG
GCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

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Figure 16

MHWGTLGFLWLWPYLFYVQAVPIQKVQDDTKTLIKTIVTRINDISHTQSVSSKQKVTGL
DFIPGLHPILTLKMDQTLAVYQQILTSMPSRNVIQISNDLENLRDLLHVLAFSKKSCHLP
WASGLETLDSLGGVLEASGYSTEVALSRLQGSLLQDMLWQLDLSPGCGVTDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYF
LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSVMSVHEALHNHYTQKSLSLSPGK

Signal sequence.

1-21

Transmembrane domain.

none

N-glycosylation site.

247-250

Tyrosine kinase phosphorylation site.

240-246

N-myristoylation site.

4-9

133-138

166-171

335-340

370-375

Immunoglobulins and major histocompatibility complex proteins signature.

373-379

Leptin.

22-167

Immunoglobulin domain.

204-273

310-377

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Figure 17

GTCGTTCCCTTTGCTCTCTCGCGCCCAGTCCTCCTCCCTGGTTCTCCTCAGCCGCTGTCCG
AGGAGAGCACCCGGAGACGCGGGCTGCAGTCGCGGGCGGCTTCTCCCCGCTGGGCGGCCT
CGCCGCTGGGCAGGTGCTGAGCGCCCCCTAGAGCCTCCCTTGCCGCTCCCTCCTCTGCC
GGCCGAGCAGTGCACATGGGGTGTGGAGGTAGATGGGCTCCCGGCCCGGGAGGCGGCG
GTGGATGCGGCGCTGGGCAGAAGCAGCCGCGGATTCCAGCTGCCCCGCGCGCCCCGGGCG
CCCCTGCGAGTCCCCGGTTCAGCCATGGGGACCTCTCCGAGCAGCAGCACCGCCCTCGCC
TCCTGCAGCCGCATCGCCCGCCGAGCCACAGCCACGATGATCGCGGGCTCCCTTCTCCTG
CTTGATTCTTAGCACCACCACAGCTCAGCCAGAACAGAAGGCCTCGAATCTCATTGGC
ACATACCGCCATGTTGACCGTGCCACCGGCCAGGTGCTAACCTGTGACAAGTGTCCAGCA
GGAACCTATGTCTCTGAGCATTGTACCAACACAAGCCTGCGCGTCTGCAGCAGTTGCCCT
GTGGGGACCTTTACCAGGCATGAGAATGGCATAGAGAAATGCCATGACTGTAGTCAGCCA
TGCCCATGGCCAATGATTGAGAAATTACCTTGTGCTGCCTTGACTGACCGAGAATGCACT
TGCCACCTGGCATGTTCCAGTCTAACGCTACCTGTGCCCCCATAACGGTGTGTCTGTG
GGTTGGGGTGTGCGGAAGAAAGGGACAGAGACTGAGGATGTGCGGTGTAAGCAGTGTGCT
CGGGGTACCTTCTCAGATGTGCCTTCTAGTGTGATGAAATGCAAAGCATACACAGACTGT
CTGAGTCAGAACCTGGTGGTGTATCAAGCCGGGGACCAAGGAGACAGACAACGTCTGTGGC
ACACTCCCGTCCCTTCTCCAGCTCCACCTCACCTTCCCTGGCACAGCCATCTTTCCACGC
CCTGAGCACATGGAAACCCATGAAGTCCCTTCCCTTATGTTCCTCAAAGGCATGAAC
TCAACAGAATCCAACCTTCTGCCTCTGTAGACCAAAGGTAAGTACTGAGTAGCATCCAGGAA
GGGACAGTCCCTGACAACACAAGCTCAGCAAGGGGGAAGGAAGACGTGAACAAGACCTC
CCAAACCTTCAGGTAGTCAACCACCAGCAAGGCCCCACCACAGACACATCCTGAAGCTG
CTGCCGTCCATGGAGGCCACTGGGGGCGAGAAGTCCAGCACGCCCATCAAGGGCCCCAAG
AGGGGACATCCTAGACAGAACCTACACAAGCATTTTGACATCAATGAGCATTGTGCCCTGG
ATGATTGTGCTTTTCCTGCTGCTGGTGTGCTTGTGGTGTGCTGCTGCTGCTGCTGCTGCT
AGCTCGAGGACTCTGAAAAGGGGCCCCGGCAGGATCCCAGTGCCATTGTGGAAAAGGCA
GGGCTGAAGAAATCCATGACTCCAACCCAGAACCAGGAGAAATGGATCTACTACTGCAAT
GGCCATGGTATCGATATCCTGAAGCTTGTAGCAGCCCAAGTGGGAAGCCAGTGGAAAGAT
ATCTATCAGTTTCTTTGCAATGCCAGTGAGAGGGAGGTTGCTGCTTTCTCCAATGGGTAC
ACAGCCGACCACGAGCGGGCCTACGCAGCTCTGCAGCACTGGACCATCCGGGGCCCCGAG
GCCAGCCTCGCCCAGCTAATTAGCGCCCTGCGCCAGCACCGGAGAAACGATGTTGTGGAG
AAGATTCGTGGGCTGATGGAAGACACCACCCAGCTGGAACTGACAAACTAGCTCTCCCG
ATGAGCCCCAGCCCGCTTAGCCCCGAGCCCCATCCCCAGCCCCAACGCGAAACTTGAGAAT
TCCGCTCTCCTGACGGTGGAGCCTTCCCCACAGGACAAGAACAAGGGCTTCTTCGTGGAT
GAGTCGGAGCCCCCTTCTCCGCTGTGACTCTACATCCAGCGGCTCCTCCGCGCTGAGCAGG
AACGGTTCCCTTTATTACCAAAGAAAAGAAGGACACAGTGTGCGGCAGGTACGCCTGGAC
CCCTGTGACTTGCAGCCTATCTTTGATGACATGCTCCACTTTCTAAATCCTGAGGAGCTG
CGGGTGATTGAAGAGATTCCCCAGGCTGAGGACAAACTAGACCGGCTATTCGAAATTATT
GGAGTCAAGAGCCAGGAAGCCAGCCAGACCCTCCTGGACTCTGTTTATAGCCATCTTCCT
GACCTGCTGTAGAACATAGGGATACTGCATTCTGGAAATTAATCAATTTAGTGGCAGGGT
GGTTTTTTTAAATTTTCTTCTGTTTTCTGATTTTTTGTGTTTGGGGTGTGTGTGTGTGTGT
GTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGT
TTCTTTCTCCTTCTCTCTCTCTTTTTTTTTTAAATAACTCTTCTGGGAAGTTGGTTTA
TAAGCCTTTGCCAGGTGTAACCTGTTGTGAAATACCCACCACTAAAGTTTTTTTAAGTTCCA
TATTTTCTCCATTTTGCCTTCTTATGTATTTTCAAGATTATTCTGTGCACTTTAAATTTA
CTTAACCTTACCATAAATGCAGTGTGACTTTTCCACACACTGGATTGTGAGGCTCTTAAC
TTCTTAAAGTATAATGGCATCTTGTGAATCCTATAAGCAGTCTTTATGTCTCTTAACAT
TCACACCTACTTTTTTAAAAACAAATATTATTACTATTTTTTATTATTGTTTGTCTTTATA
AATTTTCTTAAAGATTAAGAAAATTTAAGACCCCATGAGTTACTGTAATGCAATTCAAC
TTTGAGTTATCTTTTAAATATGTCTTGTATAGTTCATATTCATGGCTGAAACTTGACCAC
ACTATTGCTGATTGTATGGTTTTTACCTGGACACCGTGTAGAATGCTTGATTACTTGTAC
TCTTCTTATGCTAATATGCTCTGGGCTGGAGAAATGAAATCCTCAAGCCATCAGGATTTG
CTATTTAAGTGGCTTGACAACTGGGCCACCAAAGAACTTGAACCTTCACTTTTAGGATTT
GAGCTGTTCTGGAACACATTGCTGCACTTTGGAAAGTCAAAATCAAGTGCCAGTGGCGCC
CTTTCATAGAGAATTTGCCAGCTTTGCTTTAAAGATGTCTTGTTTTTTTATATACACA
TAATCAATAGGTCCAATCTGCTCTCAAGGCCTTGGTCCTGGTGGGATTCCTTCACCAATT
ACTTTAATTAAAAATGGCTGCAACTGTAAGAACCCTTGTCTGATATATTTGCAACTATGC
TCCCATTTACAAATGTACCTTCTAATGCTCAGTTGCCAGGTTCCAATGCAAAGGTGGCGT
GGACTCCCTTTGTGTGGGTGGGGTTTTGTGGGTAGTGGTGAAGGACCGATATCAGAAAAAT
GCCTTCAAGTGTACTAATTTATTAATAAACATTAGGTGTTTGTAAAAA

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Figure 18

MGTSPSSSTALASCSRIARRATATMIAGSLLLLGFLSTTTAQPEQKASNLIQTYRHVDRA
TGQVLTCDKCPAGTYVSEHCTNTSLRVCSSCPVGTFTRHENGIEKCHDCSQPCPWPMIEK
LPCAALTDRECTCPPGMFQSNATCAPHTVCPVGWGVRRKKGTETEDVRCKQCARGTFSDVP
SSVMKCKAYTDCLSQNLVVIKPGTKETDNVCGTLPSSFSSSTSPSPGTAFPRPEHMETHE
VPSSTYVPKGMNSTESNSSASVRPKVLSSIQEGTVPDNTSSARGKEDVNKTLPNLQVVNH
QQGPHHRHILKLLPSMEATGGEKSSTPIKGPGRGHPRQNLHKHFDINEHLPWMIVLFLLL
VLVVIVVCSIRKSSRTLKKGPRQDPSAIVEKAGLKKSMPTQNRKWIYYCNGHGIDILK
LVAAQVGSQWKDIYQFLCNASEREVAAFSNGYTADHERAYAALQHWTIRGPEASLAQLIS
ALRQHRNDVVEKIRGLMEDTTQLETDKLALPMSPLSPSPPIPSPNAKLENSALLTVEP
SPQDKNKGFFVDESEPLLRCDSTSSGSSALSRNGSFITKEKKDTVLRQVRLDPCDLQPIF
DDMLHFLNPEELRVIEEIPQAEDKLDRLFELIGVKSQEASQTLLDSVYSHLPDLL

Signal sequence.

1-41

Transmembrane domain.

348-368

N-glycosylation site.

82-85

141-144

252-255

257-260

278-281

289-292

439-442

573-576

cAMP- and cGMP-dependent protein kinase phosphorylation site.

19-22

158-161

371-374

581-584

N-myristoylation site.

2-7

62-67

73-78

102-107

136-141

203-208

212-217

250-255

320-325

393-398

574-579

Leucine zipper pattern.

497-518

Death domain.

416-498

TNFR/NGFR cysteine-rich region.

50-88

91-131

133-168

171-211

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Figure 19

AGATGGTCAACGACCGGTGGAAGACCATGGGCGGCGCTGCCCAACTTGAGGACCGGCCGC
GCGACAAGCCGCAGCGGCCGAGCTGCGGCTACGTGCTGTGCACCGTGCTGCTGGCCCTGG
CTGTGCTGCTGGCTGTAGCTGTACCGGTGCCGTGCTCTTCTGAACCACGCCACGCGC
CGGGCACGGCGCCCCACCTGTGCTCAGCACTGGGGCTGCCAGCGCCAACAGCGCCCTGG
TCACTGTGGAAAGGGCGGACAGCTCGCACCTCAGCATCCTCATTTGACCCGCGCTGCCCCG
ACCTCACCGACAGCTTCGCACGCCTGGAGAGCGCCAGGCCTCGGTGCTGCAGGCGCTGA
CAGAGCACCAGGCCAGCCACGGCTGGTGGGCGACCAGGAGCAGGAGCTGCTGGACACGC
TGGCCGACCAGCTGCCCCGGCTGCTGGCCCGAGCCTCAGAGCTGCAGACGGAGTGCAATGG
GGCTGCGGAAGGGGCATGGCACGCTGGGCGAGGGCCTCAGCGCCCTGCAGAGTGAGCAGG
GCCGCCTCATCCAGCTTCTCTCTGAGAGCCAGGGCCACATGGCTCACCTGGTGAACCTCCG
TCAGCGACATCCTGGATGCCCTGCAGAGGGACCGGGGGCTGGGCCGGCCCCGCAACAAGG
CCGACCTTCAGAGAGCGCCTGCCCGGGGAACCCGGCCCCGGGGCTGTGCCACTGGCTCCC
GGCCCCGAGACTGTCTGGACGTCTCTCTAAGCGGACAGCAGGACGATGGCGTCTACTCTG
TCTTTCCCACCCACTACCCGGCCGGCTTCCAGGTGTACTGTGACATGCGCACGGACGGCG
GCGGCTGGACGGTGTTCAGCGCCGGGAGGACGGCTCCGTGAACCTTCTTCCGGGGCTGGG
ACGCGTACCGAGACGGCTTTTGGCAGGCTCACCGGGGAGCACTGGCTAGGGCTCAAGAGGA
TCCACGCCCTGACCACACAGGCTGCCTACGAGCTGCACGTGGACCTGGAGGACTTTGAGA
ATGGCACGGCCTATGCCCGCTACGGGAGCTTCGGCGTGGGCTTGTTCTCCGTGGACCCTG
AGGAAGACGGGTACCCGCTCACCGTGGCTGACTATTCCGGCACTGCAGGCGACTCCCTCC
TGAAGCACAGCGGCATGAGGTTCAACACCAAGGACCGTGACAGCGACCATTCAGAGAACA
ACTGTGCCGCTTCTACCGCGGTGCCTGGTGGTACCGCAACTGCCACACGTCCAACCTCA
ATGGGCGAGTACCTGCGCGGTGCGCACGCCTCCTATGCCGACGGCGTGGAGTGGTCCTCCT
GGACCGGCTGGCAGTACTCACTCAAGTTCTCTGAGATGAAGATCCGGCCGGTCCGGGAGG
ACCGCTAGACTGGTGCACCTTGTCTTGGCCCTGCTGGTCCCTGTGCCCCATCCCCGAC
CCCACCTCACTCTTTCGTGAATGTTCTCCACCCACCTGTGCCTGGCGGACCCACTCTCCA
GTAGGGAGGGGCGGGCCATCCCTGACACGAAGCTCCCTGGGCGGGTGAAGTCACACATC
GCCTTCTCGCCGTCCCCACCCCTCCATTTGGCAGCTCACTGATCTCTTGCTCTGCTGA
TGGGGGCTGGCAAACCTTGACGACCCCAACTCCTGCCTGCCCCCACTGTGACTCCGGTGT
GTTTGCCGTCCCCTGGCCAGGATGGTGGAGTCTGCCCCAGGCACCCTCTGCCCTGCCCGG
CCAAATACCCGGCATTATGGGGACAGAGAGCAGGGGGCAGACAGCACCCTGGAGTCCTC
CTAGCAGATCGTGGGGAATGTCAGGTCTCTCTGAGGTGAGGTCTGAGGCCAGTATCCTCC
AGCCCTCCCAATGCCAACCCCCACCCGTTTCCCTGGTGCCAGAGAACCACCTCTCCC
CCAAGGGCCTCAGCCTGGCTGTGGGCTGGGTGGCCCCATCCTACCAGGCCCTGAGGTCAG
GATGGGGAGCTGCTGCCTTTGGGGACCCACGCTCCAAGGCTGAGACCAGTTCCTGGAGG
CCACCCACCCTGTGCCCCGGCAGGCCTGGGGTCTGCAGTCTCTTACCTGCTGTGCCAC
CTGCTCTCTGTCTCAAATGAGGCCCAACCCATCCCCACCCAGCTCCCGGCCGTCTCTCT
ACCTGGGGCAGCCGGGGCTGCCATCCCATTTCTCTCTGCCTCTGGAAGGTGGGTGGGGCCC
TGCACCGTGGGGCTGGACTGCGCTAATGGGAAGCTCTTGGTTTTCTGGGCTGGGGCCTAG
GCAGGGCTGGGATGAGGCTTGTAACAACCCCAACCAATTTCCAGGGACTCCAGGGTC
CTGAGGCCTCCCAGGAGGGCCTTGGGGGTGATGACCCCTTCCCTGAGGTGGCTGTCTCCA
TGAGGAGGCCAACCCTTGCCATTGACCGTGGCCACCTGGACCCAGGCCAGGCCCGGCCCG
GCGAGTGGTCAAGGGACAGGGACCACTCACCGGGCAAATGGGGTGGGGGGGACTGGGGC
ACCAGACCAGGCACCACCTGGACACTTTCTTGTGAATCCTCCCAACACCCAGCACGCTG
TCATCCCCACTCCTTGTGTGCACACATGCAGAGGTGAGACCCGAGGCTCCCAGGACCAG
CAGCCACAAGGGCAGGGCTGGAGCCGGGTCTCAGCTGTCTGCTCAGCAGCCCTGGACCC
GCGTGCGTTACGTCAGGCCCAGATGCAGGGCGGCTTTTCCAAGGCCTCCTGATGGGGGCC
TCCGAAAGGGCTGGAGTCAGCCTTGGGGAGCTGCCTAGCAGCCTCTCCTCGGGCAGGAGG
GGAGGTGGCTTCTTCCAAGGACACCCGATGGCAGGTGCCTAGGGGGTGTGGGGTTCGT
TCTCCCTTCCCCTCCCCTGAAGTTTGTGCTTAAAAACAATAAATTTGACTTGGCACCA
CTGGGGGTGGTGGGAGAGGCCGTGTGACCTGGCTCTCTGTCCCAGTGCCACCAGGTCAT
CCACATGCGCAG

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Figure 20

MVNDRWKTMGGAAQLEDPRDKPQRPSCGYVLCTVLLALAVLLAVAVTGAVLFLNHAHAP
GTAPPPVVSTGAASANSALVTVERADSSHLSILIDPRCPDLTDSFARLESAQASVLQALT
EHQAQPRLVGDQEQELDLADQLPRLARASELQTECMGLRKHGTLGQGLSALQSEQG
RLIQLLSESQGHMAHLVNSVSDILDALQDRGLGRPRNKADLQAPARGTRPRGCATGSR
PRDCLDVLLSGQQDDGVYSVFPPTHYPAGFQVYCDMRTDGGGWTVFQRRDGSVNFFRGWD
AYRDGFGRLTGEHWLGLKRIHALTTQAAYELHVDLED FENG TAYARYGSFGVGLFSVDPE
EDGYPLTVADYSGTAGDSLLKHSGMRFTTKDRSDHSENNCAAFYRGAWWYRNCHTSNLN
GQYLRGAHASADGVWSSWTGWQYSLKFSEMKIRPVREDR

Signal sequence.

1-48

Transmembrane domain.

none

N-glycosylation site.

340-343

N-myristoylation site.

71-76

160-165

169-174

234-239

279-284

341-346

384-389

426-431

434-439

Fibrinogen beta and gamma chains C-terminal domain signature.

409-421

Leucine zipper pattern.

140-161

147-168

154-175

161-182

Fibrinogen beta and gamma chains, C-term

240-457

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Figure 21

GCCAGGTGTGCAGGCCGCTCCAAGCCCAGCCTGCCCCGCTGCCGCCACCATGACGCTCCT
CCCCGGCCTCCTGTTTCTGACCTGGCTGCACACATGCCTGGCCCACCATGACCCCTCCCT
CAGGGGGCACCCCCACAGTCACGGTACCCACACTGCTACTCGGCTGAGGAACTGCCCCCT
CGGCCAGGCCCCCCCACACCTGCTGGCTCGAGGTGCCAAGTGGGGGCAGGCTTTGCCTGT
AGCCCTGGTGTCCAGCCTGGAGGCAGCAAGCCACAGGGGGAGGCACGAGAGGCCCTCAGC
TACGACCCAGTGCCCGGTGCTGCGGCCGGAGGAGGTGTTGGAGGCAGACACCCACCAGCG
CTCCATCTCACCCCTGGAGATAACCGTGTGGACACGGATGAGGACCGCTATCCACAGAAGCT
GGCCTTCGCCGAGTGCCCTGTGCAGAGGCTGTATCGATGCACGGACGGGCCGCGAGACAGC
TGCCTCAACTCCGTGCGGCTGCTCCAGAGCCTGCTGGTGCTGCGCCGCCGGCCCTGCTC
CCGCGACGGCTCGGGGCTCCCCACACCTGGGGCCTTTGCCTTCCACACCGAGTTCATCCA
CGTCCCCGTGCGCTGCACCTGCGTGCTGCCCCGTTTCAAGTGTGACCGCCGAGGCCGTGGGG
CCCCTAGACTGGACACGTGTGCTCCCCAGAGGGCACCCCTATTTATGTGTATTTATTGT
TATTTATATGCCTCCCCCAACACTACCCCTGGGGTCTGGGCATTCCCCGTGTCTGGAGGA
CAGCCCCCACTGTTCTCCTCATCTCCAGCCTCAGTAGTTGGGGGTAGAAGGAGCTCAGC
ACCTCTTCCAGCCCTTAAAGCTGCAGAAAAGGTGTCACACGGCTGCCTGTACCTTGGCTC
CCTGTCCTGCTCCCGGCTTCCCTTACCCTATCACTGGCCTCAGGCCCGCAGGCTGCCTC
TTCCCAACCTCCTTGGAAGTACCCCTGTTTCTTAAACAATTATTTAAGTGTACGTGTATT
ATTAAACTGATGAACACATCCCCAAAA

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Figure 22

MTLLPGLLFLTWLHTCLAHHDPSLRGHPHSHGTPHCYSAEELPLGQAPPHLLARGAKWGQ
ALPVALVSSLEAASHRGRHERPSATTQCPVLRPEEVLEADTHQRSISPWRYRVDTDEDY
PQKLAFAECLCRGCIDARTGRETAALNSVRLQLSLVLRRRPCSRDGSGLPPTGAFAFHT
EFIHVPVGCTCVLPRSV

Signal sequence.
1-18

Transmembrane domain.
none

Tyrosine kinase phosphorylation site.
112-120

N-myristoylation site.
32-37
55-60
133-138

Leucine zipper pattern.
3-24

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Figure 23

GGCTCGAGGCCACGCACGACTGAACACAGACAGCAGCCGCCTCGCCATGAAGCTGCTGAT
GGTCCTCATGCTGGCGGCCCTCCTCCTGCACTGCTATGCAGATTCTGGCTGCAAACCTCCT
GGAGGACATGGTTGAAAAGACCATCAATTCCGACATATCTATACCTGAATACAAAGAGCT
TCTTCAAGAGTTCATAGACAGTGATGCCGCTGCAGAGGCTATGGGGAAATTCAAGCAGTG
TTTCCTCAACCAGTCACATAGAAGCTCTGAAAACTTTGGACTGATGATGCATACAGTGTA
CGACAGCATTGTTGTAATATGAAGAGTAATTAACCTTTACCCAAGGCGTTTGGCTCAGAG
GGCTACAGACTATGGCCAGAACTCATCTGTTGATTGCTAGAAACCACTTTTCTTTCTTGT
GTTGTCTTTTTATGTGGAAACTGCTAGACAACTGTTGAAACCTCAAATTCATTTCCATTT
CAATAAACTAACTGCAAATCACT

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Figure 24

MKLLMVLMLAALLHGYADSGCKLLEDMVEKTINSDISIPEYKELLQEFIDSDAAAEAMG
KFKQCFLNQSHRTLKNFGLMMHTVYDSIWCNMKSN .

Signal sequence.
1-18

Transmembrane domain.
none

N-glycosylation site.
68-71

Uteroglobin family.
1-90

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Figure 25

AGAAGGGACACACCAGCACAGTCTGGTAGGCTACAGCAGCAAGTCTCTAAAGAAAGGCTG
AGAACACCCAGAACAGGAGAGTTCAGGTCCAGGATGGCCAGCCTGTTCCGGTCCTATCTG
CCAGCAATCTGGCTGCTGCTGAGCCAACTCCTTAGAGAAAGCCTAGCAGCAGAGCTGAGG
GGATGTGGTCCCCGATTTGGAAAACACTTGCTGTCATATTGCCCCATGCCTGAGAAGACA
TTCACCACCACCCCAGGAGGGTGGCTGCTGGAATCTGGACGTCCCAAAGAAATGGTGTCA
ACCTCCAACAACAAAGATGGACAAGCCTTAGGTACGACATCAGAATTCATTCCTAATTTG
TCACCAGAGCTGAAGAAACCACTGTCTGAAGGGCAGCCATCATTGAAGAAAATAATACTT
TCCCGCAAAAAGAGAAGTGGACGTACAGATTTGATCCATTCTGTTGTGAAGTAATTTGT
GACGATGGAAC TTCAGTTAAATTATGTACATAGTAGAGTAATCATGGACTGGACATCTCA
TCCATTCTCATATGTATTCTCAATGACAAATTCAGTATGCCCAATTAAATGATTGCTGT
TTATT

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Figure 26

MASLFRSYLPAIWLLLSQLLRESLAAELRGCGPRFGKHLLSYCPMPEKTFTTTPGGWLL
SGRPKEMVSTSNKDGQALGTTSEFIPNLSPELKKPLSEGQPSLKKIILSRKKRSGRHRF
DPFCCEVICDDGTSVKLCT

Signal sequence.
1-25

Transmembrane domain.
none

cAMP- and cGMP-dependent protein kinase phosphorylation site.
112-115

N-myristoylation site.
76-81

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Figure 27

GGAAAGGCTGAGTCTCCAGCTCAAGGTCAAAACGTCCAAGGCCGAAAGCCCTCCAGTTTC
CCCTGGACGCCTTGCTCCTGCTTCTGCTACGACCTTCTGGGGAAAACGAATTTCTCATTT
TCTTCTTAAATTGCCATTTTCGCTTTAGGAGATGAATGTTTTCTTTGGCTGTTTTGGCA
ATGACTCTGAATTAAAGCGATGCTAACGCCTCTTTTCCCCCTAATTGTTAAAAGCTATGG
ACTGCAGGAAGATGGCCCGCTTCTCTTACAGTGTGATTTGGATCATGGCCATTTCTAAAG
TCTTTGAACTGGGATTAGTTGCCGGGCTGGGCCATCAGGAATTTGCTCGTCCATCTCGGG
GATACCTGGCCTTCAGAGATGACAGCATTTGGCCCCAGGAGGAGCCTGCAATTCGGCCTC
GGTCTTCCCAGCGTGTGCCGCCCATGGGGATACAGCACAGTAAGGAGCTAAACAGAACCT
GCTGCCTGAATGGGGGAACCTGCATGCTGGGGTCTTTTGTGCCTGCCCTCCCTCCTTCT
ACGGACGGAAGTGTGAGCACGATGTGCGCAAAGAGAACTGTGGGTCTGTGCCCCATGACA
CCTGGCTGCCCAAGAAGTGTTCCCTGTGTAAATGCTGGCACGGTCAGCTCCGCTGCTTTC
CTCAGGCATTTCTACCCGGCTGTGATGGCCTTGTGATGGATGAGCACCTCGTGGCTTCCA
GGACTCCAGAAGTACCACCGTCTGCACGTACTACCACTTTTATGCTAGTTGGCATCTGCC
TTTCTATACAAAGCTACTATTAATCGACATTGACCTATTTCCAGAAATACAATTTTAGAT
ATCATGCAAATTTTCATGACCAGTAAAGGCTGCTGCTACAATGTCCTAACTGAAAGATGAT
CATTTGTAGTTGCCTTAAAATAATGAATACATTTCCAAAATGGTCTCTAACATTTCTTA
CAGAACTACTTCTTACTTCTTTGCCCTGCCCTCTCCCAAAAACTACTTCTTTTTTCAA
AGAAAGTCAGCCATATCTCCATTGTGCCTAAGTCCAGTGTTTCTTTTTTTTTTTTTTTG
AGACGGAGTCTCACTCTGTCAACCAGGCTGGACTGCAATGACGCGATCTTGGTTCCTGC
AACCTCCGCATCCGGGGTTCAAGCCATTCTCCTGCCTCAGCCTCCCAAGTAACTGGGATT
ACAGGCATGTGTCAACCATGCCAGCTAATTTTTTTGTATTTTGTAGTAGAGATGGGGGTTT
CACCATATTGGCCAGTCTGGTCTCGAACTCCTGACCTTGTGATCCACTCGCCTCAGCCTC
TCGAAGTGCTGAGATTACACACGTGAGCAACTGTGCAAGGCCTGGTGTTTCTTGATACAT
GTAATTCTACCAAGGTCTTCTTAATATGTTCTTTTAAATGATTGAATTATATGTTTCAGAT
TAT'TGGAGACTAATTCTAATGTGGACCTTAGAATACAGTTTTTGAGTAGAGTTGATCAAAA
TCAATTAAAATAGTCTCTTTAAAAGGAAAGAAAACATCTTTAAGGGGAGGAACCAGAGTG
CTGAAGGAATGGAAGTCCATCTGCGTGTGTGCAGGGAGACTGGGTAGGAAAGAGGAAGCA
AATAGAAGAGAGAGGTTGAAAAACAAAATGGGTACTTGTGATTGGTGATTAGGTGGTGGTA
GAGAAGCAAGTAAAAAGGCTAAATGGAAGGGCAAGTTTCCATCATCTATAGAAAGCTATA
TAAGACAAGAACTCCCCTTTTTTTCCCAAAGGCATTATAAAAAGAATGAAGCCTCCTTAG
AAAAAAAATTATACCTCAATGTCCCCAACAAAGATTGCTTAATAAATTGTGTTTCCTCCAA
GCTATTCAATTCTTTTAACTGTTGTAGAAGACAAAATGTTTCACAATATATTTAGTTGTAA
ACCAAGTGATCAAACCTACATATTGTAAAGCCATTTTAAAATAACATTGTATATATGTGT
ATGCACAGTAAAAATGGAACTATATTGAA

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Figure 28

MDCRKMARFSYSVIWIMAIISKVFELGLVAGLGHQEFARPSRGYLAFRDDSIWPQEEPAIR
PRSSQRVPPMGIQHSEKELNRTCCLNGGTCMLGSGFCACPPSFYGRNCEHDVRKENCGSVPH
DTWLPPKKCSLCKCWHGQLRCFPQAFLPGCDGLVMDEHLVASRTPPELPPSARTTTFMLVGI
CLSIQSY

Signal sequence.
none

Transmembrane domain.
7-27

N-glycosylation site.
79-82

cAMP- and cGMP-dependent protein kinase phosphorylation site.
126-129

N-myristoylation site.
26-31
71-76
92-97
136-141
179-184

EGF-like domain cysteine pattern signature.
95-106

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Figure 29

GGACAAGGCACTTACCAACAGAGATTGCTGATTTGCTCCTTAAGCAAGAGATTCACTGCC
GCTAAGCATGGCTCAGACCAACTCGTTCTTCATGCTGATCTCCTCCCTGATGTTCCCTGTC
TCTGAGCCAAGGCCAGGAGTCCCAGACAGAGCTGCCTAATCCCCGAATCAGCTGCCCAGA
AGGCACCAATGCCTATCGCTCCTACTGCTACTACTTTAATGAAGACCCTGAGACCTGGGT
TGATGCAGATCTCTATTGCCAGAACATGAATTCAGGCAACCTGGTGTCTGTGCTCACCCA
GGCGGAGGGTGCCTTCGTGGCCTCACTGATTAAGGAGAGTAGCACTGATGACAGCAATGT
CTGGATTGGCCTCCATGACCCAAAAAAGAACCGCCGCTGGCACTGGAGTAGTGGGTCCCT
GGTCTCCTACAAGTCCTGGGACACTGGATCCCCGAGCAGTGCTAATGCTGGCTACTGTGC
AAGCCTGACTTCATGCTCAGGATTCAAGAAATGGAAGGATGAATCTTGTGAGAAGAAGTT
CTCCTTTGTTTGCAAGTTCAAAAACCTAGAGGAAGCTGAAAAATGGATGTCTAGAACTGGT
CCTGCAATTACTATGAAGTCAAAAATTAACTAGACTATGTCTCCAACCTCAGTTCAGACC
ATCTCCTCCCTAATGAGTTTGCATCGCTGATCTTCAGTACCTTCACCTGTCTCAGTCTCT
AGAGCCCTGAAAAATAAAAACAACTTATTTTAA

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Figure 30

MAQTNSFFMLISSLMFLSLSQGQESQTELPNPRISCPEGTNAYRSYCYFNEDEPETWVDA
DLYCQNMNSGNLVSFLTQAEGAFVASLIKESSTDDSNVWIGLHDPKKNRRWHWSSGSLVS
YKSWDTGSPSSANAGYCASLTSCSGFKKWKDESCCKKFSFVCKFKN

Signal sequence.

1-22

Transmembrane domain.

none

cAMP- and cGMP-dependent protein kinase phosphorylation site.

156-159

N-myristoylation site.

70-75

81-86

116-121

127-132

C-type lectin domain signature.

137-143

Lectin C-type domain

53-164

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Figure 31

GAGATCTCAAGAGTGACATTTGTGAGACCAGCTAATTTGATTAAAATTCTCTTGGAATCA
GCTTTGCTAGTATCATACCTGTGCCAGATTTTCATCATGGGAAACAGCTGTTACAACATAG
TAGCCACTCTGTTGCTGGTCCTCAACTTTGAGAGGACAAGATCATTGCAGGATCCTTGTA
GTAAGTGGCCAGCTGGTACATTCTGTGATAATAACAGGAATCAGATTTGCAGTCCCTGTC
CTCCAAATAGTTTCTCCAGCGCAGGTGGACAAAGGACCTGTGACATATGCAGGCAGTGTA
AAGGTGTTTTTCAGGACCAGGAAGGAGTGTTCCCTCCACCAGCAATGCAGAGTGTGACTGCA
CTCCAGGGTTTTCACTGCCTGGGGGCAGGATGCAGCATGTGTGAACAGGATTGTAAACAAG
GTCAAGAACTGACAAAAAAGGTTGTAAAGACTGTTGCTTTGGGACATTTAACGATCAGA
AACGTGGCATCTGTTCGACCCTGGACAAACTGTTCTTTGGATGGAAAGTCTGTGCTTGTGA
ATGGGACGAAGGAGAGGGACGTGGTCTGTGGACCATCTCCAGCCGACCTCTCTCCGGGAG
CATCCTCTGTGACCCCGCCTGCCCCCTGCGAGAGAGCCAGGACACTCTCCGCAGATCATCT
CCTTCTTTCTTGCGCTGACGTGCGACTGCGTTGCTCTTCCTGCTGTTCTTCCTCACGCTCC
GTTTCTCTGTTGTTAAACGGGGCAGAAAGAACTCCTGTATATATTCAAACAACCATTTA
TGAGACCAGTACAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAG
AAGAAGGAGGATGTGAACTGTGAAATGGAAGTCAATAGGGCTGTTGGGACTTTCTTGAAA
AGAAGCAAGGAAATATGAGTCATCCGCTATCACAGCTTTCAAAGCAAGAACACCATCCT
ACATAATACCCAGGATTTCCCCAACACACGTTCTTTTCTAAATGCCAATGAGTTGGCCTT
TAAAAATGCACCACTTTTTTTTTTTTTTTTGGACAGGGTCTCACTCTGTCACCCAGGCTGGA
GTGCAGTGGCACCACCATGGCTCTCTGCAGCCTTGACCTCTGGGAGCTCAAGTGATCCTC
CTGCCTCAGTCTCCTGAGTAGCTGGAATAAAGGAAGGGCCACCACACCTGACTAACTT
TTTTGTTTTTTGTTTGGTAAAGATGGCATTTTCGCCATGTTGTACAGGCTGGTCTCAAAC
CCTAGGTTCACTTTGGCCTCCCAAAGTGCTGGGATTACAGACATGAACTGCCAGGCCCGG
CCAAAATAATGCACCACTTTTAAACAGAACAGACAGATGAGGACAGAGCTGGTGATA

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Figure 32

MGNSCYNIVATLLLVLNFERTRSLQDPCSNCPAGTFCDNNRNQICSPCPPNSFSSAGGQR
TCDICRQCKGVFRTRKECSSTSNAECDCTPGFHC LGAGCSMCEQDCKQGQELTKKGCKDC
CFGTFNDQKRGICRPWTNCSLDGKSVLVNGTKERDVVCGPSPADLSPGASSVTPPAPARE
PGHSPQIISFFLALTSTALLFLLFFLTLRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDG
CSCRFPEEEEEGGCEL

Signal sequence.

1-23

Transmembrane domain.

188-208

N-glycosylation site.

138-141

149-152

N-myristoylation site.

57-62

58-63

70-75

96-101

98-103

109-114

116-121

Amidation site.

215-218

2Fe-2S ferredoxins, iron-sulfur binding region signature.

94-102

TNFR/NGFR cysteine-rich region

48-86

120-158

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Figure 33

CAGAGAGTCGCAGACACTATGCTGCCTCCCATGGCCCTGCCCAGTGTATCTTGGATGCTG
CTTTCCTGCCTCATGCTGCTGTCTCAGGTTCAAGGTGAAGAACCCCAGAGGGAAGTGGCC
TCTGCACGGATCCGCTGTCCCAAAGGCTCCAAGGCCTATGGCTCCCAGTGTATGCCTTG
TTTTTGTACCAAAATCCTGGACAGATGCAGATCTGGCCTGCCAGAAGCGGCCCTCTGGA
AACCTGGTGTCTGTGCTCAGTGGGGCTGAGGGATCCTTCGTGTCTCCCTGGTGAAGAGC
ATTGGTAACAGCTACTCATACTGTCTGGATTGGGCTCCATGACCCACACAGGGCACCGAG
CCCAATGGAGAAGGTGGGAGTGGAGTAGCAGTGATGTGATGAATTACTTTGCATGGGAG
AGAAATCCCTCCACCATCTCAAGCCCCGGCCACTGTGCGAGCCTGTGAGAAGCACAGCA
TTTCTGAGGTGGAAAGATTATACTGTAATGTGAGGTTACCCTATGTCTGCAAGTTCCT
GACTAGTGCAGGAGGGAAGTCAGCAGCCTGTGTTTGGTGTGCAACTCATCATGGGCATGA
GACCAGTGTGAGGACTCACCTGGAAGAGAATATTCGCTTAATTCCCCAACCTGACCAC
CTCATTCTTATCTTTCTTCTGTTTCTCCTCCCCGCTGTCATTTCACTCTTTCATTTTG
TCATACGGCCTAAGGCTTTAAAGAGCAATAAAATTTTGTAGTCTGCA

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Figure 34

MLPPMALPSVSWMLLSCLMLLSQVQGEEPORELP SARIRCPKGSKAYGSHCYALFLSPKS
WTDADLACQKRPSGNLVSVLSGAEGSFVSSLVKSIGNSYVWIGLHDPTQGTEPNGEW
EWSSSDVMNYFAWERNPSTISSPGHCASLSRSTAF LRWKDYNCNVRLPYVCKFTD

Signal sequence.

1-26

Transmembrane domain.

none

cAMP- and cGMP-dependent protein kinase phosphorylation site.

70-73

N-myristoylation site.

74-79

82-87

85-90

96-101

112-117

C-type lectin domain signature.

146-171

Lectin C-type domain.

57-173

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Figure 35

GAGCTATTTATCCCTAGGTCCTTTCCTCCTGCACGTCAGCTTTGAGCCCCGAGCTGGTGC
TTCTGCTCTCTGAGACATGGCAGGCCTGATGACCATAGTAACCAGCCTTCTGTTCCTTGG
TGTCTGTGCCCACCACATCATCCCTACGGGCTCTGTGGTCATCCCCCTCTCCCTGCTGCAT
GTTCTTTGTTTCCAAGAGAATTCTGAGAACCGAGTGGTCAGCTACCAGCTGTCCAGCAG
GAGCACATGCCTCAAGGCAGGAGTGATCTTCACCACCAAGAAGGGCCAGCAGTTCTGTGG
CGACCCCAAGCAGGAGTGGGTCCAGAGGTACATGAAGAACCTGGACGCCAAGCAGAAGAA
GGCTTCCCCTAGGGCCAGGGCAGTGGCTGTCAAGGGCCCTGTCCAGAGATATCCTGGCAA
CCAAACCACCTGCTAATCCCCGCCAGCCCTCCAGCCCTGAGTTTGGGCCTGAGCTGCTT
GGCGGGCTACTCGGGGCCTGGAGAAGCCACAGTGATGGGGGGAAGAGCTAATTTTCCTGT
TTCTTAGCAACACTCTCCAGGGATGTGTCTCTTCTATGAAAAACCCGAGGGAGCAGGTGA
TGTGGTTCCCGGGGGCTGAGCAATGGCTCCAAGCATCCAAGGCCCTTGCCTTCTGAGAG
CTGGGTGAGAAGATCCCAGAAGGAGAGCAGTGGCAACTCTTTGCCTTCTCCTCCTGACCT
GGTTCTGATGCTTTTTTCTTTTTTTTTTTTTTCTGAGACGGAGTCTCGCTCTGTCACCCAG
GCTGGAGTGCAGTGGCACAATCTCGGTTCACTGCAACCTCCGCCTCCTGGGTTCAAGTGA
TTCTCGTGCCTCAGCCTCCCGAGTACCTGGGACTACAGGTGTGTACCACCACACCCAACT
AACTTTTGTATTTTATAGTAGAGATGAGGTTTCACCATGTTGGCCAGGCTGGTCTCAAACCT
CCTGGCCTCAAGTGATCTACCTGCCTCGGCCTCCCAAAGTGCTGGGATTACAGGCATGAG
CCACCACACCCAGCCTACTCAAACCTTTATGTTGAAAAAAAAAATCATAATTTTTTTTTT
TTTTAAAGGAAATGAACGTGGAGGACTGGGGTGAAGGGCCAGCCTGGGTAGTTTAATCTT
TTTGGGAAGACATGACTTTAAGGAGATTCCCTGCTTTGTGACAGGTTGCTCCATGCTGTC
TTGGGGACAAGGGCCTGTACTGCCTTCAAATCTGGGCTCACCCACATTTTGGTGAGGGG
AAGATAGGGTGGGGGGATTAGGGGGAGAAAAGACTCTAGCTTTTTTTTTTCTATGCATGAT
ATACTGTGTGGGTTTATCAAGAGTGTAGACACAGTTGCTGTTCTCAAATAATAGGCCAAA
TAAAATGCGATTCTTTTTTTCTTTGA

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Figure 36

MAGLMTIVTSLLEFLGVCAHHIIP TGSVVIPSPCCMFFVSKRIPENRVVSYQLSSRSTCLK
AGVIFTTKKGQQFCGDPKQEWVQRYMKNLDAKQKKASPRARAVAVKGPVQRYPGNQTTTC

Signal sequence.

1-18

Transmembrane domain.

none

N-glycosylation site.

115-118

cAMP- and cGMP-dependent protein kinase phosphorylation site.

94-97

N-myristoylation site.

62-67

70-75

114-119

Small cytokines (intecrine/chemokine)

25-89

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Figure 37

GGGGAGCAGAGAGGAGGCAATGGCCACCATGGAGAACAAGGTGATCTGCGCCCTGGTCCT
GGTGTCCATGCTGGCCCTCGGCACCCTGGCCGAGGCCAGACAGAGACGTGTACAGTGGC
CCCCGTGAAAGACAGAATTGTGGTTTTCTGGTGTACGCCCTCCCAGTGTGCAAATAA
GGGCTGCTGTTTCGACGACACCGTTCGTGGGGTCCCCTGGTGCTTCTATCCTAATACCAT
CGACGTCCCTCCAGAAGAGGAGTGTGAATTTTAGACACTTCTGCAGGGATCTGCCTGCAT
CCTGACGCGGTGCCATCCCCAGCACGGTGATTAGTCCCAGAGCTCGGCTGCCACCTCCAC
CGGACACCTCAGACACGCTTCTGCAGCTGTGCCTCGGCTCACAACACAGATTGACTGCTC
TGACTTTGACTACTCAAAATTGGCCTAAAAATTAAAAGAGCTCGATATTAAAAA

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Figure 38

MATMENKVICALVLVSMLALGTLAEAQTTETCTVAPRERQNCGFPGVTPSQCANKGCCFDD
TVRGVPWCFYPNTIDVPPEEECEF

Signal sequence.
1-24

Transmembrane domain.
none

N-myristoylation site.
45-50
64-69

P-type 'Trefoil' domain signature.
38-58

Trefoil (P-type) domain.
30-71

Gastrin/cholecystokinin family.
6-26

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Figure 39A

GAATTCCGGGCCGCTTAGTGTTGAATGTTCCCCACCGAGAGCGCATGGCTTGGGAAGCGA
GGCGCGAACCCGGGCCCCGAAGCCGCGTCCGGGAGACGGTGATGCTGTTGCTGTGCCTG
GGGGTCCCGACCGGCCGCCCTACAACGTGGACACTGAGAGCGCGCTGCTTTACCAGGGC
CCCCACAACACGCTGTTCCGGCTACTCGGTCTGTGCTGCACAGCCACGGGGCGAACCGATGG
CTCCTAGTGGGTGCGCCCCACTGCCAACTGGCTCGCCAACGCTTCAGTGATCAATCCCGGG
GCGATTTACAGATGCAGGATCGGAAAGAATCCCGGCCAGACGTGCGAACAGCTCCAGCTG
GGTAGCCCTAATGGAGAACCTTGTGGAAAGACTTGTTTGGAAGAGAGAGACAATCAGTGG
TTGGGGGTCACACTTTCCAGACAGCCAGGAGAAAATGGATCCATCGTGACTTGTGGGCAT
AGATGGAAAAATATATTTTACATAAAGAATGAAAATAAGCTCCCCACTGGTGGTTGCTAT
GGAGTGCCCCCTGATTTACGAACAGAACTGAGTAAAAGAATAGCTCCGTGTTATCAAGAT
TATGTGAAAAAATTTGGAGAAAATTTTGCATCATGTCAAGCTGGAATATCCAGTTTTTAC
ACAAAGGATTTAATTGTGATGGGGGCCCCAGGATCATCTTACTGGACTGGCTCTCTTTTT
GTCTACAATATAACTACAAATAAATAACAAGGCTTTTTTTAGACAAACAAAATCAAGTAAAA
TTTGGAAGTTATTTAGGATATTCAGTCGGAGCTGGTCATTTTTCGGAGCCAGCATACTACC
GAAGTAGTCGGAGGAGCTCCTCAACATGAGCAGATTGGTAAGGCATATATATTCAGCATT
GATGAAAAAGAACTAAATATCTTACATGAAATGAAAGGTAAAAAGCTTGGATCGTACTTT
GGAGCTTCTGTCTGTGCTGTGGACCTCAATGCAGATGGCTTCTCAGATCTGCTCGTGGGA
GCACCCATGCAGAGCACCATCAGAGAGGAAGGAAGAGTGTGTTGTGTACATCAACTCTGGC
TCGGGAGCAGTAATGAATGCAATGGAAACAAACCTCGTTGGAAGTGACAAATATGCTGCA
AGATTTGGGGAATCTATAGTTAATCTTGGCGACATTGACAATGATGGCTTTGAAGATGTT
GCTATCGGAGCTCCACAAGAAGATGACTTGCAAGGTGCTATTTATATTTACAATGGCCGT
GCAGATGGGATCTCGTCAACCTTCTCACAGAGAATTGAAGGACTTCAGATCAGCAAATCG
TTAAGTATGTTTGGACAGTCTATATCAGGACAAATTGATGCAGATAATAATGGCTATGTA
GATGTAGCAGTTGGTGCTTTTTCGGTCTGATTCTGCTGTCTTGCTAAGGACAAGACCTGTA
GTAATTGTTGACGCTTCTTTAAGCCACCCTGAGTCAGTAAATAGAACGAAATTTGACTGT
GTTGAAAATGGATGGCCTTCTGTGTGCATAGATCTAACACTTTGTTTCTCATATAAGGGC
AAGGAAGTTCCAGGTTACATTGTTTTGTTTTATAACATGAGTTTGGATGTGAACAGAAAG
GCAGAGTCTCCACCAAGATTCTATTTCTCTTCTAATGGAACCTTCTGACGTGATTACAGGA
AGCATAACAGGTGTCCAGCAGAGAAGCTAACTGTAGAACACATCAAGCATTTATGCGGAAA
GATGTGCGGGACATCCTCACCCCAATTCAGATTGAAGCTGCTTACCACCTTGGTCCTCAT
GTCATCAGTAAACGAAGTACAGAGGAATTCCCACCACCTTCAGCCAATTCTTCAGCAGAAG
AAAGAAAAAGACATAATGAAAAAACAATAAACTTTGCAAGGTTTTGTGCCCCATGAAAAT
TGTTCTGCTGATTTACAGGTTTCTGCAAAGATTGGGTTTTTTGAAGCCCCATGAAAATAAA
ACATATCTTGCTGTTGGGAGTATGAAGACATTGATGTTGAATGTGTCCTTGTTTAATGCT
GGAGATGATGCATATGAAACGACTCTACATGTCAAACCTACCCGTGGGTCTTTATTTTCATT
AAGATTTTAGAGCTGGAAGAGAAGCAAATAAACTGTGAAGTCACAGATAACTCTGGCGTG
GTACAACCTTGACTGCAGTATTGGCTATATATATGTAGATCATCTCTCAAGGATAGATATT
AGCTTTCTCCTGGATGTGAGCTCACTCAGCAGAGCGGAAGAGGACCTCAGTATCACAGTG
CATGCTACCTGTGAAAATGAAGAGGAAATGGACAATCTAAAGCACAGCAGAGTGACTGTA
GCAATACCTTTAAAATATGAGGTTAAGCTGACTGTTTCATGGGTTTGTAACCCCAACTTCA
TTTGTGTATGGATCAAATGATGAAAATGAGCCTGAAACGTGCATGGTGGAGAAAATGAAC
TTAACTTTCCATGTTATCAACACTGGCAATAGTATGGCTCCCAATGTTAGTGTGGAAATA
ATGGTACCAAATTTCTTTTAGCCCCCAAACCTGATAAGCTGTTCAACATTTTGGATGTCCAG
ACTACTACTGGAGAATGCCACTTTGAAAATTATCAAAGAGTGTGTGCATTAGAGCAGCAA
AAGAGTGCAATGCAGACCTTGAAAGGCATAGTCCGGTTCTTGTTCCAAGACTGATAAGAGG
CTATTGTACTGCATAAAAGCTGATCCACATTGTTTAAATTTCTTGTTGTAATTTTGGGAAA
ATGGAAAGTGGAAGAAGCCAGTGTTTCATATCCAACCTGGAAGGCCGGCCATCCATTTTA
GAAATGGATGAGACTTCAGCACTCAAGTTTGAATAAGAGCAACAGGTTTTTCCAGAGCCA
AATCCAAGAGTAATTGAACTAAACAAGGATGAGAATGTTGCGCATGTTCTACTGGAAGGA
CTACATCATCAAAGACCCAAACGTTATTTTACCATAGTGATTATTTCAAGTAGCTTGCTA
CTTGGACTTATTGTACTTCTGTTGATCTCATATGTTATGTGGAAGGCTGGCTTCTTTAAA
AGACAATACAAATCTATCCTACAAGAAGAAAACAGAAGAGACAGTTGGAGTTATATCAAC
AGTAAAAGCAATGATGATTAAGGACTTCTTTCAAATTGAGAGAATGGAAAACAGACTCAG
GTTGTAGTAAAGAAATTTAAAAGACACTGTTTACAAGAAAAAATGAATTTTGTGTTGGACT
TCTTTTACTCATGATCTTGTGACATATTATGTCTTCATGCAAGGGGAAAATCTCAGCAAT
GATTACTCTTTGAGATAGAAGAACTGCAAAGGTAATAATACAGCCAAAGATAATCTCTCA
GCTTTTAAATGGGTAGAGAAACACTAAAGCATTCAATTTATTCAAGAAAAGTAAGCCCTT
GAAGATATCTTGAAATGAAAGTATAACTGAGTTAAATTATACTGGAGAAGTCTTAGACTT
GAAATACTACTTACCATATGTGCTTGCTCAGTAAAATGAACCCCACTGGGTGGGCAGAG
GTTCAATTTCAAATACATCTTTGATACTTGTTCAAAATATGTTCTTTAAAATATAATTTT
TTAGAGAGCTGTTCCCAAATTTTCTAACGAGTGGACCATTATCACTTTAAAGCCCTTTAT

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Figure 39B

TTATAATACATTTCTACGGGCTGTGTTCCAACAACCATTTTTTTTCAGCAGACTATGAA
TATTATAGTATTATAGGCCAAACTGGCAAACCTTCAGACTGAACATGTACACTGGTTTGAG
CTTAGTGAAATGACTTCCGGAATCT

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Figure 40A

MFPTESAWLGKRGANPGPEAAVRETVMLLLCLGVPTGRPYNVDTESALLYQGPHNTLFGY
SVVLHSHGANRWLLVGAPTANWLANASVINPGAIYRCRIGKNPGQTCEQLQLGSPNGEPC
GKTCLEERDNQWLGVTLRQPGENGSIIVTCGHRWKNIFYIKNENKLPTGGCYGVPPDLRT
ELSKRIAPCYQDYVKKFGENFASCQAGISSFYTKDLIVMGAPGSSYWTGSLFVYNITTNK
YKAFLDKQNQVKFGSYLGYSVGAGHFRSQHTTEVVGAPQHEQIGKAYIFSIDEKELNIL
HEMKGKKLGSYFGASVCAVDLNADGFSDLLVGAPMQSTIREEGRVVFVYINSGSGAVMNAM
ETNLVGSDKYAARFGESIVNLGDIDNDGFEDVAIGAPQEDDLQGAIIYNGRADGISSTF
SQRIEGLQISKSLSMFGQSISGQIDADNNGYVDVAVGAFRSDSAVLLRTRPVVIVDASLS
HPESVNRTKFDCVENGWPSVCIDLTLCFSYKGKEVPGYIVLFYNMSLDVNRKAESPFRFY
FSSNGTSDVITGSIQVSSREANCRTHQAFMRKDV RDILTPIQIEAAYHLGPHVISKRSTE
EFPPLQPILOQKKEKDIMKKTINFARFCAHENC SADLQVSAKIGFLKPHENKTYLAVGSM
KTLMLNVSLFNAGDDAYETTLHVKLPGVGLYFIKILELEEKQINCEVTDNSGVVQLDCSIG
YIYVDHLSTRIDISFLLDVSSLSRAEEDLSITVHATCENEEEMDNLKHSRVTVAIPLKYEV
KLTVHGFVNPTSFVYGSNDENEPETCMVEKMNLTFHVINTGNSMAPNVSV EIMVPNSFSP
QTDKLFNILDVQTTTGECHFENYQRVCALEQQKSAMQTLKGIVRFLSKTDKRLLYCIKAD
PHCLNFLCNFGKMESGKEASVHIQLEGRPSILEMDETSALKFEIRATGFPEPNPRVIELN
KDENVAHVLLLEGLHHQRPKRYFTIVI ISSSLLLGLIVLLLLISYVMWKAGFFKRQYKSILQ
EENRRDSWSYINSKSNDD

Signal sequence.

1-37

Transmembrane domain.

985-1005

N-glycosylation site.

85-88

144-147

235-238

486-489

524-527

544-547

632-635

651-654

666-669

812-815

827-830

Glycosaminoglycan attachment site.

351-354

cAMP- and cGMP-dependent protein kinase phosphorylation site.

596-599

1024-1027

Tyrosine kinase phosphorylation site.

511-518

647-654

N-myristoylation site.

33-38

76-81

113-118

134-139

145-150

169-174

220-225

254-259

309-314

313-318

354-359

415-420

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Figure 40B

426-431
437-442
442-447
457-462
658-663

Amidation site.
9-12
304-307

Integrins alpha chain signature.
1006-1013

FG-GAP repeat
55-117
254-306
309-368
371-430
433-485

Integrin A Integrin alpha cytoplasmic region.
1007-1021

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Figure 41

TAAACACAGCTTTTCTGCTTTACCTGTCCAGGTAGCCTCTGTTTTTCATTTTCAGTCTTAAT
GAAAACCTTTCTAACTTATATCTCAAGTTTCTTTTCAAAGCAGTGTAAGTAGTATTTAAAA
TGTTATACTTCAAGAAAGAAAGACTTTAACGATATTCAGCGTTGGTCTTGTAACGCTGAA
GGTAATTCATTTTTTAATCGGTCTCGCACAGCAAGAACTGAAACGAATGGGGATTGAACT
GCTTTGCCTGTTCTTTCTATTTCTAGGAAGGAATGATTCACGTACAAGGTGGCTGTGCCT
GGGAGGTGCAGAAACCTGTGAAGACTGCCTGCTTATTGGACCTCAGTGTGCCTGGTGTGC
TCAGGAGAATTTTACTCATCCATCTGGAGTTGGCGAAAGGTGTGATACCCACAGCAAACCT
TTTAGCTAAAGGATGTCAATTAACTTCATCGAAAACCCCTGTCTCCCAAGTAGAAATACT
TAAAAATAAGCCTCTCAGTGTAGGCAGACAGAAAAATAGTTCTGACATTGTTTCAGATTGC
ACCTCAAAGCTTGATCCTTAAGTTGAGACCAGGTGGTGCAGACTCTGCAGGTGCATGT
CCGCCAGACTGAGGACTACCCGGTGGATTTGTATTACCTCATGGACCTCTCCGCCTCCAT
GGATGACGACCTCAACACAATAAAGGAGCTGGGCTCCGGCCTTTCCAAAGAGATGTCTAA
ATTAACCAGCAACTTTAGACTGGGCTTCGGATCTTTTGTGGAAAAACCTGTATCCCCTTT
TGTGAAAACAACACCAGAAGAAATTGCCAACCCCTTGCAAGTAGTATTCCATACTTCTGTTT
ACCTACATTTGGATTCAAGCACATTTTGCCATTGACAAATGATGCTGAAAGATTCAATGA
AATTGTGAAGAATCAGAAAATTTCTGCTAATATTGACACACCCGAAGGTGGATTTGATGC
AATTATGCAAGCTGCTGTGTGTAAGGAAAAAATTGGCTGGCGGAATGACTCCCTCCACCT
CCTGGTCTTTGTGAGTGATGCTGATTCTCATTTTGGAATGGACAGCAAACCTAGCAGGCAT
CGTCATTCCTAATGACGGGCTCTGTCACTTGGACAGCAAGAATGAATACTCCATGTCAAC
TGTCTTGGAATATCCAACAATTGGACAACCTCATTGATAAACTGGTACAAAACAACGTGTT
ATTGATCTTCGCTGTAACCCAAGAACAAGTTCAATTTATATGAGAATTACGCAAAACTTAT
TCCTGGAGCTACAGTAGGTCTACTTCAGAAGGACTCCGGAAACATTTCTCCAGCTGATCAT
CTCAGCTTATGAAGAACTGCGGTCTGAGGTGGAACCTGGAAGTATTAGGAGACACTGAAGG
ACTCAACTTGTCAATTTACAGCCATCTGTAACAACGGTACCCTCTTCCAACACCAAAGAA
ATGCTCTCACATGAAAGTGGGAGACACAGCTTCCTTCAGCGTGACTGTGAATATCCCACA
CTGCGAGAGAAGAAGCAGGCACATTATCATAAAGCCTGTGGGGCTGGGGGATGCCCTGGA
ATTACTTGTGAGCCAGAAATGCAACTGCGACTGTGAGAAAGAAGTGAAGTGAACAGCTC
CAAATGTCACCACGGGAACGGCTCTTTCCAGTGTGGGGTGTGTGCCTGCCACCCTGGCCA
CATGGGGCCTCGCTGTGAGTGTGGCGAGGACATGCTGAGCACAGATTCCTGCAAGGAGGC
CCCAGATCATCCCTCCTGCAGCGGAAGGGGTGACTGCTACTGTGGGCAGTGTATCTGCCA
CTTGTCTCCCTATGGAAACATTTATGGACCTTATTGCCAGTGTGACAATTTCTCCTGCGT
GAGACACAAAGGGCTGCTCTGCGGAGGTAACGGCGACTGTGACTGTGGTGAATGTGTGTG
CAGGAGCGGCTGGACTGGCGAGTACTGCAACTGCACCACCAGCACGGACTCCTGCGTCTC
TGAAGATGGAGTGCTCTGCAGCGGGCGCGGGGACTGTGTTTGTGGCAAGTGTGTTTGCAC
AAACCCTGGAGCCTCAGGACCAACCTGTGAACGATGTCCTACCTGTGGTGACCCCTGTAA
CTCTAAACGGAGCTGCATTGAGTGCCACCTGTCAGCAGCTGGCCAAGCCGGAGAAGAATG
TGTGGACAAGTGCAAACTAGCTGGTGGCACCATCAGTGAAGAAGAAGATTTCTCAAAGGA
TGGTTCTGTTTCCTGCTCTCTGCAAGGAGAAAATGAATGTTTAATTACATTCCTAATAAC
TACAGATAATGAGGGGAAAACCATCATTACAGCATCAATGAAAAAGATTGTCCGAAGCC
TCCAAACATTTCCCATGATCATGTTAGGGGTTTCCCTGGCTACTCTTCTCATCGGGGTGT
CCTACTGTGCATCTGGAAGCTACTGGTGTCAATTTTCATGATCGTAAAGAAGTTGCCAAATT
TGAAGCAGAACGATCAAAAGCCAAGTGGCAAACGGGAACCAATCCACTCTACAGAGGATC
CACAAGTACTTTTAAAAATGTAACTTATAAACACAGGGAAAAACAAAAGGTAGACCTTTC
CACAGATTGCTAGAACTACTTTATGCATAAAAAAAGTCTGTTTCACTGATATGAAATGTT
AATG

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Figure 42A

MGIELLCFLFFLFLGRNDSRTRWLC LGGAETCEDCLLIGPQCAWCAQENFTHPSGVGERCD
TPANLLAKGCQLNFIENPVSQVEILKNKPLSVGRQKNSSDIVQIAPQSLILKLRPGGAQT
LQVHVRQTEDYPVDLYYLMDL SASMDDDLNTIKELGSGLSKEMSKLTSNFR LGFGSFVEK
PVSPFVKTTPEEIANPCSSIPYFCLPTFGFKHILPLTND AERFNEIVKNQKISANIDTPE
GGFDAIMQAAVCKEKIGWRNDSLHLLV FVSDADSHFGMDSKLAGIVI PNDGLCHLDSKNE
YSMSTVLEYPTIGQLIDKLVQNNVLLI FAVTQEQVHLYENYAKLI PGATVGLLQKDSGNI
LQLIISAYEELRSEVELEVLGDTEGLNLSFTAI CNNGTLFQHQKKCSHMKVGD TASFSVT
VNIPH CERRSRHII IKPVGLGDALELLVSPECNDCQKEVEVNSSKCHHGNGSFQCGVCA
CHPGHMGPRCEGEDMLSTDSCKEAPDH PSCSGRGDCYCGQCI CHLSPYGN IYGPYCQCD
NFSCVRHKGLLCGGNGDCDCGECVCRSGWTGEYCNCTTSTDSCVSE DGVLCSGRGDCVCG
KCVCTNPGASGPTCERCPTCGDPCNSKRSCIECHLSAAGQAGEECVDKCKLAGATISEEE
DFSKDGSVSCSLQGENECLITFLITTDNEGKTI IHSINEKDCPKPPNI PMIMLGVSLATL
LIGVVLLCIWKLLVSFHDRKEVAKFEAERSKAKWQTGTNPLYRGSTSTFKNVTYKHREKQ
KVDLSTDC

Signal sequence.

1-18

Transmembrane domain.

710-730

N-glycosylation site.

16-19

48-51

97-100

260-263

387-390

396-399

463-466

471-474

541-544

575-578

771-774

Glycosaminoglycan attachment site.

53-56

512-515

592-595

cAMP- and cGMP-dependent protein kinase phosphorylation site.

404-407

N-myristoylation site.

26-31

27-32

69-74

116-121

156-161

241-246

347-352

385-390

439-444

472-477

477-482

520-525

549-554

554-559

588-593

653-658

666-671

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Figure 42B

714-719

764-769

Cell attachment sequence.

514-517

594-597

EGF-like domain cysteine pattern signature.

479-490

563-574

Cytochrome c family heme-binding site signature.

630-635

Integrins beta chain cysteine-rich domain signature.

511-524

552-535

591-604

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Figure 43

GGCAGCCTTCCCCAGGTGAGCAGCAACAAGGCCACGTGCTGCTGGGTCTCAGTCCTCCAC
TTCCCGTGTCTCTGGAAGTTGTCAGGAGCAATGTTGCGCTTGTACGTGTTGGTAATGGG
AGTTTCTGCCTTCACCCCTTCAGCCTGCGGCACACACAGGGGCTGCCAGAAGCTGCCGGTT
TCGTGGGAGGCATTACAAGCGGGAGTTCAGGCTGGAAGGGGAGCCTGTAGCCCTGAGGTG
CCCCCAGGTGCCCTACTGGTTGTGGGCCTCTGTCAGCCCCCGCATCAACCTGACATGGCA
TAAAAATGACTCTGCTAGGACGGTCCCAGGAGAAGAAGAGACACGGATGTGGGCCCAGGA
CGGTGCTCTGTGGCTTCTGCCAGCCTTGCAGGAGGACTCTGGCACCTACGTCTGCACTAC
TAGAAATGCTTCTTACTGTGACAAAATGTCCATTGAGCTCAGAGTTTTTTGAGAATACAGA
TGCTTTCCTGCCGTTTCATCTCATACCCGCAAATTTTAACCTTGTCAACCTCTGGGGTATT
AGTATGCCCTGACCTGAGTGAATTCACCCGTGACAAAACCTGACGTGAAGATTCAATGGTA
CAAGGATTCTCTTCTTTTGGATAAAGACAATGAGAAATTTCTAAGTGTGAGGGGGACCAC
TCACTTACTCGTACACGATGTGGCCCTGGAAGATGCTGGCTATTACCGCTGTGTCCTGAC
ATTTGCCCATGAAGGCCAGCAATACAACATCACTAGGAGTATTGAGCTACGCATCAAGAA
AAAAAAGAAGAGACCATTCCTGTGATCATTTCCCCCCTCAAGACCATATCAGCTTCTCT
GGGGTCAAGACTGACAATCCCGTGTAAAGGTGTTTCTGGGAACCGGCACACCCCTTAACCAC
CATGCTGTGGTGGACGGCCAATGACACCCACATAGAGAGCGCCTACCCGGGAGGCCGCGT
GACCGAGGGGCCACGCCAGGAATATTCAGAAAATAATGAGAACTACATTGAAGTGCCATT
GATTTTGTATCCTGTCACAAGAGAGGATTTGCACATGGATTTTAAATGTGTTGTCCATAA
TACCCTGAGTTTTTCAGACACTACGCACCACAGTCAAGGAAGCCTCCTCCACGTTCTCCTG
GGGCATTGTGCTGGCCCCACTTTCACTGGCCTTCTTGGTTTTTGGGGGGAATATGGATGCA
CAGACGGTGCAAACACAGAACTGGAAAAGCAGATGGTCTGACTGTGCTATGGCCTCATCA
TCAAGACTTTCAATCCTATCCCAAGTGAAATAAATGGAATGAAATAATTCAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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Figure 44

MLRLYVLVMGVSAFTLQPAAHGAARSCRFRGRHYKREFRLEGEPVALRCPQVPYWLWAS
VSPRINLTWHKNDSTVPGEEETRMWAQDQALWLLPALQEDSGTYVCTTRNASYCDKMS
IELRVFENTDAFLPFISYPQILTLSTSGVLVCPDLSEFTRDKTDVKIQWYKDSLLLDKDN
EKFLSVRGTTTHLLVHDVALEDAGYYRCVLTFAHEGQQYNITRSIELRIKKKKEETIPVII
SPLKTISASLGSRLTIPCKVFLGTGTPLTTMLLWWTANDTHIESAYPGGRVTEGPRQEYSE
NNENYIEVPLIFDPVTREDLHMDFKCVVHNTLSFQTLRTTVKEASSTFSWGIVLAPLSLA
FLVLGGIWMHRRCKHRTGKADGLTVLWPHHQDFQSYPK

Signal sequence.

1-13

Transmembrane domain.

347-367

N-glycosylation site.

66-69

72-75

112-115

219-222

277-280

N-myristoylation site.

23-28

104-109

215-220

251-256

265-270

287-292

Immunoglobulin domain.

43-110

165-209

251-328

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Figure 45

CATGCCGCTGCCGCGCTGCTGCTGTTGCTCCTGGCGGCGCCTTGGGGACGGGCAGTTCC
CTGTGTCTCTGGTGGTTTGCCTAAACCTGCAAACATCACCTTCTTATCCATCAACATGAA
GAATGTCCTACAATGGACTCCACCAGAGGGTCTTCAAGGAGTTAAAGTTACTTACACTGT
GCAGTATTTTCATATATATGGGCAAAAGAAATGGCTGAATAAATCAGAATGCAGAAATATCAA
TAGAACCTACTGTGATCTTTCTGCTGAAACTTCTGACTACGAACACCAGTATTATGCCAA
AGTTAAGGCCATTTGGGGAACAAAGTGTTCCAAATGGGCTGAAAGTGGACGGTTCTATCC
TTTTTTAGAAACACAAATTGGCCCACCAGAGGTGGCACTGACTACAGATGAGAAGTCCAT
TTCTGTTGTCCTGACAGCTCCAGAGAAGTGGAAGAGAAATCCAGAAGACCTTCCTGTTTC
CATGCAACAAATATACTCCAATCTGAAGTATAACGTGTCTGTGTTGAATACTAAATCAAA
CAGAACGTGGTCCCAGTGTGTGACCAACCACACGCTGGTGCTCACCTGGCTGGAGCCGAA
CACTCTTTACTGCGTACACGTGGAGTCCTTCGTCCCAGGGCCCCCTCGCCGTGCTCAGCC
TTCTGAGAAGCAGTGTGCCAGGACTTTGAAAGATCAATCATCAGAGTTCAAGGCTAAAT
CATCTTCTGGTATGTTTTTGCCCATATCTATTACCGTGTTTCTTTTTTCTGTGATGGGCTA
TTCCATCTACCGATATATCCACGTTGGCAAAGAGAAACACCCAGCAAATTTGATTTTGAT
TTATGGAAATGAATTTGACAAAAGATTCTTTGTGCCTGCTGAAAAAATCGTGATTAACTT
TATCACCCCTCAATATCTCGGATGATTCTAAAATTTCTCATCAGGATATGAGTTTACTGGG
AAAAAGCAGTGATGTATCCAGCCTTAATGATCCTCAGCCCAGCGGGAACCTGAGGCCCCC
TCAGGAGGAAGAGGAGGTGAAACATTTAGGGTATGCTTCGCATTTGATGGAAATTTTTTG
TGACTCTGAAGAAAACACGGAAGGTACTTCTCTCACCAGCAAGAGTCCCTCAGCAGAAC
AATACCCCGGATAAAACAGTCATTGAATATGAATATGATGTCAGAACCACTGACATTTG
TGCGGGGCTGAAGAGCAGGAGCTCAGTTTGCAGGAGGAGGTGTCCACACAAGGAACATT
ATTGGAGTCGCAGGCAGCGTTGGCAGTCTTGGGCCCCGAAACGTTACAGTACTCATAAC
CCCTCAGCTCCAAGACTTAGACCCCTGGCGCAGGAGCACACAGACTCGGAGGAGGGGCC
GGAGGAAGAGCCATCGACGACCCTGGTCGACTGGGATCCCCAACTGGCAGGCTGTGTAT
TCCTTCGCTGTCCAGCTTCGACCAGGATTCAGAGGGCTGCGAGCCTTCTGAGGGGGATGG
GCTCGGAGAGGAGGGTCTTCTATCTAGACTCTATGAGGAGCCGGCTCCAGACAGGCCACC
AGGAGAAAATGAAACCTATCTCATGCAATTCATGGAGGAATGGGGGTATATGTGCAGAT
GGAAAACCTGATGCCAACACTTCCTTTTGCCTTTTGTTCCTGTGCAAACAAGTGAGTCAC
CCCTTTGATCCCAGCCATAAAGTACCTGGGATGAAAGAAGTTTTTTCCAGTTTGTGAGTG
TCTGTGAGAA

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Figure 46

MPLPPLLLLLLLAAPWGRAVPCVSGGLPKPANITFLSINMKNVLQWTPPEGLQGVKVTYTV
QYFIYGQKKWLNKSECRNINRTYCDLSAETSDYEHQYYAKVKAIWGTKCSKWAESGRFYP
FLETQIGPPEVALTTDEKSISVVLTAPEKWKRNPEDLPVSMQQIYSNLKYNVSVLNTKSN
RTWSQCVTNHTLVLTWLEPNTLYCVHVESFVPGPPRAQPSEKQCARTLKDQSSEFKAKI
IFWYVLPISITVFLFSVMGYSIYRYIHVGKEKHPANLILYGNFEDKRFFVPAEKIVINF
ITLNISSDDSKISHQDMSLLGKSSDVSSLNDPQPSGNLRPPQEEEEVKHLGYASHLMEIFC
DSEENTEGTSLTQQESLSRTIPDKTVIEYEYDVRTTDCAGPEEQELSLQEEVSTQGT
LESQAALAVLGPQTLQYSYTPQLQDLPLAQEHTDSEEGPEEEPPSTTLVDWDPQTGRLCI
PSLSSFDQDSEGCEPSEGDGLGEEGLLSRLYEPPAPDRPPGENETYLMQFMEEWGLYVQM
EN

signal sequence.
1-18

Transmembrane domain.
239-259

N-glycosylation site.
31-34
72-75
80-83
171-174
180-183
189-192
304-307
523-526

Tyrosine kinase phosphorylation site.
385-392
518-526

N-myristoylation site.
53-58
106-111
368-373
492-497

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Figure 47

GCCGCAGGCACCTCCTCGCCAGCTCTTCCGCTCCTCTCACAGCCGCCAGACCCGCCTGCT
GAGCCCCATGGCCCGCGCTGCTCTCTCCGCCGCCCCCAGCAATCCCCGGCTCCTGCGAGT
GGCACTGCTGCTCCTGCTCCTGGTAGCCGCTGGCCGGCGCGCAGCAGGAGCGTCCGTGGC
CACTGAACTGCGCTGCCAGTGCTTGCAGACCCTGCAGGGAATTCACCCCAAGAACATCCA
AAGTGTGAACGTGAAGTCCCCCGGACCCCACTGCGCCCAAACCGAAGTCATAGCCACACT
CAAGAAATGGGCGGAAAGCTTGCCTCAATCCTGCATCCCCCATAGTTAAGAAAATCATCGA
AAAGATGCTGAACAGTGACAAATCCAAGTACCAGAAGGGAGGAGGAAGCTCACTGGTGG
CTGTTCTGAAGGAGGCCCTGCCCTTATAGGAACAGAAGAGGAAAGAGAGACACAGCTGC
AGAGGCCACCTGGATTGTGCCTAATGTGTTTGAGCATCGCTTAGGAGAAGTCTTCTATTT
ATTTATTTATTCATTAGTTTTGAAGATTCTATGTTAATATTTTAGGTGTAAAATAATTAA
GGGTATGATTAACTCTACCTGCACACTGTCCTATTATATTCATTCTTTTTGAAATGTCAA
CCCCAAGTTAGTTCAATCTGGATTCATATTTAATTTGAAGGTAGAATGTTTTCAAATGTT
CTCCAGTCATTATGTTAATATTTCTGAGGAGCCTGCAACATGCCAGCCACTGTGATAGAG
GCTGGCGGATCCAAGCAAATGGCCAATGAGATCATTGTGAAGGCAGGGGAATGTATGTGC
ACATCTGTTTTGTAACTGTTTAGATGAATGTCAGTTGTTATTTATTGAAATGATTTACA
GTGTGTGGTCAACATTTCTCATGTTGAACTTTAAGAACTAAAATGTTCTAAATATCCCT
TGGACATTTTATGTCTTTCTTGTAAGGCATACTGCCTTGTTTAATGGTAGTTTTACAGTG
TTTCTGGCTTAGAACAAAGGGGCTTAATTATTGATGTTTTTCATAGAGAATATAAAAATAA
AGCACTTATAGAAAAAAAAA

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Figure 48

MARAALSAAPSNPRLRLVALLLLLLLVAAGRRAAGASVATELRCQCLQTLQGIHPKNIQSV
NVKSPGPHCAQTEVIATLKNGRKACLNPASPIVKKII EKMLNSDKSN

.

Signal sequence.
1-29

Transmembrane domain.
none

N-myristoylation site.
34-39

Amidation site.
28-31
80-83

Small cytokines (intecrine/chemokine).
35-101

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Figure 49

GCCCTTATCGATCCATGACTAGCATCTTCCATTTTGCCATTATCTTCATGTTAATACTTC
AGATCAGAATACAATTATCTGAAGAAAGTGAATTTTGTAGTTGATAGGTCAAAAAACGGTC
TCATCCACGTTCTTAAAGACCTATCCCAGAAAACAACAATCTTAAATATATCGCAAAATT
ATATATCTGAGCTTTGGACTTCTGACATCTTATCACTGTCAAAACTGAGGATTTTGATAA
TTTCTCATAATAGAATCCAGTATCTTGATATCAGTGTTTTCAAATTCAACCAGGAATTGG
AATACTTGGAATTTGTCCCACAACAAGTTGGTGAAGATTTCTTGCCACCCTACTGTGAACC
TCAAGCACTTGGAACCTGTCATTTAATGCATTTGATGCCCTGCCCTATATGCAAAGAGTTTG
GCAATATGTCTCAACTAAAATTTCTGGGGTTGAGCACCACACACTTAGAAAAATCTAGTG
TGCTGCCAATTGCTCATTTGAATATCAGCAAGGTCTTGCTGGTCTTAGGAGAGACTTATG
GGGAAAAAGAAGACCCCTGAGGGCCTTCAAGACTTTAACACTGAGAGTCTGCACATTGTGT
TCCCCACAAACAAAGAATTCCATTTTATTTTGGATGTGTGTCAGTCAAGACTGTAGCAAATC
TGGAATCTCTAATATCAAATGTGTGCTAGAAGATAACAAATGTTCTTACTTCCTAAGTA
TTCTGGCGAAACTTCAAACAAATCCAAAGTTATCAAGTCTTACCTTAAACAACATTGAAA
CAACTTGGAATTCCTTTCATTAGGATCCTCCAGCTGGTTTGGCATACAACTGTATGGTATT
TCTCAATTTCAAACGTGAAGCTACAGGGTCAGCTGGACTTCAGAGATTTTGATTATTCTG
GCACTTCCTTGAAGGCCTTGTCTATACACCAAGTTGTGTCAGCGATGTGTTCCGTTTTCCGC
AAAGTTATATCTATGAAATCTTTTCGAATATGAACATCAAAAATTTTACAGTGTCTGGTA
CACGCATGGTCCACATGCTTTGCCCATCCAAAATTAGCCCGTTCCTGCATTTGGATTTT
CCAATAATCTCTTAACAGACACGGTTTTTGAAAATTGTGGGCACCTTACTGAGTTGGAGA
CACTTATTTTACAAATGAATCAATTAAAAGAACTTTCAAAAATAGCTGAAATGACTACAC
AGATGAAGTCTCTGCAACAATTGGATATTAGCCAGAATTCTGTAAGCTATGATGAAAAGA
AAGGAGACTGTTCTTGGACTAAAAGTTTATTAAGTTTAAATATGTCTTCAAATATACTTA
CTGACACTATTTTCAGATGTTTACCTCCCAGGATCAAGGTACTTGATCTTCACAGCAATA
AAATAAGAGCATTCTTAAACAAGTCGTAAAACCTGGAAGCTTTGCAAGAACTCAATGTTG
CTTTCAATTCCTTAACTGACCTTCCTGGATGTGGCAGCTTTAGCAGCCTTTCTGTATTGA
TCATTGATCACAATTCAGTTTCCCACCCATCAGCTGATTTCTTCCAGAGCTGCCAGAAGA
TGAGGTCAATAAAAGCAGGGGACAATCCATTCCAATGTACCTGTGAGCTAGGAGAATTG
TCAAAAATATAGACCAAGTATCAAGTGAAGTGTAGAGGGCTGGCCTGATTCTTATAAGT
GTGACTACCCGGAAAGTTATAGAGGAACCTACTAAAGGACTTTTACATGTCTGAATTAT
CCTGCAACATAACTCTGCTGATCGTCACCATCGTTGCCACCATGCTGGTGTGCTGTGA
CTGTGACCTCCCTCTGCATCTACTTGGATCTGCCCTGGTATCTCAGGATGGTGTGCCAGT
GGACCCAGACCCGGCGCAGGGCCAGGAACATAACCTTAGAAGAACTCCAAAGAAATCTCC
AGTTTCATGCATTTATTTTCATATAGTGGGCACGATTCTTTCTGGGTGAAGAATGAATTAT
TGCCAAACCTAGAGAAAGAAGGTATGCAGATTTGCCTTCATGAGAGAACTTTGTTCTTG
GCAAGAGCATTGTGGAATAATCATCACCTGCATTGAGAAGAGTTACAAGTCCATCTTTG
TTTTGTCTCCCAACTTTGTCCAGAGTGAATGGTGCCATTATGAACTCTACTTTGCCCATC
ACAATCTCTTTTCATGAAGGATCTAATAGCTTAATCCTGATCTTGCTGGAACCCATTCCGC
AGTACTCCATTCCTAGCAGTTATCACAAGCTCAAAGTCTCATGGCCAGGAGGACTTATT
TGGAATGGCCCAAGGAAAAGAGCAAACGTGGCCTTTTTTGGGCTAACTTAAGGGCAGCCA
TTAATATTAAGCTGACAGAGCAAGCAAAGAAATAGAAGGGC

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Figure 50

MTSIFHFALIFMLILQIRIQLSESESEFLVDRSKNGLIHVPKDLSQKTTILNISQNYISEL
WTSIDILSLSKLRILII SHNRIQYLDISVFKFNQELEYLDLSHNKLVKISCHPTVNLKHLD
LSFNALFDALPICKEFGNMSQLKFLGLSTTHLEKSSVLPIAHLNISKVLLVLGETYGEKED
PEGLQDFNTESLHIVFPTNKEFHFI LDVSVKTVANLELSNICKVLEDNKCSYFLSILAKL
QTNPKLSSSLTLNNIETTWNSFIRILQLVWHTTVWYFSISNVKLQGQLDFRDFDYSGTSLK
ALSIHQVVS DVFGFPQSYIYEI FSNMNIKNFTVSGTRMVHMLCPSKISPFLHLDFSNNLL
TDTVFENCGLHTELETLILQMNQLKELSKIAEMTTQMKSLLQQLDISQNSVSYDEKKGDCS
WTKSLLSLNMSSNILTDTIFRCLPPRIKVLDLHSNKIKSIPKQVVKLEALQELNVAFNSL
TDLPGCGSFSSLSVLIIDHNSVSHPSADFFQSCQKMRSIKAGDNPFOCTCELGEFVKNID
QVSSEVLEGWPD SYKCDYPESYRGTLKDFHMSSELSCNITLLIVTIVATMLVLAVTVTSL
CIYLDLPWYLRMVCQWTQTRRRARNI PLEELQRNLQFHAFISYSGHDSFWVKNELLPNLE
KEGMQICLHERNFVPGKSIVENIITCIEKSYKSIFVLSPNFVQSEWCHYELYFAHHNLFH
EGNSLILILLEPI PQYSIPSSYHKLKSLMARRTYLEWPKEKSKRGLFWANLRAAINIKL
TEQAKK

Signal sequence.

none

Transmembrane domain.

1-15

582-602

N-glycosylation site.

51-54

137-140

163-166

330-333

429-432

578-581

Tyrosine kinase phosphorylation site.

90-97

N-myristoylation site.

145-150

487-492

663-668

766-771

TIR domain.

639-775

Leucine rich repeat C-terminal domain.

524-578

Leucine Rich Repeat.

70-93

94-113

115-136

140-163

349-372

373-394

399-420

424-444

446-468

469-490

491-514

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Figure 51

CACTGCCTTGCTGCAGTCACAGAATGGAAATCTGCAGAGGCCTCCGCAGTCACCTAATCA
CTCTCCTCCTCTTCTGTTCCATTCAGAGACGATCTGCCGACCCTCTGGGAGAAAATCCA
GCAAGATGCAAGCCTTCAGAATCTGGGATGTTAACCAGAAGACCTTCTATCTGAGGAACA
ACCAACTAGTTGCCGGATACTTGCAAGGACCAAATGTCAATTTAGAAGAAAAGATAGATG
TGGTACCCATTGAGCCTCATGCTCTGTTCTTGGGAATCCATGGAGGGAAGATTTGCCTGT
CCTGTGTCAAGTCTGGTGATGAGACCAGACTCCAGCTGGAGGCAGTTAACATCACTGACC
TGAGCGAGAACAGAAAGCAGGACAAGCGCTTCGCCTTCATCCGCTCAGACAGTGGCCCCA
CCACCAGTTTTTGAGTCTGCCGCCTGCCCCGGTTGGTTCCTCTGCACAGCGATGGAAGCTG
ACCAGCCCGTCAGCCTCACCAATATGCCTGACGAAGGCGTCATGGTCACCAAATTCTACT
TCCAGGAGGACGAGTAGTACTGCCCAGGCCTGCCTGTTCCCATTTCTTGCATGGCAAGGAC
TGCAGGGACTGCCAGTCCCCCTGCCCCAGGGCTCCCGGCTATGGGGGCACTGAGGACCAG
CCATTGAGGGGTGGACCCTCAGAAGGCGTCACAACAACCTGGTCACAGGACTCTGCCTCC
TCTTCAACTGACCAGCCTCCATGCTGCCTCCAGAATGGTCTTTCTAATGTGTGAATCAGA
GCACAGCAGCCCCTGCACAAAGCCCTTCCATGTCGCCTCTGCATTCAGGATCAAACCCCG
ACCACCTGCCCAACCTGCTCTCCTCTTGCCACTGCCTCTTCCTCCCTCATTCCACCTTCC
CATGCCCTGGATCCATCAGGCCACTTGATGACCCCCAACCAAGTGGCTCCACACCCTGT
TTTACAAAAAAGAAAAGACCAGTCCATGAGGGAGGTTTTTAAGGGTTTGTGGAATGAA
AATTAGGATTTTCATGATTTTTTTTTTTTTCAGTCCCCGTGAAGGAGAGCCCTTCATTTGGAG
ATTATGTTCTTTCGGGGAGAGGCTGAGGACTTAAAATATTCTGCATTTGTGAAATGATG
GTGAAAGTAAGTGGTAGCTTTTCCCTTCTTTTTTCTTTTGTGATGTCCCAACTTG
TAAAAATTAAAAGTTATGGTACTATGTT

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Figure 52

MEICRGLRSHLITLLFLFHSETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYL
QGPVNLEEKIDVVPIEPHALFLGIHGGKICLSCVKSGDETRLQLEAVNITDLSENKQD
KRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE

Signal sequence.

1-25

Transmembrane domain.

none

N-glycosylation site.

109-112

cAMP- and cGMP-dependent protein kinase phosphorylation site.

30-33

N-myristoylation site.

84-89

87-92

165-170

Amidation site.

28-31

Interleukin-1 signature.

136-156

Interleukin-1 / 18

40-177

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Figure 54

MQHRGFLLLTLLALLALTSAVAKKKDKVKKGGPGSECAEWAWGPCTPSSKDCGVGFREGT
CGAQTQRIRCRVPCNWKKEFGADCKYKFENWGACDGGTGTKVRQGTLLKKARYNAQCQETI
RVTKPCTPKTKAKAKAKKGKGKD

Signal sequence.
1-20

Transmembrane domain.
none

N-myristoylation site.
31-36
34-39
59-64
92-97
96-101

PTN/MK heparin-binding protein family signature 1.
35-59

PTN/MK heparin-binding protein family signature 2.
70-97

PTN/MK heparin-binding protein family.
1-143

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Figure 55

AGGAAAGGCTAAAGTTCTCTGGAGGATGTGGCTGCAGAGCCTGCTGCTCTTGGGCACTGT
GGCCTGCAGCATCTCTGCACCCGCCCCGCTCGCCCAGCCCCAGCACGCAGCCCTGGGAGCA
TGTGAATGCCATCCAGGAGGCCCGGCGTCTCCTGAACCTGAGTAGAGACACTGCTGCTGA
GATGAATGAAACAGTAGAAGTCATCTCAGAAATGTTTGACCTCCAGGAGCCGACCTGCCT
ACAGACCCGCTGGAGCTGTACAAGCAGGGCCTGCGGGGCAGCCTCACCAAGCTCAAGGG
CCCCCTTGACCATGATGGCCAGCCACTACAAGCAGCACTGCCCTCCAACCCCGGAAACTTC
CTGTGCAATCCAGACTATCACCTTTGAAAGTTTCAAAGAGAACCTGAAGGACTTTCTGCT
TGTCATCCCCCTTTGACTGCTGGGAGCCAGTCCAGGAGTGAGACCGGCCAGATGAGGCTGG
CCAAGCCGGGGAGCTGCTCTCTCATGAAACAAGAGCTAGAAACTCAGGATGGTCATCTTG
GAGGGACCAAGGGGTGGGCCACAGCCATGGTGGGAGTGGCCTGGACCTGCCCTGGGCCAC
ACTGACCCTGATACAGGCATGGCAGAAGAATGGGAATATTTTATACTGACAGAAATCAGT
AATATTTATATATTTATATTTTTTAAAATATTTATTTATTTATTTAAGTTCATATTC
CATATTTATTCAAGATGTTTTACCGTAATAATTATTATTAAAAATATGCTTCTACTTA

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Figure 56

MWLQSLLLLGTVACSI SAPARSPSPSTQPWEHVNAIQEARRLLNLSRDTAAEMNETVEVI
SEMFDLQEP TCLQTRLELYKQGLRGSLTKLKGPLTMMASHYKQHCPPTPETS CAIQTITF
ESFKENLKDFLLVIPFDCWEPVQE

Signal sequence.
1-17

Transmembrane domain.
none

N-glycosylation site.
44-47
54-58

N-myristoylation site.
10-15
82-87

Granulocyte-macrophage colony-stimulating factor signature.
105-113

Granulocyte-macrophage colony-stimulating factor
18-139

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Figure 57

AAGGCTCGATTTCATCGCCTTCGTTTGCATACGGCGATGCTGACAGCTCTCCAACCTCTCCC
CTAGGATGGGGGACAAGATGGGGGCTTGAGATAAGCCCCCTTCCCCTCCCTGGGAGGAGCC
AATGGCTGGGCCTGCCATCCACACCGCTCCCATGCTGTTCTCGTCCTCCTGCTGCCCCCT
GGAGCTGAGCCTGGCAGGCGCCCTTGACCTGGGACCCCTGCCCGGAACCTCCCTGAGAA
TCACATTGACCTCCCAGGCCCAGCGCTGTGGACGCCTCAGGCCAGCCACCACCGCCGGCG
GGGCCCCGGGCAAGAAGGAGTGGGGCCCAGGCCTGCCAGCCAGGCCAGGATGGGGCTGT
GGTCACCGCCACCAGGCAGGCCTCCAGGCTGCCAGAGGCTGAGGGGCTGCTGCCTGAGCA
GAGTCCTGCAGGCCTGCTGCAGGACAAGGACCTGCTCCTGGGACTGGCATTGCCCTACCC
CGAGAAGGAGAACCGACCTCCAGGTTGGGAGAGGACCAGGAAACGCAGCAGGGAGCACA
GAGACGCAGGGACAGGTTGAGGCTGCACCAAGGCCGAGCCTTGGTCCGAGGTCCCAGCTC
CCTGATGAAGAAGGCAGAGCTCTCCGAAGCCCAGGTGCTGGATGCAGCCATGGAGGAATC
CTCCACCAGCCTGGCGCCCACCATGTTCTTTCTCACCACCTTTGAGGCAGCACCTGCCAC
AGAAGAGTCCCTGATCCTGCCCCGTCACCTCCCTGCGGGCCCCAGCAGGCACAGCCCAGGTC
TGACGGGGAGGTGATGCCACGCTGGACATGGCCTTGTTTCGACTGGACCGATTATGAAGA
CTTAAACCTGATGGTTGGCCCTCTGCAAAGAAGAAAGAGAAACACCGCGGTAAACTCTC
CAGTGATGGTAACGAAACATCACCAGCCGAAGGGGAACCATGCGACCATCACCAAGACTG
CCTGCCAGGGACTTGCTGCGACCTGCGGGAGCATCTCTGCACACCCCACAACCGAGGCCT
CAACAACAAATGCTTCGATGACTGCATGTGTGTGGAAGGGCTGCGCTGCTATGCCAAATT
CCACCGGAACCGCAGGGTTACACGGAGGAAAGGGCGCTGTGTGGAGCCCGAGACGGCCAA
CGGCGACCAGGGATCCTTCATCAACGTCTAGCGGCCCCGTGGGACTGGGGACTGAGCCCA
GGAGGTTTGCACAAGCCGGGCGATTTGTTTGTAAGTAGCAGTGGGAGATCAAGTTGGGGA
ACAGATGGCTGAGGCTGCAGACTCAGGCCCAGGACACTCAACCCCAGGAGGGGAGCCGCT
CGGCGAATGAGCTGGGTGGGTGCCAGGAGCCGGCCCCGAGCACCTGCACACACGAAGTC
CGGACCCACGCAGCCTCCATCCCGCGTGTCTTGCTCTCCGCGATGGCAATGCCGAGAGTG
CCCTATACTGTCCGACTCCAGCACTGCAACAGCTTCAAGTTCAAAACCAAGAGGCGTTTT
TGAGAGTGGAAGAAATTTAAACTTCCCGAAAGAAGGTCCACCATCAGGAGATGAATAT
GGAACATCTCCTATGTACCAGGCACTGT

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Figure 58

MAGPAIHTAPMLFLVLLLPLELSLAGALAPGTPARNLPENHIDLPGPALWTPQASHHRRR
GPGKKEWGPGGLPSQAQDGAVVTATRQASRLPEAEGLLPEQSPAGLLQDKDLLLGLALPYP
EKENRPPGWERTRKRSREHKRRRDRLRLHQGRALVRGPSSLMKKAELSEAQVLDAAMEES
STSLAPTMFFLTTFEAPATEESLILPVTSLRPQQAQPRSDGEVMPITLDMALFDWTDYED
LKPDGWPSAKKKEKHRGKLSSDGNETSPAEGEPCDHHQDCLPGTCCDLREHLCTPHNRGL
NNKCFDDCMCVEGLRCYAKFHRNRRVTRRKGRGCVETANGDQGSFINV

Signal sequence.

1-25

Transmembrane domain.

none

N-glycosylation site.

264-267

cAMP- and cGMP-dependent protein kinase phosphorylation site.

133-136

324-327

N-myristoylation site.

78-83

344-349

Amidation site.

62-65

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Figure 59

GGGAGGGCTCTGTGCCAGCCCCGATGAGGACGCTGCTGACCATCTTGACTGTGGGATCCC
TGGCTGCTCACGCCCCCTGAGGACCCCTCGGATCTGCTCCAGCACGTGAAATTCCAGTCCA
GCAACTTTGAAAACATCCTGACGTGGGACAGCGGGCCAGAGGGCACCCCAGACACGGTCT
ACAGCATCGAGTATAAGACGTACGGAGAGAGGGACTGGGTGGCAAAGAAGGGCTGTCAGC
GGATCACCCGGAAGTCCTGCAACCTGACGGTGGAGACGGGCAACCTCACGGAGCTCTACT
ATGCCAGGGTCACCGCTGTCAGTGCGGGAGGCCGGTCAGCCACCAAGATGACTGACAGGT
TCAGCTCTCTGCAGCACACTACCCCTCAAGCCACCTGATGTGACCTGTATCTCCAAAGTGA
GATCGATTTCAGATGATTGTTTCATCCTACCCCCACGCCAATCCGTGCAGGCGATGGCCACC
GGCTAACCCTGGAAGACATCTTCCATGACCTGTTCTACCACTTAGAGCTCCAGGTCAACC
GCACCTACCAAATGCACCTTGGAGGGGAAGCAGAGAGAATATGAGTTCTTCGGCCTGACCC
CTGACACAGAGTTCCTTGGCACCATCATGATTTGCGTTCCCACCTGGGCCAAGGAGAGTG
CCCCCTACATGTGCCGAGTGAAGACACTGCCAGACCGGACATGGACCTACTCCTTCTCCG
GAGCCTTCCTGTTCTCCATGGGCTTCCTCGTCGCAGTACTCTGCTACCTGAGCTACAGAT
ATGTCACCAAGCCGCTGCACCTCCCAACTCCCTGAACGTCCAGCGAGTCCCTGACTTTCC
AGCCGCTGCGCTTCATCCAGGAGCACGTCCCTGATCCCTGTCTTTGACCTCAGCGGCCCA
GCAGTCTGGCCCAGCCTGTCCAGTACTCCAGATCAGGGTGTCTGGACCCAGGGAGCCCCG
CAGGAGCTCCACAGCGGCATAGCCTGTCCGAGATCACCTACTTAGGGCAGCCAGACATCT
CCATCCTCCAGCCCTCCAACGTGCCACCTCCCCAGATCCTCTCCCCACTGTCCTATGCCC
CAAACGCTGCCCCCTGAGGTCGGGCCCCCATCCTATGCACCTCAGGTGACCCCCGAAGCTC
AATTCCCATTCTACGCCCCACAGGCCATCTCTAAGGTCCAGCCTTCCTCCTATGCCCCCTC
AAGCCACTCCGGACAGCTGGCCTCCCTCCTATGGGGTATGCATGGAAGGTTCTGGCAAAG
ACTCCCCCACTGGGACACTTTCTAGTCCTAAACACCTTAGGCCTAAAGGTCAGCTTCAGA
AAGAGCCACCAGCTGGAAGCTGCATGTTAGGTGGCCTTTCTCTGCAGGAGGTGACCTCCT
TGGCTATGGAGGAATCCCAAGAAGCAAAATCATTGCACCAGCCCCTGGGGATTTGCACAG
ACAGAACATCTGACCCAAATGTGCTACACAGTGGGGAGGAAGGGACACCACAGTACCTAA
AGGGCCAGCTCCCCCTCCTCTCCTCAGTCCAGATCGAGGGCCACCCCATGTCCCTCCCTT
TGCAACCTCCTTCCGGTCCATGTTCCCCCTCGGACCAAGGTCCAAGTCCCTGGGGCCTGC
TGGAGTCCCTTGTGTGTCCCAAGGATGAAGCCAAGAGCCCAGCCCCTGAGACCTCAGACC
TGGAGCAGCCCACAGAACTGGATTCTCTTTTCAGAGGCCTGGCCCTGACTGTGCAGTGGG
AGTCCTGAGGGGAATGGGAAGGCTTGGTGCTTCCTCCCTGTCCCTACCCAGTGTACAT
CCTTGGCTGTCAATCCCATGCCTGCCATGCCACACACTCTGCGATCTGGCCTCAGACGG
GTGCCCTTGAGAGAAGCAGAGGGAGTGGCATGCAGGGCCCCCTGCCATGGGTGCGCTCCTC
ACCGGAACAAAGCAGCATGATAAGGACTGCAGCGGGGGAGCTCTGGGGAGCAGCTTGTGT
AGACAAGCGCGTGCTCGCTGAGCCCTGCAAGGCAGAAATGACAGTGCAAGGAGGAAATGC
AGGGAAACTCCCGAGGTCCAGAGCCCCACCTCCTAACACCATGGATTCAAAGTGCTCAGG
GAATTTGCCTCTCCTTGCCCCATTCTGGCCAGTTTCACAATCTAGCTCGACAGAGCATG
AGGCCCTGCCTCTTCTGTCAATTGTTCAAAGGTGGGAAGAGAGCCTGGAAAAGAACCAGG
CCTGGAAAAGAACCAGAAGGAGGCTGGGCAGAACCAGAACAACCTGCACTTCTGCCAAGG
CCAGGGCCAGCAGGACGGCAGGACTCTAGGGAGGGGTGTGGCCTGCAGCTCATTTCCAGC
CAGGGCAACTGCCTGACGTTGCACGATTTTCAGCTTCATTCCTCTGATAGAACAAAGCGAA
ATGCAGGTCCACCAGGGAGGGAGACACACAAGCCTTTTCTGCAGGCAGGAGTTTCAGACC
CTATCCTGAGAATGGGGTTTGAAAGGAAGGTGAGGGCTGTGGCCCCCTGGACGGGTACAAT
AACACACTGTACTGATGTCACAACCTTTGCAAGCTCTGCCTTGGGTTTCAGCCCATCTGGGC
TCAAATTCAGCCTCACCCTCACAAGCTGTGTGACTTCAAACAAATGAAATCAGTGCCC
AGAACCTCGGTTTCTCATCTGTAATGTGGGGATCATAACACCTACCTCATGGAGTTGTG
GTGAAGATGAAATGAAGTCATGTCTTTAAAGTGCTTAATAGTGCCTGGTACATGGGCAGT
GCCCAATAAACGGTAGCTATTTAAAAA

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Figure 60

MRTLLTILTVGSLAAHAPEDPSDLLQHVKEFQSSNFENILTWDSGPEGTPDTVYSIEYKTY
GERDWVAKKGCQRITRKSCNLTVETGNLTELYARVTAVSAGGRSATKMTDRFSSLQHTT
LKPPDVTCTISKVRSIQMIVHPTPTPIRAGDGHRLTLEDIFHDLFYHLELQVNRTYQMHLG
GKQREYEFFGLTPDTEFLGTIMICVPTWAKESAPYMCRVKTLPDRTWTYSFSGAFLFSMG
FLVAVLCYLSYRYVTKPPAPPNSLNVQRVLTQPLRFIQEHVLI PVFDLSGPSSLAQPVQ
YSQIRVSGPREPAGAPQRHSLSEITYLGQPDISILOPSNVPPPQILSPLSYAPNAAPEVG
PPSYAPQVTPAQFPFYAPQAIKVVQPSYAPQATPDSWPSPSYGVCMEGSGKDSPTGTLS
SPKHLRPKGQLQKEPPAGSCMLGGLSLQEVTS LAMEESQEAKSLHQPLGICTDRTSDPNV
LHSGEEGTPQYLKGQLPLLSSVQIEGHPMSLPLQPPSGPCSPSDQGPSPWGLLESLVCPK
DEAKSPAPETSDLEQPTELDSLFRGLALTVQWES

Signal sequence.

1-17

Transmembrane domain.

229-249

N-glycosylation site.

80-83

87-90

172-175

N-myristoylation site.

11-16

47-52

102-107

531-536

565-570

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Figure 61

AGCCACCAGCGCAACATGACAGTGAAGACCCTGCATGGCCCAGCCATGGTCAAGTACTTG
CTGCTGTCGATATTGGGGCTTGCCTTTCTGAGTGAGGCGGCAGCTCGGAAAATCCCCAAA
GTAGGACATACTTTTTTCCAAAAGCCTGAGAGTTGCCCGCCTGTGCCAGGAGGTAGTATG
AAGCTTGACATTGGCATCATCAATGAAAACCAGCGCGTTTCCATGTCACGTAACATCGAG
AGCCGCTCCACCTCCCCCTGGAATTACACTGTCACTTGGGACCCCAACCGGTACCCCTCG
GAAGTTGTACAGGCCCCAGTGTAGGAACTTGGGCTGCATCAATGCTCAAGGAAAGGAAGAC
ATCTCCATGAATTCCGTTCCCATCCAGCAAGAGACCCTGGTCGTCCGGAGGAAGCACCAA
GGCTGCTCTGTTTCTTTCCAGTTGGAGAAGGTGCTGGTGACTGTTGGCTGCACCTGCGTC
ACCCCTGTCATCCACCATGTGCAGTAAGAGGTGCATATCCACTCAGCTGAAGAAG

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Figure 62

MTVKTLHGPAMVKYLLLSILGLAFLSEAAARKIPKVGHTFFQKPESCPPVPGGSMKLDIG
IINENQRVSMRNIESRSTSPWNYTVTWDPNRYPSEVVQAQCRNLGCINAQGKEDISMNS
VPIQQETLVVRRKHQGCSVSFQLEKVLVTVGCTCVTPVIHHVQ

Signal sequence.
1-30

Transmembrane domain.
none

N-glycosylation site.
83-88

N-myristoylation site.
106-111
136-141

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Figure 63

AATGAGCACCAAACCTGATATGATTCAAAAGTGTTTGTGGCTTGAGATCCTTATGGGTAT
ATTCATTGCTGGCACCCCTATCCCTGGACTGTAACCTTACTGAACGTTACCTGAGAAGAGT
CACCTGGCAAAATCTGAGACATCTGAGTAGTATGAGCAATTCATTTCTGTAGAATGTCT
ACGAGAAAACATAGCTTTTGTAGTTGCCCCAAGAGTTTCTGCAATACACCCAACCTATGAA
GAGGGACATCAAGAAGGCCTTCTATGAAATGTCCCTACAGGCCTTCAACATCTTCAGCCA
ACACACCTTCAAATATTGGAAAGAGAGACACCTCAAACAAATCCAAATAGGACTTGATCA
GCAAGCAGAGTACCTGAACCAATGCTTGGAGGAAGACGAGAATGAAAATGAAGACATGAA
AGAAATGAAAGAGAATGAGATGAAACCCTCAGAAGCCAGGGTCCCCCAGCTGAGCAGCCT
GGAAGTGAAGGAGATATTTCCACAGGATAGACAATTTCTGAAAGAAAAGAAATACAGTGA
CTGTGCCTGGGAGATTGTCCGAGTGGAAATCAGAAGATGTTTGTATTACTTTTACAAATT
TACAGCTCTATTCAGGAGGAAATAAGGTATAT

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Figure 64

MSTKPDMIQKCLWLEILMGIFIAGTSLDCNLLNVHLRRVTWQNLRLHLSSMSNSFPVECL
RENIAFELPQEFLOYTQPMKRDIKKAFYEMSLQAFNIFSQHTFKYWKERHLKQIQIGLDQ
QAEYLNQCLEEDENENEDMKEMKENEMKPSEARVPQLSSLELRRYFHRIDNFLKEKKYSD
CAWEIVRVEIRRCLYYFYKFTALFRRK

Signal sequence.
1-27

Transmembrane domain.
none

cAMP- and cGMP-dependent protein kinase phosphorylation site.
38-41
176-179

N-myristoylation site.
19-24

Interferon alpha, beta and delta family signature.
165-183

Interferon Interferon alpha/beta domain.
7-207

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Figure 65

GTCCGGGAGTTTGGGACCGGCCCGGGCAGCATTTGTGAGGTCTCGTCTCTGCGGAGAATAC
GGAAGTTAGCTGAGCATGGTGGTACACACCTGTGGTCCCGGCTGCTTGGGAGGCTGGGGT
GGGGGGATCATTTGAGCCCCGGGAATTC AAGGCTGCAGTGAGCTATGTTGCCGCCACTGCA
ATCCAGCCTGGGCAACATAGCCAGACCCTGTCTCTGAAAAAAGAAAAAAGTCT
GGTTTCTGAACCAGCAGGATCAATGTCACCTGGGAACTGGTTGGAAATGCAGATTCTTAG
ATATGTTCCATACCTGTTGAGTCAGGAGCTCTGCAGGTGGGACACAAAGATATGTGTTTT
GTTTGTTTGTTTTTGAGACTCCGTCTAAACAAGCAAACAAATAAACAATAAAATGC
TTACAGTAGTGTGCCTGGCCTCGTAGCACATACTGCACTGGGCGTTCACTGCTATTATGA
TCTTCGAAGAGGTCCAGGACCCTAACGTTGTGGGGATCTGGTTGTGTACCTTACCCCGC
CTTTTGGGATTATGCGTTTCTGGTCTCTGCAGGTTGGAGACCTTCTCGCCTCTCTGTCAA
TGATGTTGACAATAAGCTGGGCCACATCACCTGTCCCTAGCGAAAGGTTATCACTTCGC
TGGGGACATGAGAAAGGTCGGGTTGGGGGGGCGTGCCTGTCTCCCCTCTGCTGGAGAAG
ATAAGGGAGGCACTCAGCTTTCCTCAGGCAGAGTGTGGGGGAGCCACGATGTATAAATGG
GGGGCCAAGAGGCAGCAGAGACACTGGCCCACTCTCACGTTCAAAGCGTCTCCGTCCAGC
ATGGCCAGGTACATGCTGCTGCTGCTCCTGGCGGTATGGGTGCTGACCGGGGAGCTGTGG
CCGGGAGCTGAGGCCCGGGCAGCGCCTTACGGGGTCAGGCTTTGCGGCCGAGAATTCATC
CGAGCAGTCATCTTCACCTGCGGGGGCTCCCGGTGGAGACGATCAGACATCCTGGCCAC
GAGGCTATGGGAGATACCTTCCCGGATGCAGATGCTGATGAAGACAGTCTGGCAGGCGAG
CTGGATGAGGCCATGGGGTCCAGCGAGTGGCTGGCCCTGACCAAGTCACCCAGGCCTTT
TACAGGGGGCGACCCAGCTGGCAAGGAACCCCTGGGGTTCTTCGGGGCAGCCGAGATGTC
CTGGCTGGCCTTTCCAGCAGCTGCTGCAAGTGGGGGTGTAGCAAAAGTGAAATCAGTAGC
CTTTGCTAGTTTGAGGGCTGGGCAGCCGTGGGCACCAGGACCAATGCCCCAGTCCTGCCA
TCCACTCAACTAGTGTCTGGCTGGGCACCTGTCTTTTCGAGCCTCACACATTCATTCATTC
ATCTACAAGTCACAGAGGCACTGTGGGCTCAGGCACAGTCTCCCGACACCACCTATCCAA
CCCTGCCCTTTGACCAGCCTATCATGACCCTGGCCCCCTAAGGAAGCTGTGCCCTGCCTG
GTCAAGTGGGGACCCCCCATCCTGACCCCTGACCTCTCCCCAGCCCTAACCATGCGTTT
GCCTGGCCTACACACTCCACTGCCACAACCTGGGTCCCTACTCTACCTAGGCTGGCCACAC
AGAGACCCCTGCCCCCTTCCAGTCCAAACTGTGGCCATTTGTCCCCTGACCAGCTAAAAAT
CAAGCCTCTGTCTCAGTCCAGCCTTTGCACGCACGCTTCCTTTGCCCTGCTTTCCATCCC
CTCTCCCTCCAACCTCCCTGCCAGAGTTCCAAGGCTGTGGACCCAGAGAAGGTGGCAGG
TGGCCCCCTAGGAGAGCTCTGGGCACATTCGAATCTTCCCAAACCTCCAATAATAAAAT
TCGAAGACTTTGGCNGAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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Figure 66

MYKWGAKRQQRHWPTLTFKASPSSMARYMLLLLLLAVWVLTGELWPGAEARAAPYGVRLCG
REFIRAVIFTCCGSRWRRSDILAHEAMGDTFPDADADEDSLAGELEAMGSSEWLALTKS
PQAFYRGRPSWQGTPGVLRGSRDVLAGLSSSCCKWGCSKSEISLC

Signal sequence.
1-41

Transmembrane domain.
none

N-myristoylation site.
55-60
136-141
147-152
156-161

Insulin family signature.
152-166

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Figure 67

ATGGAACAACGGGGACAGAACGCCCCGGCCGCTTCGGGGGGCCCGGAAAAGGCACGGCCCA
GGACCCAGGGAGGCGCGGGGAGCCAGGCCTGGGCCCCGGGTCCCCAAGACCCTTGTGCTC
GTTGTCGCCGCGGTCTTGCTGTTGGTCTCAGCTGAGTCTGCTCTGATCACCCAACAAGAC
CTAGCTCCCCAGCAGAGAGCGGGCCCCACAACAAAAGAGGTCCAGCCCCCTCAGAGGGATTG
TGTCCACCTGGACACCATATCTCAGAAGACGGTAGAGATTGCATCTCCTGCAAATATGGA
CAGGACTATAGCACTCACTGGAATGACCTCCTTTTCTGCTTGCGCTGCACCAGGTGTGAT
TCAGGTGAAGTGGAGCTAAGTCCCTGCACCACGACCAGAAACACAGTGTGTGTCAGTGCGAA
GAAGGCACCTTCCGGGAAGAAGATTCTCCTGAGATGTGCCGGAAGTGCCGCACAGGGTGT
CCCAGAGGGATGGTCAAGGTCGGTGATTGTACACCCTGGAGTGACATCGAATGTGTCCAC
AAAGAATCAGGCATCATCATAGGAGTCACAGTTGCAGCCGTAGTCTTGATTGTGGCTGTG
TTTGTTTGCAAGTCTTTACTGTGGAAGAAAGTCCTTCCTTACCTGAAAGGCATCTGCTCA
GGTGGTGGTGGGGACCCTGAGCGTGTGGACAGAAGCTCACACGACCTGGGGCTGAGGAC
AATGTCCTCAATGAGATCGTGAGTATCTTGCAGCCCACCCAGGTCCCTGAGCAGGAAATG
GAAGTCCAGGAGCCAGCAGAGCCAACAGGTGTCAACATGTTGTCCCCCGGGGAGTCAGAG
CATCTGCTGGAACCGGCAGAAGCTGAAAGGTCTCAGAGGAGGAGGCTGCTGGTTCCAGCA
AATGAAGGTGATCCCACTGAGACTCTGAGACAGTGCTTCGATGACTTTGCAGACTTGGTG
CCCTTTGACTCCTGGGAGCCGCTCATGAGGAAGTTGGGCCTCATGGACAATGAGATAAAG
GTGGCTAAAGCTGAGGCAGCGGGCCACAGGGACACCTTGTACACGATGCTGATAAAGTGG
GTCAACAAAACCGGGCGAGATGCCTCTGTCCACACCCTGCTGGATGCCTTGGAGACGCTG
GGAGAGAGACTTGCCAAGCAGAAGATTGAGGACCACTTGTGAGCTCTGGAAAGTTCATG
TATCTAGAAGGTAATGCAGACTCTGCCATGTCCTAA

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Figure 68

MEQRGQNAPAAASGARKRHGPGPREARGARPGPRVPKTLVLVVAAVLLLVSAESALITQQD
LAPQQRAAPQQKRSSPSEGLCPPGHHISEDGRDCISCKYGQDYSTHWNDLLFCLRCTRCD
SGEVELSPCTTTRNTVCQCEEGTFREEDSPEMCRKCRTGCPRGMVKVGDCTPWSDIECVH
KESGIIIGVTVAAVVLIVAVFVCKSLLWKKVLPYLGICSGGGGDPERVDRSSQRPGAED
NVLNEIVSILQPTQVPEQEMEVEQEPAEPTGVNMLSPGESEHLLPEAEAEERSQRRRLVPA
NEGDPTETLRQCFDDFADLVPFDSWEPLMRKLGLMDNEIKVAKAEAAGHRDTLYTMLIKW
VNKTGRDASVHTLLDALETGERLAKQKIEDHLLSSGKFMYLEGNADSAMS

Signal sequence.
none

Transmembrane domain.
32-52
186-206

N-glycosylation site.
362-365

Glycosaminoglycan attachment site.
220-223

cAMP- and cGMP-dependent protein kinase phosphorylation site.
72-75.

N-myristoylation site.
100-105
159-164
184-189
188-193
217-222
237-242
333-338
404-409

TNFR/NGFR cysteine-rich region.
97-137
139-178

Death domain.
311-393

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Figure 69

ATGAGGATATTTGCTGTCTTTATATTCATGACCTACTGGCATTGCTGAACGCATTTACT
GTCACGGTTCCCAAGGACCTATATGTGGTAGAGTATGGTAGCAATATGACAATTGAATGC
AAATTCCCAGTAGAAAAACAATTAGACCTGGCTGCACTAATTGTCTATTGGGAAATGGAG
GATAAGAACATTATTCAATTTGTGCATGGAGAGGAAGACCTGAAGGTTTCAGCATAGTAGC
TACAGACAGAGGGCCCGGCTGTTGAAGGACCAGCTCTCCCTGGGAAATGCTGCACTTCAG
ATCACAGATGTGAAATTGCAGGATGCAGGGGTGTACCGCTGCATGATCAGCTATGGTGGT
GCCGACTACAAGCGAATTACTGTGAAAGTCAATGCCCCATACAACAAAATCAACCAAAGA
ATTTTGGTTGTGGATCCAGTCACCTCTGAACATGAACTGACATGTCAGGCTGAGGGCTAC
CCAAGGCCGAAGTCATCTGGACAAGCAGTGACCATCAAGTCCTGAGTGGTAAGACCACC
ACCACCAATTCCAAGAGAGAGGAGAAGCTTTTCAATGTGACCAGCACACTGAGAATCAAC
ACAACAATAATGAGATTTTCTACTGCACTTTTAGGAGATTAGATCCTGAGGAAAACCAT
ACAGCTGAATTGGTCATCCCAGAACTACCTCTGGCACATCCTCCAAATGAAAGGACTCAC
TTGGTAATTCTGGGAGCCATCTTATTATGCCTTGGTGTAGCACTGACATTCATCTTCCGT
TTAAGAAAAGGGAGAATGATGGATGTGAAAAAATGTGGCATCCAAGATACAAACTCAAAG
AAGCAAAGTGATACACATTTGGAGGAGACGTAA

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Figure 70

MRIFAVFIFMTYWHLNNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEME
DKNIIQFVHGEE DLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGG
ADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTT
TTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTH
LVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQDTNSKKQSDTHLEET

Signal sequence.

1-18

Transmembrane domain.

238-258

N-glycosylation site.

35-38

192-195

200-203

219-222

Tyrosine kinase phosphorylation site.

105-112

N-myristoylation site.

33-38

110-115

252-257

273-278

Immunoglobulin domain.

33-116

148-211

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Figure 71

AAGCTTGCGCGCCATGTAAGGTAAAGTGACTGATTCTATAGCAATCCAATTGTTTCCTTTG
TCTGCCCCGTTTACATATAACAATGTTGTCAATGTTTGATTGAAAATACCTAGCAGGCGAC
ACACACACACCTAGCTCCTCAGGCGGAGAGCACCCCTTTCTTGGCCACCCGGGTATCCCC
CAGGGAGTACGGGGCTCAAAACACCCTTTTGGAGAACAAGGTGGAAGCAAATTTTCAGGAA
GTAAAACTTCCTGAAATAAAATAAAATATCGAATGCCTTGAGACCCATACATTTTTCAGGT
TTTCCTAATTAAAGCAATTACTTTCACCACCCCTCCAACCTGGAATCACCAACTTGTTT
AGAGAACTGATTTTTCTTTTTCTTTTTTTTTTCCCAAAGAGTACATCTGATCATTTTA
GCCTGCAACTAATGATAGAGATATTAGGGCTAGTTAACCACAGTTTTTACAAGACTCCTCT
CCCGCGTGTGGGCCATTGTCATGCTGTCGGTCCCGCCACCTGAAAGGTCTCCCCGCCCC
GACTGGGGTTTGTGTTGAAGAAGGAGAATCCCCGGAAGGCTGAGTCTCCAGCTCAAGG
TCAAAACGTCCAAGGCCGAAAGCCCTCCAGTTTCCCCTGGACACCTTGCTCCTGCTTCTG
CTACGACCTTCTGGGAACGCGAATTTCTCATTTTTCTTCTTAAATTGCCATTTTCGCTTTA
GGAGATGAATGTTTTCTTTGGCTGTTTTTGGCAATGACTCTGAATTAAAGCGATGCTAAC
GCCTCTTTTCCCCCTAATTGTTAAAAGCTATGGACTGCAGGAAGATGGTCCGCTTCTCTT
ACAGTGTGATTTGGATCATGGCCATTTCTAAAGCCTTTGAACTGGGATTAGTTGCCGGGC
TGGGCCATCAGGAATTTGCTCGTCCATCTCGGGGAGACCTGGCCTTCAGAGATGACAGCA
TTTGGCCCCAGGAGGAGCCTGCAATTCGGCCTCGGTCTTCCCAGCGTGTGCTGCCCATGG
GAATACAGCACAGTAAGGAGCTAAACAGAACCTGCTGCCTGAATGGGGGAACCTGCATGC
TGGAGTCCTTTTGTGCCTGCCCTCCCTCCTTCTACGGACGGAACCTGTGAGCACGATGTGC
GCAAAGAGAACTGTGGGTCTGTGCCCCATGACACCTGGCTGCCCAAGAAGTGTTCCTGT
GTAAATGCTGGCACGGTCAGCTCCGCTGCTTTCTCAGGCATTTCTACCCGGCTGTGATG
GCCTTGTGATGGATGAGCACCTCGTGGCTTCCAGGACTCCAGAACTACCACCGTCTGCAC
GTACTACCACTTTTATGCTAGCTGGCATCTGCCTTTCTATACAAAGCTACTATTAATCGA
CATTGACCTATTTCCAGAAATACAATTTTAGATATTTATGCAAATTTTCATGACCCGTAAAG
GCTGCTGCTACAATGTCCTAACTGAAAGATGATCATTTGTAGTTGCCTTAAAATAATGAA
TACAATTTCCAAAACGGTCTCTAACATTTCTTACAGAACTAACTACTTCTTACCTCTTT
GCCCTGCCCTCTCCCAAAAACTACTTCTTTTTTCAAAGAAAGTCAGCCATATCTCCAT
TGTGCCCAAGTCCAGTGTTTCTTTTTTTTTTTTTTGAGACGGAGTCTCACTCTGTCACCCAG
GCTGGACTGCAATGACGCGATCTCGGTTCACTGCAACCTCCGCATCCGGGGTTCAAGCCA
TTCTCCTGCCTCAGCCTCCCAAGTAGCTGGGATTACAGGCATGTGTCACCATGCCGGCTA
ATTTTTTTGTATTTTAGTAGAGACGGGGGTTTCACCATATTGGCCAGCTGGTCTCGAACT
CTGACCTTGTGATCCATCGCTCGCCTCTCGAGTGCTGAGATTACACACGTGAGCAACTGT
GCAAGGCCTGGTGTTTCTTGATACATGTAATTCTACCAAGGTCTTCTTAATATGTTCTTT
TAAATGATTGAATTATACACTCAGATTATTGGAGACTAAGTCTAATGTGGACCTTAGAAT
ACAGTTTTGAGTAGAGTTGATCAAAATCAATTAAAATAGTCTCTTTAAAAGGAAAGAAAA
CATCTTTAAGGGGAGGAACCAGAGTGCTGAAGGAATGGAAGTCCATCTGCGTGTGTGCAG
GGAGACTGGGTAGGAAAGAGGAAGCAAATAGAAGAGAGAGGTTGAAAAACAAAATGGGTT
ACTTGATTGGTGATTAGGTGGTGGTAGAGAAGCAAGTAAAAAGGCTAAATGGAAGGGCAA
GTTTCCATCATCTATAGAAAGCTATGTAAGACAAGGACTCCCCTTTTTTTTCCCAAAGGCA
TTGTAAAAAGAATGAAGTCTCCTTAGAAAAAAAATTATACCTCAATGTCCCAACAAGAT
TGCTTAATAAATTGTGTTTCTCCTCAAGCTATTCAATTCTTTTAACTGTTGTAGAAGAGAA
AATGTTTCACAATATATTTAGTTGTAAACCAAGTGATCAAACCTACATATTGTAAAGCCCAT
TTTTTAAATACATTGTATATATGTGTATGCACAGTAAAAATGGAACTATATTGACCTAA
AAAAAAAAAAGGAAACCACCTTAGGCAGGCAGGACATGCTCTTCAGAACTCTGCTCTT
CAGAGTTCCAAAGAAGGGATAAAACATCTTTTATXXCCATCAAATAGC

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Figure 72

MDCRKMVRFSYSVIWIMAIKAFELGLVAGLGHQEFARPSRGDLAFRDDSIWPQEEPAIR
PRSSQRVLPMTGIQHSKELNRTCCLNGGTCMLESFCACPPSFYGRNCEHDVRKENCGSVPH
DTWLPKKCSLCKCWHGQLRCFPQAFLPGCDGLVMDEHLVASRTPELPPSARTTTFMLAGI
CLSIQSY

Signal sequence.
1-18

Transmembrane domain.
none

N-glycosylation site.
79-82

cAMP- and cGMP-dependent protein kinase phosphorylation site.
126-129

N-myristoylation site.
26-31
71-76
136-141
179-184

Cell attachment sequence.
41-43

EGF-like domain cysteine pattern signature.
95-106

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Figure 73

GTGAAGGGAGCCGGGATCAGCCAGGGGCCAGCATGAGCCGGAGGGAGGGAAGTCTGGAAG
ACCCCCAGACTGATTCCCTCAGTCTCACTTCTTCCCCACTTGGAGGCCAAGATCCGTCAGA
CACACAGCCTTGCGCACCTCCTCACCAAATACGCTGAGCAGCTGCTCCAGGAATATGTGC
AGCTCCAGGGAGACCCCTTCGGGCTGCCAGCTTCTCGCCGCCGCGGCTGCCGGTGGCCG
GCCTGAGCGCCCCGGCTCCGAGCCACGCGGGGCTGCCAGTGCACGAGCGGCTGCGGCTGG
ACGCGGCGGCGCTGGCCGCGCTGCCCCGCTGCTGGACGCAGTGTGTTCGCCGCCAGGCCG
AGCTGAACCCGCGCGCGCCGCGCCTGCTGCGCCGCTGGAGGACGCGGCGCGCCAGGCC
GGGCCCTGGGCGCCGCGCTGGAGGCCTTGCTGGCCGCGCTGGGCGCCGCCAACC GCGGGC
CCCGGGCCGAGCCCCCGCCGCCACCGCCTCAGCCGCCTCCGCCACCGGGGTCTTCCCCG
CCAAGGTGCTGGGGCTCCGCGTTTGCGGCCTCTACCGCGAGTGGCTGAGCCGCACCGAGG
GCGACCTGGGCCAGCTGCTGCCCGGGGCTCGGCCTGAGCGCCGCGGGGCAGCTCGCCCC
GCCTCCTCCCGCTGGGTTCGCTCTCTCCTTCCGCTTCTTTGTCTTTCTCTGCCGCTGTGC
GTGTCTGTCTGTCTGCTCTTAGCTGTCTCCATTGCCTCGGCCTTCTTTGCTTTTTGTGGG
GGAGAGGGGAGGGGACGGGCAGGGTCTCTGTGCCCCAGGCTGGGGTGCA GTGGCGCGATC
CCAGCACTGCAGCCTCAACCTCCTGGGCTCAAGCCATCCTTCCGCCCTCAGCTTCCCCAGC
AGCTGGGACTACAGGCACGCGCCACCACAGCCGGCTAATTTTTTATTTAATTTTTTGTAG
AGACGAGGTTTCGCCATGTTGCCCAGGCTGGTCTTGA ACTCCGGGGCTCAAGCGATCCTC
CCGCTTCAGCCTCCCTAAGTGCTGGGATTGCAGGCGTGAGCCACTTTCCCAGCCTCTCTT
TGCTTTGCCTGCCCCGTTCTCTTA ACTCTTGGACCTCCTCGTCTGCATGGTAACTCCGT
CTGAGTCTACCATTTTCTTGCTCTCCCTCCTTCCCTTGGGCCTGCCTCAGTTCCCTTTGGC
CTCCCCCTTTACCCAGCTCTTGGGGTGTCTCTGTTTTTTCCATCCCCACTTCCTGCCTTC
TCGTGGCCCTGTGTGAGCACATGTGTACATCTCAGCCTTATCTCAAGGAGGTGACACCTT
CTCTCCTTGTCCCCATCTGGCCGTCTCTCTGTGCTTCCCTGGCCAGGGGCGTGCTGCTG
GTCCTATGGGGGGAAGGCTACTCCGCATCTCAGCCACCTTCCTCAGGCTCACTCCACCTA
CATCCCCAGTCTGCCACACCCCATCCCTTTGGGCCTCAGCCCTGTCCCTTTGATGTCCTC
CTTTCCTTCAGCCCCTCTGCCCTGTCCCTGCACACCTCC

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Figure 74

MSRREGSLEDPQTDSSVSLPHLEAKIRQTHSLAHLTKYAEQLLQEYVQLQGDPFGLPS
FSPPRLPVAGLSAPAPSHAGLPVHERLRDLAAALAAPLLDAVCCRQAELNPAPRLLR
RLEDAAARQARALGAAVEALLAALGAANRGPRAEPPAATASAASATGVFPAKVLGLRVCGL
YREWLSRTEGDLGQLLPGGSA

Signal sequence.
none

Transmembrane domain.
84-104
126-146
159-179

N-myristoylation site.
166-171
174-179

Leucine zipper pattern.
37-58

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Figure 75

ATGGCTTGCCTTGGATTTTCAGCGGCACAAGGCTCAGCTGAACCTGGCTGCCAGGACCTGG
CCCTGCACTCTCCTGTTTTTTCTTCTCTTCATCCCTGTCTTCTGCAAAGCAATGCACGTG
GCCCAGCCTGCTGTGGTACTGGCCAGCAGCCGAGGCATCGCCAGCTTTGTGTGTGAGTAT
GCATCTCCAGGCAAAGCCACTGAGGTCCGGGTGACAGTGCTTCGGCAGGCTGACAGCCAG
GTGACTGAAGTCTGTGCGGCAACCTACATGACGGGGAATGAGTTGACCTTCCTAGATGAT
TCCATCTGCACGGGCACCTCCAGTGGAAATCAAGTGAACCTCACTATCCAAGGACTGAGG
GCCATGGACACGGGACTCTACATCTGCAAGGTGGAGCTCATGTACCCACCGCCATACTAC
CTGGGCATAGGCAACGGAACCCAGATTTATGTAATTGATCCAGAACCGTGCCCAGATTCT
GACTTCCTCCTCTGGATCCTTGCAGCAGTTAGTTCGGGGTTGTTTTTTTATAGCTTTCTC
CTCACAGCTGTTTCTTTGAGCAAAATGCTAAAGAAAAGAAGCCCTCTTACAACAGGGGTC
TATGTGAAAATGCCCCAACAGAGCCAGAAATGTGAAAAGCAATTCAGCCTTATTTTATT
CCCATCAATTGA

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Figure 76

MACLGFORHKAQLNLAARTWPCTLLFFLLFIPVFCKAMHVAQPAVVLASSRGIASFVCEY
ASPGKATEVRVTVLRQADSQVTEVCAATYMTGNELTFLDDSICTGTSSGNQVNLTIQGLR
AMDTGLYICKVELMYPPPYLIGINGTQIYVIDPEPCPDSDFLWILAAVSSGLFFYSFL
LTAVSLSKMLKKRSPLTTGVYVKMPPTPEPECEKQFQPYFIPIN

Signal sequence.

1-35

Transmembrane domain.

163-183

N-glycosylation site.

113-116

145-148

cAMP- and cGMP-dependent protein kinase phosphorylation site.

191-194

Tyrosine kinase phosphorylation site.

120-127

N-myristoylation site.

92-97

105-110

109-114

125-130

142-147

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Figure 77

ATGGGCAGCCCCCGCTCCGCGCTGAGCTGCCTGCTGTTGCACTTGCTGGTCCTCTGCCTC
CAAGCCCAGGAAGGCCCGGGCAGGGGCCCTGCGCTGGGCAGGGAGCTCGCTTCCCTGTTT
CGGGCTGGCCGGGAGCCCCAGGGTGTCTCCCAACAGCATGTGAGGGAGCAGAGCCTGGTG
ACGGATCAGCTCAGCCGCCGCCTCATCCGGACCTACCAACTCTACAGCCGCACCAGCGGG
AAGCACGTGCAGGTCCCTGGCCAACAAGCGCATCAACGCCATGGCAGAGGACGGCGACCCC
TTCGCAAAGCTCATCGTGGAGACGGACACCTTTGGAAGCAGAGTCCGAGTCCGAGGAGCC
GAGACGGGCCTCTACATCTGCATGAACAAGAAGGGGAAGCTGATCGCCAAGAGCAACGGC
AAAGGCAAGGACTGCGTCTTCACGGAGATTGTGCTGGAGAACAACCTACACAGCGCTGCAG
AATGCCAAGTACGAGGGCTGGTACATGGCCTTCACCCGCAAGGGCCGGCCCCGCAAGGGC
TCCAAGACGCGGCAGCACCAGCGTGAGGTCCACTTCATGAAGCGGCTGCCCCGGGGCCAC
CACACCACCGAGCAGAGCCTGCGCTTCGAGTTCCTCAACTACCCGCCCTTCACGCGCAGC
CTGCGCGGCAGCCAGAGGACTTGGGCCCCGGAGCCCCGATAG

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Figure 78

MGSPRSALSCLLLHLLVLCLQAQEGPGRGPALGRELASLFRAGREPQGVSSQQHVREQSLV
TDQLSRRLIRTYQLYSRTSGKHVQVLANKRINAMAEDGDPFAKLIVETDTFGSRVRVRGA
ETGLYICMNKKKGKLIAKSNGKGKDCVFTEIVLENNYTALQNAKYEGWYMAFTRKGRPRKG
SKTRQHOREVHFMKRLPRGHHTTEQSLRFEFLNYPPFTRSLRGSQRTWAPEPR

Signal sequence.

1-22

Transmembrane domain.

none

N-glycosylation site.

155-158

cAMP- and cGMP-dependent protein kinase phosphorylation site.

178-181

Tyrosine kinase phosphorylation site.

118-125

N-myristoylation site.

2-7

119-124

123-128

223-228

HBGF/FGF family signature.

132-156

Fibroblast growth factor.

68-196

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Figure 79

GAAGGGTTAAAGGCCCCCGGCTCCCTGCCCCCTGCCCTGGGGAACCCCTGGCCCTGTGGG
GACATGAACTGTGTTTGCCGCCTGGTCCTGGTCGTGCTGAGCCTGTGGCCAGATACAGCT
GTCGCCCCCTGGGCCACCACCTGGCCCCCCTCGAGTTTCCCCAGACCCTCGGGCCGAGCTG
GACAGCACCGTGCTCCTGACCCGCTCTCTCCTGGCGGACACGCGGCAGCTGGCTGCACAG
CTGAGGGACAAATTCCCAGCTGACGGGGACCACAACCTGGATTCCCTGCCCCACCTGGCC
ATGAGTGCGGGGGCACTGGGAGCTCTACAGCTCCCAGGTGTGCTGACAAGGCTGCGAGCG
GACCTACTGTCTTACCTGCGGCACGTGCAGTGGCTGCGCCGGGCAGGTGGCTCTTCCCTG
AAGACCCTGGAGCCCCGAGCTGGGCACCCTGCAGGCCCGACTGGACCGGCTGCTGCGCCGG
CTGCAGCTCCTGATGTCCCGCCTGGCCCTGCCCCAGCCACCCCGGACCCGCGGGCGCCC
CCGCTGGCGCCCCCCTCCTCAGCCTGGGGGGGCATCAGGGCCGCCACGCCATCCTGGGG
GGGCTGCACCTGACACTTGACTGGGCCGTGAGGGGACTGCTGCTGCTGAAGACTCGGCTG
TGACCCGGGGGCCCAAAGCCACCACCGTCCTTCCAAAGCCAGATCTTATTTATTTATTTAT
TTCAGTACTGGGGGCGAAACAGCCAGGTGATCCCCCGCCATTATCTCCCCCTAGTTAGA
GACAGTCCTTCCGTGAGGCCTGGGGGACATCTGTGCCTTATTTATACTTATTTATTTTTCAG
GAGCAGGGGTGGGAGGCAGGTGGACTCCTGGGTCCCCGAGGAGGAGGGGACTGGGGTCCC
GGATTCTTGGGTCTCCAAGAAGTCTGTCCACAGACTTCTGCCCTGGCTCTTCCCCATCTA
GGCCTGGGCAGGAACATATATTATTTATTTAAGCAATTACTTTTCATGTTGGGGTGGGGA
CGGAGGGGAAAGGGAAGCCTGGGTTTTGTACAAAAATGTGAGAAACCTTTGTGAGACAG
AGAACAGGGAATTAAATGTGTACATATCCACTTGAGGGCGATTTGTCTGAGAGCTGG
GGCTGGATGCTTGGGTAACCTGGGGCAGGGCAGGTGGAGGGGAGACCTCCATTCAGGTGGA
GGTCCCGAGTGGGCGGGGCAGCGACTGGGAGATGGGTCCGTCACCCAGACAGCTCTGTGG
AGGCAGGGTCTGAGCCTTGCTGGGGCCCCGCACTGCATAGGGCCGTTTGTGTTGTTTTT
GAGATGGAGTCTCGCTCTGTTGCCTAGGCTGGAGTGCAGTGAGGCAATCTAAGGTCACTG
CAAGCTCCACCTCCCGGGTTCAAGCAATTCTCCTGCCTCAGCCTCCCGATTAGCTGGGAT
CACAGGTGTGCACCACCATGCCAGCTAATTATTTATTTCTTTTGTATTTTATAGTAGAGA
CAGGGTTTCACCATGTTGGCCAGGCTGGTTTCGAACTCCTGACCTCAGGTGATCCTCCTG
CCTCGGCCTCCCAAAGTGCTGGGATTACAGGTGTGAGCCACCACACCTGACCCATAGGTC
TTCAATAAATATTTAATGGAAGGTTCCACAAGTCACCCTGTGATCAACAGTACCCGTATG
GGACAAAGCTGCAAGGTCAAGATGGTTCATTATGGCTGTGTTACCCATAGCAAACCTGGAA
AGAATCTAGATATCCAACAGTGAGGGTTAAGCAACATGGTGCATCTGTGGATAGAACACC
ACCCAGCCGCCCCGAGCAGGGACTGTCATTTCAGGGAGGCTAAGGAGAGAGGCTTGCTTGG
GATATAGAAAGATATCCTGACATTGGCCAGGCATGGTGGCTCACGCCTGTAATCCTGGCA
CTTTGGGAGGACGAAGCGAGTGGATCACTGAAGTCCAAGAGTTTGAGACCGGCCTGCGAG
ACATGGCAAAACCCTGTCTCAAAAAAGAAAGAATGATGTCCTGACATGAAACAGCAGGCT
ACAAAACCACTGCATGCTGTGATCCCAATTTTGTGTTTTTCTTTCTATATATGGATTAAA
ACAAAAATCCTAAAGGGAAATACGCCAAAATGTTGACAATGACTGTCTCCAGGTCAAAGG
AGAGAGGTGGGATTGTGGGTGACTTTTAATGTGTATGATTGTCTGTATTTTACAGAATTT
CTGCCATGACTGTGTATTTTGCATGACACATTTTAAAAATAATAAACACTATTTTATAGAA
T

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Figure 80

MNCVCRLVLVVLVSLWPD TAVAPGPPPGPPRVSPDPRAELDSTVLLTRSL LADTRQLAAQL
RDKFPADGDHNLDSLPTLAMSAGALGALQLPGVLTRLRADLLSYLRHVQWLRRAGGSSLK
TLEPELGTLQARLDRLRLRLQLLMSRLALPQPPDPFPAPPLAPPSSAWGGIRAAHAILGG
LHLTLDWAVRGLLLLKTRL

Signal sequence.

1-21

Transmembrane domain.

175-195

Tyrosine kinase phosphorylation site.

96-104

N-myristoylation site.

83-88

127-132

169-174

170-175

180-185

Leucine zipper pattern.

119-140

122-143

126-147

178-199

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Figure 81

AGCTGCCAGCCAGAGAGGGAGTCATTTTCATTGGCGTTTGAGTCAGCAAAGAAGTCAAGAT
GGCCAAAGTTCCAGACATGTTTGAAGACCTGAAGAAGTGTACAGTGAAAATGAAGAAGA
CAGTTCCTCCATTGATCATCTGTCTCTGAATCAGAAATCCTTCTATCATGTAAGCTATGG
CCCACTCCATGAAGGCTGCATGGATCAATCTGTGTCTCTGAGTATCTCTGAAACCTCTAA
AACATCCAAGCTTACCTTCAAGGAGAGCATGGTGGTAGTAGCAACCAACGGGAAGGTTCT
GAAGAAGAGACGGTTGAGTTTAAGCCAATCCATCACTGATGATGACCTGGAGGCCATCGC
CAATGACTCAGAGGAAGAAATCATCAAGCCTAGGTCAACCTTTTAGCTTCCTGAGCAA
TGTGAAATACAACCTTTATGAGGATCATCAAATACGAATTCATCCTGAATGACGCCCTCAA
TCAAAGTATAATTCGAGCCAATGATCAGTACCTCACGGCTGCTGCATTACATAATCTGGA
TGAAGCAGTGAAATTTGACATGGGTGCTTATAAGTCATCAAAGGATGATGCTAAAATTAC
CGTGATTCTAAGAATCTCAAAAACCTCAATTGTATGTGACTGCCCAAGATGAAGACCAACC
AGTGCTGCTGAAGGAGATGCCTGAGATACCCAAAACCATCACAGGTAGTGAGACCAACCT
CCTCTTCTTCTGGGAAACTCACGGCACTAAGAAGTATTTTACATCAGTTGCCCATCCAAA
CTTGTTTTATTGCCACAAAGCAAGACTACTGGGTGTGCTTGGCAGGGGGGCCACCCTCTAT
CACTGACTTTCAGATACTGGAAAACCAAGGCGTAGGTCTGGAGTCTCACTTGTCTCACTTG
TGCAGTGTGACAGTTCATATGTACCATGTACATGAAGAAGCTAAATCCTTTACTGTTAG
TCATTTGCTGAGCATGTACTGAGCCTTGTAATTCATAATGAATGTTTACACTCTTTGTAA
GAGTGGAACCAACACTAACATATAATGTTGTTATTTAAAGAACACCCTATATTTTGCATA
GTACCAATCATTTTAATTATTATTCTTCATAACAATTTTAGGAGGACCAGAGCTACTGAC
TATGGCTACCAAAAAGACTCTACCCATATTACAGATGGGCAAATTAAGGCATAAGAAAAC
TAAGAAATATGCACAATAGCAGTCGAAACAAGAAGCCACAGACCTAGGATTTTCATGATTT
CATTTCAACTGTTTGCCTTCTGCTTTTAAAGTTGCTGATGAACTCTTAATCAAATAGCATA
AGTTTCTGGGACCTCAGTTTTTATCATTTTCAAATGGAGGGAATAATACCTAAGCCTTCC
TGCCGCAACAGTTTTTTTATGCTAATCAGGGAGGTCATTTTTGGTAAATACTTCTCGAAGC
CGAGCCTCAAGATGAAGGCAAAGCACGAAATGTTATTTTTTAATTATTATTATATATGT
ATTTATAAATATATTTAAGATAATTATAATATACTATATTTATGGGAACCCCTTCATCCT
CTGAGTGTGACCAGGCATCCTCCACAATAGCAGACAGTGTTTTTCTGGGATAAGTAAGTTT
GATTTCAATTAACAGGGCATTTTGGTCCAAGTTGTGCTTATCCCATAGCCAGGAAACTC
TGCAATCTAGTACTTGGGAGACCTGTAATCATATAATAAATGTACATTAATTACCTTGAG
CCAGTAATTGGTCCGATCTTTGACTCTTTTGCCATTAACTTACCTGGGCATTCTTGTTT
CATTC AATTCCACCTGCAATCAAGTCCTACAAGCTAAAATTAGATGAACTCAACTTTGAC
AACCATGAGACCACTGTTATCAAAACTTTCTTTTCTGGAATGTAATCAATGTTTCTTCTA
GGTTCTAAAATTGTGATCAGACCATAATGTTACATTATTATCAACAATAGTGATTGATA
GAGTGTTATCAGTCATAACTAAATAAAGCTTGCAACAAAATTCTCTG

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Figure 82

MAKVPDMFEDLKNCYSENEEDSSSIDHLSLNQKSFYHVSYGPLHEGCMQSVSLSISETS
KTSKLTfKESMVVVATNGKVLKKRRLSLSQSITDDDLAIANDSEEEI IKPRSSPFSFLS
NVKYNFMRI IKYEFILNDALNQSI IRANDQYLTAALHNLDEAVKFDMGAYKSSKDDAKI
TVILRISK TQLYVTAQDEDQPVLLKEMPEI PKTITGSETNLLFFWETHGTKNYFTSVAHP
NLFIATKQDYWVCLAGGPPSITDFQILENQA

Signal sequence.
none

Transmembrane domain.
none

N-glycosylation site.
102-105
141-144

cAMP- and cGMP-dependent protein kinase phosphorylation site.
84-87

N-myristoylation site.
169-174
216-221
256-261

TonB-dependent receptor proteins signature 1.
1-76

Interleukin-1 signature.
234-254

Interleukin-1 / 18
136-270

Interleukin-1 propeptide
1-127

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Figure 83

TTCGAGGCACAAGGCACAACAGGCTGCTCTGGGATTCTCTTCAGCCAATCTTCATTGCTC
AAGTGTCTGAAGCAGCCATGGCAGAAGTACCTGAGCTCGCCAGTGAAATGATGGCTTATT
ACAGTGGCAATGAGGATGACTTGTTCTTTGAAGCTGATGGCCCTAAACAGATGAAGTGCT
CCTTCCAGGACCTGGACCTCTGCCCTCTGGATGGCGGCATCCAGCTACGAATCTCCGACC
ACCACTACAGCAAGGGCTTCAGGCAGGCCGCGTCAGTTGTTGTGGCCATGGACAAGCTGA
GGAAGATGCTGGTTCCTGCCCACAGACCTTCCAGGAGAATGACCTGAGCACCTTCTTTC
CCTTCATCTTTGAAGAAGAACCTATCTTCTTTGACACATGGGATAACGAGGCTTATGTGC
ACGATGCACCTGTACGATCACTGAACTGCACGCTCCGGGACTCACAGCAAAAAAGCTTGG
TGATGTCTGGTCCATATGAACTGAAAGCTCTCCACCTCCAGGGACAGGATATGGAGCAAC
AAGTGGTGTCTCCATGTCCTTTGTACAAGGAGAAGAAAGTAATGACAAAATACCTGTGG
CCTTGGGCCTCAAGGAAAAGAATCTGTACCTGTCCTGCGTGTGAAAGATGATAAGCCCA
CTCTACAGCTGGAGAGTGTAGATCCCCAAAATTACCCAAAGAAGAAGATGGAAAAGCGAT
TTGTCTTCAACAAGATAGAAATCAATAACAAGCTGGAATTTGAGTCTGCCCAGTTCCCCA
ACTGGTACATCAGCACCTCTCAAGCAGAAAACATGCCCGTCTTCCTGGGAGGGACCAAAG
GCGGCCAGGATATAACTGACTTCACCATGCAATTTGTGTCTTCCTAAAGAGAGCTGTACC
CAGAGAGTCCTGTGCTGAATGTGGACTCAATCCCTAGGGCTGGCAGAAAGGGAACAGAAA
GGTTTTTTGAGTACGGCTATAGCCTGGACTTTCCTGTTGTCTACACCAATGCCCAACTGCC
TGCCTTAGGGTAGTGCTAAGAGGATCTCCTGTCCATCAGCCAGGACAGTCAGCTCTCTCC
TTTCAGGGCCAATCCCCAGCCCTTTTGTGAGCCAGGCCTCTCT

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Figure 84

MAEVP ELASEMMAY YSGNEDDLFF EADGPKQMKCSFQDL DLCPLDGGIQLRISDHHYSKG
FRQAASVVVAMD KLRKMLVPCPQTFQENDLSTFFPFIFEEEP IFFDTWDNEAYVHDAPVR
SLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVF SMSFVQGEESNDKIPVALGLKE
KNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEKR FVFNKIEINN KLEFESAQFPNWIIST
SQAENMPVFLGGTKGGQDITDFTMQFVSS

Signal sequence.
none

Transmembrane domain.
none

N-glycosylation site.
123-126

Tyrosine kinase phosphorylation site.
51-57

N-myristoylation site.
251-256
256-261

Interleukin-1 signature.
228-248

Interleukin-1 propeptide.
1-122

Interleukin-1 / 18
126-268

89/169

Figure 85

GAATTCCTCTGGTCCTCATCCAGGTGCGCGGGAAGCAGGTGCCCAGGAGAGAGGGGATAA
TGAAGATTCCATGCTGATGATCCCAAAGATTGAACCTGCAGACCAAGCGCAAAGTAGAAA
CTGAAAGTACACTGCTGGCGGATCCTACGGAAGTTATGGAAAAGGCAAAGCGCAGAGCCA
CGCCGTAGTGTGTGCCGCCCCCTTGGGATGGATGAACTGCAGTCGCGGCGTGGGTAAAG
AGGAACCAGCTGCAGAGATCACCTGCCCAACACAGACTCGGCAACTCCGCGGAAGACCA
GGGTCTCTGGGAGTGACTATGGGCGGTGAGAGCTTGCTCCTGCTCCAGTTGCGGTCATCAT
GACTACGCCCCGCTCCCGCAGACCATGTTCCATGTTTCTTTTAGGTATATCTTTGGACTT
CCTCCCCCTGATCCTTGTTCTGTTGCCAGTAGCATCATCTGATTGTGATATTGAAGGTAAA
GATGGCAAACAATATGAGAGTGTTCTAATGGTCAGCATCGATCAATTATTGGACAGCATG
AAAGAAATTGGTAGCAATTGCCTGAATAATGAATTTAACTTTTTTAAAAGACATATCTGT
GATGCTAATAAGGAAGGTATGTTTTTATTCCGTGCTGCTCGCAAGTTGAGGCAATTTCTT
AAAATGAATAGCACTGGTGATTTTGATCTCCACTTATTAAAAGTTTCAGAAGGCACAACA
ATACTGTTGAACTGCACTGGCCAGGTTAAAGGAAGAAAACCAGCTGCCCTGGGTGAAGCC
CAACCAACAAAGAGTTTGGAAGAAAATAAATCTTTAAAGGAACAGAAAAAACTGAATGAC
TTGTGTTTCTTAAAGAGACTATTACAAGAGATAAAAACCTTGTTGGAATAAAATTTTGATG
GGCACTAAAGAACACTGAAAAATATGGAGTGGCAATATAGAAACACGAACTTTAGCTGCA
TCCTCCAAGAATCTATCTGCTTATGCAGTTTTTCAGAGTGGAATGCTTCCTAGAAGTTAC
TGAATGCACCATGGTCAAAACGGATTAGGGCATTTGAGAAATGCATATTGTATTACTAGA
AGATGAATACAAACAATGGAACTGAATGCTCCAGTCAACAACTATTTCTTATATATGT
GAACATTTATCAATCAGTATAATTCTGTACTGATTTTTTGTAAGACAATCCATGTAAGGTA
TCAGTTGCAATAATACTTCTCAAACCTGTTTAAATATTTCAAGACATTAAATCTATGAAG
TATATAATGGTTTCAAAGATTCAAATTTGACATTGCTTTACTGTCAAAATAATTTTATGG
CTCACTATGAATCTATTATACTGTATTAAGAGTGAAAATTGTCTTCTTCTGTGCTGGAGA
TGTTTTAGAGTTAACAATGATATATGGATAATGCCGGTGAGAATAAGAGAGTCATAAACC
TTAAGTAAGCAACAGCATAACAAGGTCCAAGATACCTAAAAGAGATTTCAAGAGATTTAA
TTAATCATGAATGTGTAACACAGTGCCTTCAATAAATGGTATAGCAAATGTTTTGACATG
AAAAAAGGACAATTTCAAAAAAATAAAAT

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Figure 86

MFHVSFRYIFGLPPLILVLLPVASSDCDIEGKDGKQYESVLMVSIQQLDSMKEIGSNCL
NNEFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQ
VKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLEIKTCWNKILMGTKEH

Signal sequence.

1-27

Transmembrane domain.

none

N-glycosylation site.

95-98

116-119

141-144

N-myristoylation site.

119-124

Amidation site.

122-125

Interleukin-7 signature.

154-160

Interleukin 7/9 family

28-173

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Figure 87A

CGCCCTCGCCGCCCGCGGCGCCCCGAGCGCTTTGTGAGCAGATGCGGAGCCGAGTGGAGG
GCGCGAGCCAGATGCGGGGCGACAGCTGACTTGCTGAGAGGAGGCGGGGAGGCGCGGAGC
GCGCGTGTGGTCCTTGCGCCGCTGACTTCTCCACTGGTTCCCTGGGCACCGAAAGATAAAC
CTCTCATAATGAAGGCCCCCGCTGTGCTTGCACCTGGCATCCTCGTGCTCCTGTTTACCT
TGGTGCAGAGGAGCAATGGGGAGTGTAAGAGGGCACTAGCAAAGTCCGAGATGAATGTGA
ATATGAAGTATCAGCTTCCCAACTTCACCGCGGAAACACCCATCCAGAATGTCATTCTAC
ATGAGCATCACATTTTCTTGGTGCCACTAACTACATTTATGTTTTAAATGAGGAAGACC
TTCAGAAGGTTGCTGAGTACAAGACTGGGCCTGTGCTGGAACACCCAGATTGTTTCCCAT
GTCAGGACTGCAGCAGCAAAGCCAATTTATCAGGAGGTGTTTGGAAAGATAACATCAACA
TGGCTCTAGTTGTGACACCTACTATGATGATCAACTCATTAGCTGTGGCAGCGTCAACA
GAGGGACCTGCCAGCGACATGTCTTTCCCCACAATCATACTGCTGACATACAGTCGGAGG
TTCAGTGCATATTCTCCCCACAGATAGAAGAGCCCAGCCAGTGTCTGACTGTGTGGTGA
GCGCCCTGGGAGCCAAAGTCCTTTCATCTGTAAAGGACCGGTTTCATCAACTTCTTTGTAG
GCAATACCATAAATTCTTCTTATTTCCCAGATCATCCATTGCATTTCGATATCAGTGAGAA
GGCTAAAGGAAACGAAAGATGGTTTTATGTTTTTGACGGACCAGTCCTACATTGATGTTT
TACCTGAGTTCAGAGATTCTTACCCCATTAAGTATGTCCATGCCCTTTGAAAGCAACAATT
TTATTTACTTCTTGACGGTCCAAAGGGAAACTCTAGATGCTCAGACTTTTTCACACAAGAA
TAATCAGGTTCTGTTCCATAAACTCTGGATTGCATTCCTACATGGAAATGCCTCTGGAGT
GTATTTCTCACAGAAAAGAGAAAAAGAGATCCACAAAGAAGGAAGTGTTTAATATACTTC
AGGCTGCGTATGTCAGCAAGCCTGGGGCCAGCTTGCTAGACAAATAGGAGCCAGCCTGA
ATGATGACATTCTTTTTCGGGGTGTTCGCACAAAGCAAGCCAGATTCTGCCGAACCAATGG
ATCGATCTGCCATGTGTGCATTCCCTATCAAATATGTCAACGACTTCTTCAACAAGATCG
TCAACAAAAACAATGTGAGATGTCTCCAGCATTTTTTACGGACCCAATCATGAGCACTGCT
TTAATAGGACACTTCTGAGAAATTCATCAGGCTGTGAAGCGCGCCGTGATGAATATCGAA
CAGAGTTTACCACAGCTTTGCAGCGCGTTGACTTATTCATGGGTCAATTCAGCGAAGTCC
TCTTAACATCTATATCCACCTTCATTAAAGGAGACCTCACCATAGCTAATCTTGGGACAT
CAGAGGGTCGCTTCATGCAGGTTGTGGTTCCTCGATCAGGACCATCAACCCCTCATGTGA
ATTTTCTCCTGGACTCCCATCCAGTGTCTCCAGAAGTGATTGTGGAGCATACATTAAACC
AAAATGGCTACACACTGGTTATCACTGGGAAGAAGATCACGAAGATCCCATTTGAATGGCT
TGGGCTGCAGACATTTCCAGTCCTGCAGTCAATGCCTCTCTGCCCCACCCTTTGTTTCACT
GTGGCTGGTGCCACGACAAATGTGTGCGATCGGAGGAATGCCTGAGCGGGACATGGACTC
AACAGATCTGTCTGCCTGCAATCTACAAGGTTTTCCCAAATAGTGCACCCCTTGAAGGAG
GGACAAGGCTGACCATATGTGGCTGGGACTTTGGATTTCGGAGGAATAATAAATTTGATT
TAAAGAAAAGTAGAGTTCTCCTTGGAAATGAGAGCTGCACCTTGACTTTAAGTGAGAGCA
CGATGAATACATTGAAATGCACAGTTGGTCTGCCATGAATAAGCATTTCAATATGTCCA
TAATTATTTCAAATGGCCACGGGACAACACAATACAGTACATTCTCCTATGTGGATCCTG
TAATAACAAGTATTTTCGCCGAAATACGGTCCTATGGCTGGTGGCACTTTACTTACTTTAA
CTGGAAATTACCTAAACAGTGGGAATTCTAGACACATTTCAATTGGTGGAAAAACATGTA
CTTTTAAAAGTGTTGTTCAAACAGTATTCTTGAATGTTATACCCAGCCCAAACCATTTCAA
CTGAGTTTGCTGTTAAATTGAAAATTGACTTAGCCAACCGAGAGACAAGCATCTTCAGTT
ACCGTGAAGATCCCATTTGTCTATGAAATTCATCCAACCAAATCTTTTATTAGTACTTGGT
GGAAAGAACCTCTCAACATTGTCAGTTTTCTATTTTGCTTTGCCAGTGGTGGGAGCACAA
TAACAGGTGTTGGGAAAAACCTGAATTCAGTTAGTGTCCCGAGAATGGTCATAAATGTGC
ATGAAGCAGGAAGGAACTTTACAGTGGCATGTCAACATCGCTCTAATTCAGAGATAATCT
GTTGTACCACTCCTTCCCTGCAACAGCTGAATCTGCAACTCCCCCTGAAAACCAAAGCCT
TTTTTCATGTTAGATGGGATCCTTTTCCAAATACTTTGATCTCATTTATGTACATAATCCTG
TGTTTAAAGCCTTTTGAAGGAGGAGTGTGATCTCAATGGGCAATGAAAATGTACTGGAAA
TTAAGGGAAATGATATTGACCCTGAAGCAGTTAAAGGTGAAGTGTTAAAAGTTGGAAATA
AGAGCTGTGAGAAATATACACTTACATTCTGAAGCCGTTTTATGCACGGTCCCCAATGACC
TGCTGAAATTGAACAGCGAGCTAAATATAGAGTGGAAGCAAGCAATTTCTTCAACCGTCC
TTGGAAAAGTAATAGTTCAACCAGATCAGAATTTACAGGATTGATTGCTGGTGTGTCT
CAATATCAACAGCACTGTTATTACTACTTGGGTTTTTCTGTGGCTGAAAAAGAGAAAGC
AAATTAAAGATCTGGGCAGTGAATTAGTTTCGCTACGATGCAAGAGTACACACTCCTCATT
TGGATAGGCTTGTAAGTGCCCGAAGTGTAAGCCCAACTACAGAAATGGTTTCAAATGAAT
CTGTAGACTACCGAGCTACTTTTCCAGAAGATCAGTTTCCTAATTCATCTCAGAACGGTT
CATGCCGACAAGTGCAGTATCCTCTGACAGACATGTCCCCCATCCTAACTAGTGGGGACT
CTGATATATCCAGTCCATTACTGCAAAATACTGTCCACATTGACCTCAGTGCTCTAAATC
CAGAGCTGGTCCAGGCAGTGCAGCATGTAGTGATTGGGCCCAGTAGCCTGATTGTGCATT
TCAATGAAGTCATAGGAAGAGGGCATTTTGGTTGTGTATATCATGGGACTTTGTTGGACA
ATGATGGCAAGAAAATTCAGTGTGCTGTGAAATCCTTGAACAGAATCACTGACATAGGAG
AAGTTTCCCAATTTCTGACCGAGGGAATCATCATGAAAGATTTTAGTCATCCCAATGTCC

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Figure 87B

TCTCGCTCCTGGGAATCTGCCTGCGAAGTGAAGGGTCTCCGCTGGTGGTCCTACCATACA
TGAAACATGGAGATCTTCGAAATTTTCATTCGAAATGAGACTCATAATCCAAGTGTAAAAG
ATCTTATTGGCTTTGGTCTTCAAGTAGCCAAAGCGATGAAATATCTTGCAAGCAAAAAGT
TTGTCCACAGAGACTTGGCTGCAAGAACTGTATGCTGGATGAAAAATTCACAGTCAAGG
TTGCTGATTTTGGTCTTGCCAGAGACATGTATGATAAAGAATACTATAGTGTACACAACA
AAACAGGTGCAAAGCTGCCAGTGAAGTGGATGGCTTTGGAAAGTCTGCAAAGTCAAAAGT
TTACCACCAAGTCAGATGTGTGGTCCTTTGGCGTCGTCCTCTGGGAGCTGATGACAAGAG
GAGCCCCACCTTATCCTGACGTAAACACCTTTGATATAACTGTTTACTTGTGCAAGGGA
GAAGACTCCTACAACCCGAATACTGCCCAGACCCCTTATATGAAGTAATGCTAAAATGCT
GGCACCCCTAAAGCCGAAATGCGCCCATCCTTTTCTGAACTGGTGTCCCGGATATCAGCGA
TCTTCTCTACTTTCATTGGGGAGCACTATGTCCATGTGAACGCTACTTATGTGAACGTAA
AATGTGTGCTCGCTCCGTATCCTTCTCTGTTGTCATCAGAAGATAACGCTGATGATGAGGTGG
ACACACGACCAGCCTCCTTCTGGGAGACATCATAGTGCTAGTACTATGTCAAAGCAACAG
TCCACACTTTGTCCAATGGTTTTTTCACTGCCTGACCTTTAAAAGGCCATCGATATTCTT
TGCTCCTTGCCATAGGACTTGTATTGTTATTTAAATTACTGGATTCTAAGGAATTTCTTA
TCTGACAGAGCATCAGAACCAGAGGCTTGGTCCCACAGGCCAGGGACCAATGCGCTGCAG

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Figure 88A

MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQNVILHEH
HIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFPQCDCSSKANLSGGVWKDNINMAL
VVDITYYDDQLISCGSVNRGTCQRHVFPHNHTADIQSEVHCIFSPQIEEPSQCPDCVVSAL
GAKVLSSVKDRFINFFVGNTINSSYFPDHPLHSISVRRLKETKDGMFLTDQSYIDVLPE
FRDSYPIKYVHAFESNNFIYFLTVQRETLDQAQTFHTRIIRFCSINSGLHSEMPLECIL
TEKRKKRSTKKEVFNILQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRS
AMCAFPPIKYVNDFFNKI VNKNNVRCLQHFYGNHEHCFNRTLRLNSSGCEARRDEYRTEF
TTALQRVDLFGMGQFSEVLLTSISTFIKGLDTIANLGTSEGRFMQVVVSRSGPSTPHVNFL
LDSEHPVSPEVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGW
CHDKCVRSEECLSGTWTQQICLPAIYKVPNSAPLEGGTRLTICGWDFGFRNNKFDLKK
TRVLLGNESCTLTLESTMTNLKCTVGPAMNKHFNMSIIISNGHGTTOYSTFSYVDPVIT
SISPKYGPAGGTLLTLTGNYLNSGNSRHISIGGKTCTLKSVSNSILECYTPAQTI STEF
AVKLKIDLANRETSIFS YREDPIVYEIHPTKSFISTWWKEPLNIVSFLFCFASGGSTITG
VGKNLNSVSVPRMVINVHEAGRNF TVACQHRSNSEIICCTTPSLQQNLNLQLPLKTKAFFM
LDGILSKYFDLIYVHNPFVKPFKEKPVMI SMGNENVLEIKGNDIDPEAVKGEVLKVGKNSC
ENIHLHSEAVLCTVPNDLLKLNSELNI EWKQAISSTVLGKVIVQPDQNF TGLIAGVVSIS
TALLLLLGGFFLWLKKRKQIKDLGSELVRYDARVHTPHLDRLVSARSVSPTTEMVSNESVD
YRATFPEDQFPNSSQNGSCRQVQYPLTDMSPILTSGDS DISSPLLQNTVHIDLSALNP EL
VQAVQHVVIGPSSLIVHFNEVIGRGHFGCVYHGTL LDNDGKKIHC AVKSLNRITDIGEVS
QFLTEGIIMKDFSHPNVLSLLGICLRSEGSP LVVLPYMKHGD LRFNETHNPTVKDLI
GFG LQVAKAMKYLASKKFVHRDLAARN CMLDEKFTVKVAD FGLARDMYDKEYYSVHNKTG
AKLPVKWMALES LQTQKFTTKSDVWSFGVVLWELMTRGAPPYPDVNTFDITVYLLQGRRL
LQPEYCPDPLYEVM LKCVHPKAEMRPSFSELVSRISAIFSTFIGEHYVHV NATYVNVKCV
APYPSLLSSEDNADDEV DTRPASFWETS

Signal sequence.

1-24

Transmembrane domain.

950-970

N-glycosylation site.

45-51

106-111

149-152

202-205

399-402

405-408

607-610

635-638

803-806

897-900

948-951

1016-1019

1032-1035

1036-1039

1189-1192

1257-1260

1371-1374

cAMP- and cGMP-dependent protein kinase phosphorylation site.

305-308

306-309

508-511

Tyrosine kinase phosphorylation site.

847-853

1245-1253

N-myristoylation site.

198-203

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Figure 88B

326-331
334-339
456-461
578-583
606-611
672-677
679-684
693-698
775-780
780-785
896-901
951-956
1203-1208

Amidation site.
506-509
1119-1122
1316-1319

Tyrosine protein kinases specific active-site signature:
1218-1230

Sema domain.
55-500

Protein kinase domain.
1096-1355

IPT/TIG domain.
563-655
657-739
762-854

Plexin repeat.
519-562

Integrins, beta chain.
525-543

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Figure 89

CAAGAGCACTGGCCAAGTCAGCTTCTTCTGAGAGAGTCTCTAGAAGACATGATGCTACAC
TCAGCTTTGGGTCTCTGCCTCTTACTCGTCACAGTTTCTTCCAACCTTGCCATTGCAATA
AAAAAGGAAAAGAGGCCTCCTCAGACACTCTCAAGAGGATGGGGAGATGACATCACTTGG
GTACAAACTTATGAAGAAGGTCTCTTTTATGCTCAAAAAAGTAAGAAGCCATTAATGGTT
ATTCATCACCTGGAGGATTGTCAATACTCTCAAGCACTAAAGAAAGTATTTGCCCAAAT
GAAGAAATACAAGAAATGGCTCAGAAATAAGTTCATCATGCTAAACCTTATGCATGAAACC
ACTGATAAGAATTTATCACCTGATGGGCAATATGTGCCTAGAATCATGTTTGTAGACCCT
TCTTTAACAGTTAGAGCTGACATAGCTGGAAGATACTCTAACAGATTGTACACATATGAG
CCTCGGGATTTACCCCTATTGATAGAAAAACATGAAGAAAGCATTAAAGACTTATTCAGTCA
GAGCTATAAGAGATGATAGAAAAAAGCCTTCACTTCAAAGAAGTCAAATTTTCATGAAGAA
AACCTCTGGCACATTGACAAATACTAAATGTGCAAGTATATAGATTTTGTAATATTACTA
TTTAGTTTTTTTAAATGTGTTTGCAATAGTCTTATTAAAATAAATGTTTTTTAAAAAAA
AAAAAAA

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Figure 90

MMLHSALGLCLLLVTVSSNLAIKKEKRPPQTLRGWGDDITWVQTYEEGLFYAQKSKK
PLMVIHHLEDCQYSQALKKVFAQNEEIQEMAQNKFIMLNLMHETTDKNLSPDGQYVPRIM
FVDPSLTVRADIAGRYSNRLYTYEPRDLPLLIENMKKALRLIQSEL

Signal sequence.
1-23

Transmembrane domain.
none

N-myristoylation site.
51-56

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Figure 91

ATGGCCGTAGGGAAGTTCCTGCTGGGCTCTCTGCTGCTCCTGTCCCTGCAGCTGGGACAG
GGCTGGGGCCCCGATGCCCCGTGGGGTTCCTCGTGGCCGATGGAGAGTTCTCGTCTGAACAG
GTGGCAAAGGCTGGAGGGACCTGGCTGGGCACCCACCGCCCCCTTGCCCGCCTGCGCCGA
GCCCTGTCTGGTCCATGCCAGCTGTGGAGCCTGACCCTGTCCGTGGCAGAGCTAGGCCTG
GGCTACGCCTCAGAGGAGAAGGTCATCTTCCGCTACTGCGCCGGCAGCTGCCCCCGTGGT
GCCCCACCCAGCATGGCCTGGCGCTGGCCCCGGCTGCAGGGCCAGGGCCGAGCCCACGGT
GGGCCCTGCTGCCGGCCCCACTCGCTACACCGACGTGGCCTTCCTCGATGACCGCCACCGC
TGGCAGCGGCTGCCCCAGCTCTCGGCGGCTGCCTGCGGCTGTGGTGGCTGA

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Figure 92

MAVGKFLLGSLLLLSLQLGQGWGPDARGVPVADGEFSSEQVAKAGGTWLGTHRPLARLRR
ALSGPCQLWSLTLSVAELGLGYASEEKVIFRYCAGSCPRGARTQHGLALARLQGQGRAHG
GPCCRPTRYTDVAFLDDRHRWQRLPQLSAAACGCGG

Signal sequence.
1-23

Transmembrane domain.
none

N-myristoylation site.
28-33
46-51
79-84
106-111
114-119
120-125

Transforming growth factor beta like domain.
63-155

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Figure 93

CTCXTGTGXTCXGGGCGCCTGGCCTATTGAAGGTTTTTAATCTTCAGAGTTTCGACTTTA
TCAACAACACTTAGAAGCCACCAAAGAATTGCAGATGGATCCTAATAGAATATCAGAAGA
TGGCACTCACTGCATTTATAGAATTTTGAGACTCCATGAAAATGCAGATTTTCAAGACAC
AACTCTGGAGAGTCAAGATACAAAATTAATACCTGATTCATGTAGGAGAATTAAACAGGC
CTTTCAAGGAGCTGTGCAAAAGGAATTACAACATATCGTTGGATCACAGCACATCAGAGC
AGAGAAAGCGATGGTGGATGGCTCATGGTTAGATCTGGCCAAGAGGAGCAAGCTTGAAGC
TCAGCCTTTTGCTCATCTCACTATTAATGCCACCGACATCCCATCTGGTTCCCATAAAGT
GAGTCTGTCCTCTTGGTACCATGATCGGGGTTGGGCCAAGATCTCCAACATGACTTTTAG
CAATGGAAAACATAAGTTAATCAGGATGGCTTTTATTACCTGTATGCCAACATTTGCTT
TCGACATCATGAACTTCAGGAGACCTAGCTACAGAGTATCTTCAACTAATGGTGTACGT
CACTAAAACCAGCATCAAAATCCCAAGTTCTCATAACCCTGATGAAAGGAGGAAGCACCAA
GTATTGGTCAGGGAATTCTGAATTCCATTTTATTCCATAAACGTTGGTGGATTTTTTAA
GTTACGGTCTGGAGAGGAAATCAGCATCGAGGTCTCCAACCCCTCCTTACTGGATCCGGA
TCAGGATGCAACATACTTTGGGGCTTTTAAAGTTCGAGATATAGATTGAGCCCCAGTTTT
TGGAGTGTTATGTATTTCTTGGATGTTTGGAAACATTTTTTAAACAAGCCAAGAAAGAT
GTATATAGGTGTGTGAGACTACTAAGAGGC

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Figure 94

MDPNRI SEDGTHCIYRILRLHENADFQDTTLESQDTKLIPDSCRRIKQAFQGAVQKELQH
IVGSQH IRAEKAMVDG SWLDLAKRSKLEAQPF AHLTINATDIPSGSHKVSLS SWYHDRGW
AKISNMTFSNGKLIVNQDGFYYLYANICFRHHETSGDLATEYLQLMVYVTKTSIKIPSSH
TLMKGGSTKYWSGNSEFHFYSINVGGFFKLRSGEESISIEVSNPSLLDPDQDATYFGAFKV
RDID

Signal sequence.
none

Transmembrane domain.
none

N-glycosylation site.
98-101
125-128

TNF (Tumor Necrosis Factor) family.
113-240

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Figure 95

CACTCCCAAAGAACTGGGTACTCAACACTGAGCAGATCTGTTCTTTGAGCTAAAAACCAT
GTGCTGTACCAAGAGTTTGTCTCCTGGCTGCTTTGATGTCAGTGCTGCTACTCCACCTCTG
CGGCGAATCAGAAGCAGCAAGCAACTTTGACTGCTGTCTTGGATACACAGACCGTATTCT
TCATCCTAAATTTATTGTGGGCTTCACACGGCAGCTGGCCAATGAAGGCTGTGACATCAA
TGCTATCATCTTTACACAAAGAAAAAGTTGTCTGTGTGCGCAAATCCAAAACAGACTTG
GGTGAAATATATTGTGCGTCTCCTCAGTAAAAAAGTCAAGAACATGTAAAAACTGTGGCT
TTTCTGGAATGGAATTGGACATAGCCCAAGAACAGAAAGAACCCTTGCTGGGGTTGGAGGT
TTCACCTGCACATCATGGAGGGTTTAGTGCTTATCTAATTTGTGCCTCACTGGACTTGTC
CAATTAATGAAGTTGATTTCATATTGCATCATAGTTTGCTTTGTTTAAGCATCACATTAAA
GTAAACTGTATTTTATGTTATTTATAGCTGTAGGTTTTCTGTGTTTAGCTATTTAATAC
TAATTTTCCATAAGCTATTTTGGTTTAGTGCAAAGTATAAAATTATATTTGGGGGGGAAT
AAGATTATATGGACTTTCTTGCAAGCAACAAGCTATTTTTTAAAAAACTATTTAACATT
CTTTTGTTTATATTGTTTTGTCTCCTAAATTGTTGTAATTGCATTATAAAATAAGAAAAA
CATTAATAAGACAAATATT

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Figure 96

MCCTKSLLLLAALMSVLLLHLGGESEAASNFDCCCLGYTDRILHPKFIVGFTRQLANEGCDI
NAIIFHTKKKLSVCANPKQTWVKYIVRLLSKKVKNM

Signal sequence.
1-26

Transmembrane domain.
none

cAMP- and cGMP-dependent protein kinase phosphorylation site.
69-72

N-myristoylation site.
57-62

Small cytokines (intecrine/chemokine)
24-89

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Figure 97

CGGCACGAGCACAGTGCTCCGGATCCTCCAATCTTCGCTCCTCCAATCTCCGCTCCTCCA
CCCAGTTCAGGAACCCGCGACCGCTCGCAGCGCTCTCTTGACCACTATGAGCCTCCTGTC
CAGCCGCGCGGCCCGTGTCCCCGGTCCTTCGAGCTCCTTGTGCGCGCTGTTGGTGCTGCT
GCTGCTGCTGACGCAGCCAGGGCCCATCGCCAGCGCTGGTCCTGCCGCTGCTGTGTTGAG
AGAGCTGCGTTGCGTTTGTGTTACAGACCACGCAGGGAGTTCATCCCAAATGATCAGTAA
TCTGCAAGTGTTGCGCCATAGGCCACAGTGCTCCAAGGTGGAAGTGGTAGCCTCCCTGAA
GAACGGGAAGGAAATTTGTCTTGATCCAGAAGCCCCCTTTCTAAAGAAAGTCATCCAGAA
AATTTTGGACGGTGGAACAAGGAAAACCTGATTAAGAGAAATGAGCACGCATGGAAAAGT
TTCCCAGTCTACAGCAGAGAAGTTTTCTGGAGGTCTCTGAACCCAGGGAAGACAAGAAGG
AAAGATTTTGTGTTGTTGTTTGTGTTTATTTGGTTTCCCCAGTAGTTAGCTTTCTTCCCTGGAT
TCCTCACTTTTGAAGAGTGTGAGGAAAACCTATGTTTGGCGCTTAAGCTTTCAGCTCAGC
TTAATGAAGTGTTTAGCATAGTACCTCTGCTATTTGCTGTTATTTTATCTGCTATGCTAT
TGAAGTTTTGGCAATTGACTATAGTGTGAGCCAGGAATCACTGGCTGTTAATCTTACAAA
GTGTCTTGGAATTGTAGGTGACTATTATTTTCCAAGAAATATCCCTTAAGATATTAAC
GAGAAGGCTGGGGGTTTAATGTGGAATGATGTTTCAAAGGAATCCTGTGATGGAAATA
CAACTGGTATCTTCACCTTTTGTAGGAATTGGGAAATATTTTAATGTTTCTTGGGGAATAT
GTTAGAGAATTCCCTTACTCTTGATTGTGGGATACTATTTAATTATTTCACTTTAGAAAG
CTGAGTGTTTCACACCTTATCTATGTAGAATATATTTCTTATTCAGAATTTCTAAAAGT
TTAAGTTCTATGAGGGCTAATATCTTATCTTCTATAATTTTAGACATTGCTTTAACTTT
TTAGTAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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Figure 98

MSLLSSRAARVPGPSSSLCALLVLLLLLTQPGPIASAGPAAAVLRELRCVCLQTTQGVHP
KMISNLQVFAIGPQCSKVEVVASLKNGKEICLDPEAPFLKKVIQKILDGGNKEN

Signal sequence.
1-31

Transmembrane domain.
none

Small cytokines (intecrine/chemokine).
41-107

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Figure 99

CCCAATCAAGAGAAATTCCATACTATCACCAGTTGGCCGACTTTCCAAGTCTAGTGCAGA
AATCCAAGGCACCTCACACCTAGAGTTCTTATACCTCTGAGACTCCAGAGGAAAGAACAA
GACAGTGCAGAAGGATATGTTAGAACCCACTGAAAACCTAGAAGGTTGAAAAGGAAGCAT
ACCCTCCTGACCTATAAGAAAATTTTCAGTCTGCAGGGGGATATCCTTGTGGCCCAAGAC
ATTGGTGTTATCATTTGACTAAGAGGAAATTATTTGTGGTGAGCTCTGAGTGAGGATTAG
GACCAGGGAGATGCCAAGTTTCTATCACTTACCTCATGCCTGTAAGACAAGTGTTTTGT
CCAATTGATGAATGGGGAGAAAACAGTTCAGCCAATCACTTATGGGCACAGAATGGAATT
TGAAGGGTCTGGTGCCTGCCCTTGTCTACGTAACAAGAGAGGCATCGATGAGTTTTAT
CTGAGTCATTTGGGAAAGGATAATTCTTGACCAAGCCATTTTCCTAAACACAGAAGAAT
AGGGGGATTCCTTAACCTTCATTGTTCTCCAGGATCATAGGTCTCAGGATAAATTAAAAA
TTTTTCAGGTCAGACCACTCAGTCTCAGAAAGGCAAAGTAATTTGCCCCAGGTCAGTAGTC
CAAGATGTTATTCTCTTTGAACAAATGTGTATGTCCAGTCACATATTCTTCATTCATTCC
TCCCCAAAGCAGTTTTTTAGCTGTTAGGTATATTCGATCACTTTAGTCTATTTTGAAAATG
ATATGAGACGCTTTTTTAAGCAAAGTCTACAGTTTCCCAATGAGAAAATTAATCCTCTTTC
TTGTCTTTCCAGTTGTGAGACAACTCCCACACAGCACTTTAAAAATCAGTTCCCAGCTC
TGCACTGGGAACTAGAACTAGGCCTGGCCTTCACCAAGAACCGAATGAACTATACCAACA
AATTCCTGCTGATCCCAGAGTCGGGAGACTACTTCATTTACTCCCAGGTCACATTCGGTG
GGATGACCTCTGAGTGCAGTGAAATCAGACAAGCAGGCCGACCAAACAAGCCAGACTCCA
TCACTGTGGTCATCACCAAGGTAACAGACAGCTACCCTGAGCCAACCCAGCTCCTCATGG
GGACCAAGTCTGTATGCGAAGTAGGTAGCAACTGGTTCAGCCCATCTACCTCGGAGCCA
TGTTCTCCTTGCAAGAAGGGGACAAGCTAATGGTGAACGTCAGTGACATCTCTTTGGTGG
ATTACACAAAAGAAGATAAAACCTTCTTTGGAGCCTTCTTACTATAGGAGGAGAGCAAAT
ATCATTATATGAAAATCCTCTGCCACCGAGTTCCTAATTTTCTTTGTTCAAATGTAATTA
TAACCAGGGGTTTTCTTGGGGCCGGGAGTAGGGGGCATTCACAGGGACAACGGTTTTAGC
TATGAAATTTGGGGCCAAAATTTACACTTCATGTGCCTTACTGATGAGAGTACTAACTG
GAAAAAGGCTGAAGAGAGCAAATATATTATTAAGATGGGTTGGAGGATTGGCGAGTTTCT
AAATATTAAGACACTGATCACTAAATGAATGGATGATCTACTCGGGTCAGGATTGAAAGA
GAAATATTTCAACACCTCCCTGCTATACAATGGTCACCAGTGGTCCAGTTATTGTTCAAT
TTGATCATAAATTTGCTTCAATTCAGGAGCTTTGAAGGAAGTCCAAGGAAAGCTCTAGAA
AACAGTATAAACTTTTCAGAGGCAAAATCCTTCACCAATTTTTTCCACATACTTTCATGCCT
TGCCTAAAAAAAATGAAAAGAGAGTTGGTATGTCTCATGAATGTTACACAGAAGGAGTT
GGTTTTTCATGTCATCTACAGCATATGAGAAAAGCTACCTTTCTTTTGATTATGTACACAG
ATATCTAAATAAGGAAGTTTGAGTTTCACATGTATATCCCAAATACAACAGTTGCTTGTA
TTCAGTAGAGTTTTCTTGCCACCTATTTTGTGCTGGGTTCTACCTTAACCCAGAAGACA
CTATGAAAAACAAGACAGACTCCACTCAAAATTTATATGAACACCACTAGATACTTCCTG
ATCAAACATCAGTCAACATACTCTAAAGAATAACTCCAAGTCTTGGCCAGGCGCAGTGGC
TCACACCTGTAATCCCAACACTTTGGGAGGCCAAGGTGGGTGGATCATCTAAGGCCGGGA
GTTCAAGACCAGCCTGACCAACGTGGAGAAACCCCATCTCTACTXAAAATACXAAATTAG
CCGGGCGTGGTAGCGCATGGCTGTAAXCCTGGCTACTCAGGAGGCCGAGGCAGAAAXAATT
XCTTGAAGTGGGGAGGCAGAGGTTGCGGTGAGCCCAGAXCGCGCCATTGCACTCCAGCCT
GGGTAACAAGAGCAAACTCTGTCCAAAAA

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Figure 100

MRRFLSKVYSFPMRKLILFLVFPVVRQTPTQHFKNQFPALHWELELGLAFTKNRMNYTNK
FLLIPESGDYFIYSQVTFRGMTSECSEIRQAGRPNKPDSITVVITKVTDSYPEPTQLLMG
TKSVCEVGSNWFQPIYLGAMFSLQEGDKLMVNVSDISLVDYTKEDKTFFGAFL

Signal sequence.
1-27

Transmembrane domain.
none

N-glycosylation site.
56-59
152-155

N-myristoylation site.
47-52
138-143

TNF(Tumor Necrosis Factor) family.
40-174

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Figure 101

ATGACAACCTCACTAGATACAGTTGAGACCTTTGGTACCACATCCTACTATGATGACGTG
GGCCTGCTCTGTGAAAAAGCTGATACCAGAGCACTGATGGCCCAGTTTGTGCCCCCGCTG
TACTCCCTGGTGTTCACTGTGGGCCTCTTGGGCAATGTGGTGGTGGTGTATGATCCTCATA
AAATACAGGAGGCTCCGAATTATGACCAACATCTACCTGCTCAACCTGGCCATTTTCGGAC
CTGCTCTTCCTCGTCACCCCTTCCATTCTGGATCCACTATGTCAGGGGGCATAACTGGGTT
TTTGGCCATGGCATGTGTAAGCTCCTCTCAGGGTTTTATCACACAGGCTTGTACAGCGAG
ATCTTTTTTCATAATCCTGCTGACAATCGACAGGTACCTGGCCATTGTCCATGCTGTGTTT
GCCCTTCGAGCCCGGACTGTCACTTTTGGTGTTCATCACCAGCATCGTCACCTGGGGCCTG
GCAGTGCTAGCAGCTCTTCCTGAATTTATCTTCTATGAGACTGAAGAGTTGTTTGAAGAG
ACTCTTTGCAGTGCTCTTTACCCAGAGGATACAGTATATAGCTGGAGGCATTTCCACACT
CTGAGAATGACCATCTTCTGTCTCGTTCTCCCTCTGCTCGTTATGGCCATCTGCTACACA
GGAATCATCAAAACGCTGCTGAGGTGCCCCAGTAAAAAAAAGTACAAGGCCATCCGGCTC
ATTTTTGTCATCATGGCGGTGTTTTTTCATTTTCTGGACACCCTACAATGTGGCTATCCTT
CTCTCTTCCTATCAATCCATCTTATTTGGAAATGACTGTGAGCGGAGCAAGCATCTGGAC
CTGGACATGCTGGTGACAGAGGTGATCGCCTACTCCCCTGGTGCTGCCTCAATCCCCTC
ATCTACGCCTTTGTTGGAGAGAGGTTCCGGAAGTACCTGCGCCACTTCTTCCACAGGCAC
TTGCTCATGCACCTGGGCAGATACATCCCATTCCTTCTAGTGAGAAGCTGGAAAGAACC
AGCTCTGTCTCTCCATCCACAGGAGAGCCGGAACCTCTCTATTGTGTTTTAG

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Figure 102

MTTSLDVTVETFGTTSSYYDDVGLLCEKADTRALMAQFVPPLYSLVFTVGLLGNVVVVMILI
KYRRLRIMTNIYLLNLAISDLLFLVTLPFWIHVVRGHNWVFGHGMCKLLSGFYHTGLYSE
IFFIILLTIDRYLAIVHAVFALRARTVTFGVITSIVTWGLAVLAALPEFIFYETEELFEE
TLCSALYPEDTVYSWRHFHTLRMTIFCLVLP LLVMAICYTGIIKTLLRCPSKKKYKAIRL
IFVIMAVFFIFWTPYNVAILLSSYQSILFGNDCERSKHLDDLMLVTEVIAYSHWCCLNPL
IYAFVGERFRKYLRHFFHRHLLMHLGRYIPFLPSEKLERTSSVSPSTGEPELSIVF

Signal sequence.
none

Transmembrane domain.
36-56
70-90
114-134
148-168
201-221
240-260
283-303

N-myristoylation site.
48-53
150-155
221-226

7 transmembrane receptor (rhodopsin family).
51-302

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Figure 103

ATACAGGACAGAGCATGGCTCGCCTACAGACTGCACTCCTGGTTGTCCTCGTCCTCCTTG
CTGTGGCGCTTCAAGCAACTGAGGCAGGCCCCCTACGGCGCCAACATGGAAGACAGCGTCT
GCTGCCGTGATTACGTCCGTTACCGTCTGCCCCCTGCGCGTGGTGAAACACTTCTACTGGA
CCTCAGACTCCTGCCCCGAGGCCTGGCGTGGTGTGCTAACCTTCAGGGATAAGGAGATCT
GTGCCGATCCCAGAGTGCCCTGGGTGAAGATGATTCTCAATAAGCTGAGCCAATGAAGAG
CCTACTCTGATGACCGTGGCCTTGGCTCCTCCAGGAAGGCTCAGGAGCCCTACCTCCCTG
CCATTATAGCTGCTCCCCGCCAGAAGCCTGTGCCAACTCTCTGCATTCCCTGATCTCCAT
CCCTGTGGCTGTCACCCCTTGGTCACCTCCGTGCTGTCACTGCCATCTCCCCCCTGACCCC
TCTAACCCATCCTCTGCCTCCCTCCCTGCAGTCAGAGGGTCCTGTTCCCATCAGCGATTCT
CCCTGCTTAAACCCTTCCATGACTCCCCACTGCCCTAAGCTGAGGTCAGTCTCCCAAGCC
TGGCATGTGGCCCTCTGGATCTGGGTTCATCTCTGTCTCCAGCCTGCCCACTTCCCTTC
ATGAATGTTGGGTCTAGCTCCCTGTTCTCCAAACCCATACTACACATCCCACTTCTGGG
TCTTTGCCTGGGATGTTGCTGACACTCAGAAAGTCCCACCACCTGCACATGTGTAGCCCC
ACCAGCCCTCCAAGGCATTGCTCGCCCAAGCAGCTGGTAATTCCATTTTCATGTATTAGAT
GTCCCCTGGCCCTCTGTCCCCTCTTAATAACCCTAGTCACAGTCTCCGCAGATTCTTGGG
ATTTGGGGGTTTTCTCCCCCACCTCTCCACTA

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Figure 104

MARLQTALLVVLVLLAVALQATEAGPYGANMEDSVCCRDYVRYRLPLRVVKH FYWTS DSC
PRPGVVLLTFRDKEICADPRVPWVKMILNKLSQ

Signal sequence.
1-24

Transmembrane domain.
none

Small cytokines (intecrine/chemokine).
28-91

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Figure 105

CAGATGGCTCCATAATGACAGCTTCATAATGGCAGTGGGTGAGCCCCTGGTGCACATCAG
GGTCACTCTTCTGCTGCTCTGGTTGGGGATGTTTTTGTCTATTTCTGGCCACTCTCAGGC
CAGGCCCTCCCAGTATTTCACTTCTCCAGAAGTGGTGATCCCTTTGAAGGTGATCAGCAG
GGGCAGAGGTGCAAAGGCTCCTGGATGGCTCTCCTATAGCCTGCGGTTTGGGGGACAGAG
ATACATTGTCCACATGAGGGTAAATAAGCTGTTGTTTGCTGCACACCTTCCTGTGTTCAC
CTACACAGAGCAGCATGCCCTGCTCCAGGATCAGCCCTTCATCCAGGATGACTGGTACTA
CCATGGTTATGTGGAGGGGGTCCCTGAGTCCTTGGTTGCCCTTAGTACCTGTTCTGGGGG
CTTTCTTGGAATGCTACAGATAAATGACCTTGTTTATGAAATCAAGCCAATTAGTGTTTC
TGCCACATTTGAACACCTAGTATATAAGATAGACAGTGATGATACACAGTTTCCACCTAT
GAGATGTGGGTTAACAGAAGAGAAAAATAGCACACCAGATGGAGTTGCAATTGTCATATAA
TTTCACTCTGAAGCAAAGTTCTTTTGTGGGCTGGTGGACCCATCAGCGGTTTGTGAGCT
GGTAGTGGTCGTGGATAATATTAGATATCTTTTCTCTCAAAGTAATGCAACAACAGTGCA
GCATGAAGTATTTAACGTTGTCAATATAGTGGATTCCTTCTATCATCCTTTGGAGGTTGA
TGTAATTTTGACTGGAATTGATATATGGACTGCATCAAATCCACTTCCTACCAGTGGAGA
CCTAGATAATGTTTTAGAGGACTTTTCTATTTGGAAGAATTATAACCTTAATAATCGACT
ACAACATGATGTTGCACATCTTTTCATAAAAGACACACAAGGCATGAAGCTTGGTGTTGC
CTATGTTAAAGGAATATGCCAGAATCCTTTTAATACTGGAGTTGATGTTTTTGAAGACAA
CAGGTTGGTCGTTTTTGAATTACTTTGGGCCACGAGCTTGGTCATAATTTGGGTATGCA
ACATGACACCCAGTGGTGTGTGTGCGAGCTACAGTGGTGCATAATGCATGCCTATAGAAA
GGTGACAACATAAATTTAGCAACTGCAGTTATGCCCAATATTGGGACAGTACTATCAGTAG
TGGATTATGTATTCAACCGCCTCCATATCCAGGGAATATATTTAGACTGAAGTACTGTGG
GAATCTAGTGGTTGAAGAAGGGGAGGAATGTGACTGTGGAACCATAACGGCAGTGTGCAA
AGATCCCTGTTGTCTGTTAAACTGTACTCTACATCCTGGGGCTGCTTGTGCTTTTGGAAT
ATGTTGCAAAGACTGCAAATTTCTGCCATCAGGAACCTTTATGTAGACAACAAGTTGGTGA
ATGTGACCTTCCAGAGTGGTGCAATGGGACATCCCATCAATGCCCAGATGATGTGTATGT
GCAGGACGGGATCTCCTGTAATGTGAATGCCTTCTGCTATGAAAAGACGTGTAATAACCA
TGATATACAATGTAAAGAGATTTTTGGCCAAGATGCAAGGAGTGCATCTCAGAGTTGCTA
CCAAGAAATCAACACCCAAGGAAACCGTTTCGGTCACTGTGGTATTGTAGGCACAACATA
TGTAATAATGTTGGACCCCTGATATCATGTGTGGGAGGGTTCAGTGTGAAAATGTGGGAGT
AATTTCCAATCTGATAGAGCATTCTACAGTGCAGCAGTTTCACCTCAATGACACCACTTG
CTGGGGCACTGATTATCATTTAGGGATGGCTATACCTGATATTGGTGAGGTGAAAGATGG
CACAGTATGTGGTCCAGAAAAGATCTGCATCCGTAAGAAGTGTGCCAGTATGGTTCATCT
GTCACAAGCCTGTCAGCGTAAGACCTGCAACATGAGGGGAATCTGCAACAACAACAACA
CTGTCACTGCAACCATGAATGGGCACCCCATACCTGCAAGGACAAAGGCTATGGAGGTAG
TGCTGATAGTGGCCACCTCCTAAGAACAACATGGAAGGATTAAATGTGATGGGAAAGTT
GCGTTACCTGTCACTATTGTGCCTTCTTCCTTTGGTTGCTTTTTTTATTATTTTGCTTACA
TGTGCTTTTTTAAGAAACGCACAAAAAGTAAAGAAGATGAAGAAGGATAAGAGAAATGGGA
AAAAGAAGGAGACTAACTTTATACTTCATTTTTTAATATCCAATTTTTTAATAGAAAAAT
ATGAAGCCATGTCTCACTGTTTAAATAAACTTCATGGACATTTTCATGTCAGGATTGCAA
GCATTAGCTATCACAGCAAAGGATTCCTAGCCTATTCTTACTTACTTTACAGTGTCTTAA
GCAATATTAAAGGTTCCTTTTCCCAAAAAAAAAAAAAAAAAAAAAA

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Figure 106

MAVGEPLVHIRVTLLLLLWLGMFSLISGHSQARPSQYFTSPEVVIPLKVISRGRGAKAPGW
LSYSLRFGGQRYIVHMRVNKLLFAAHLPVFTYTEQHALLQDQPFIQDDWYYHGYVEGVPE
SLVALSTCSGGFLGMLQINDLVYEIKPISVSATFEHLVYKIDSDDTQFPPMRCGLTEEKI
AHQMELQLSYNFTLKQSSFVGWWT HQRFVELVVVDNIRYLFSQSNATTVQHEVFNVVNI
VDSFYHPLEVDVILTGIDIWTASNPLPTSGDLDNVLEDFSIWKNYNLNNRLQHDVAHLFI
KDTQGMKLGVAIVKIGICQNPFGVDVFEDNRLVVFAITLGHELGHNLGMQHDTQWCVC
LQWCIMHAYRKVTTKFSNCSYAQYWDSTISSGLCIQPPYPGNI FRLKYCGNLVVEEGEE
CDCGTIRQCAKDPCCLLNCTLHPGAACAFGICCKDCKFLPSGTLCRQQVGECDLPEWCNG
TSHQCPDDVYVQDGISCNVNAFCYEKTCNNHDIQCKEIFGQDARSASQSCYQEINTQGNR
FGHCGIVGTTYVKCWTPDIMCGRVQCENGVIPNLIEHSTVQQFHLNDTTCWGTDYHLGM
AIPDIGEVKDGTVCGPEKICIRKKCASMVHLSQACQRKTCNMRGICNNKQHCHCNHEWAP
PYCKDKGYGGSADSGPPPKNNMEGLNVMGKLRYLSLLCLLPLVAFLLFCLHVLFFKKRTKS
KEDEEG

Signal sequence.
1-27

Transmembrane domain.
689-709

N-glycosylation site.
191-194
226-229
378-381
438-441
479-482
587-590

cAMP- and cGMP-dependent protein kinase phosphorylation site.
370-373
715-718

N-myristoylation site.
20-25
117-122
130-135
305-310
444-449
494-499
538-543
545-550
570-575
644-649
670-675

Neutral zinc metallopeptidases, zinc-binding region signature.
339-348

Reprolysin (M12B) family zinc metalloprotease.
207-399

Reprolysin family propeptide.
75-192

Disintegrin.
416-491

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Figure 107

TATTTACCATATCAGATTCACATTCAGTCCTCAGCAAAATGAAGGGCTCCATTTTCACTC
TGTTTTTATTCTCTGTCCTATTTGCCATCTCAGAAGTGCGGAGCAAGGAGTCTGTGAGAC
TCTGTGGGCTAGAATACATACGGACAGTCATCTATATCTGTGCTAGCTCCAGGTGGAGAA
GGCATCTGGAGGGGATCCCTCAAGCTCAGCAAGCTGAGACAGGAAACTCCTTCCAGCTCC
CACATAAACGTGAGTTTTCTGAGGAAAATCCAGCGCAAAACCTTCCGAAGGTGGATGCCT
CAGGGGAAGACCGTCTTTGGGGTGGACAGATGCCCACTGAAGAGCTTTGGAAGTCAAAGA
AGCATTCAGTGATGTCAAGACAAGATTTACAAACTTTGTGTTGCACTGATGGCTGTTCCA
TGACTGATTTGAGTGCTCTTTGCTAAGACAAGAGCAAATACCCAATGGGTGGCAGAGCTT
TATCACATGTTTAATTACAGTGTTTTACTGCCTGGTAGAACACTAATATTGTGTTATTAA
AATGATGGCTTTTGGGTAGGCAAACTTCTTTTCTAAAAGGTATAGCTGAGCGGTTGAAA
CCACAGTGATCTCTATTTTCTCCCTTTGCCAAGGTTAATGAACTGTTCTTTTCAAATTCT
ACTAATGCTTTGAAATTTCAAATGCTGCGCAAAATTGCAATAAAAATGCTA
TAAA

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Figure 108

MKGSIFTLFLFSVLFAISEVRSKESVRLCGLEYIRTVIYICASSRWRRLHLEGI PQAQQAE
TGNSFQLPHKREFSEENPAQNLPKVDASGEDRLWGGQMPTEELWKS KKHVMSRQDLQTL
CCTDGCSMTDLSALC

signal sequence

1-18

Transmembrane domain

none

cAMP- and cGMP-dependent protein kinase phosphorylation site.
107-110

N-myristoylation site.

3-8

52-57

96-101

125-130

Insulin family signature.

121-135

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Figure 109

CCAGGCCGGGAGGCGACGCGCCCAGCCGTCTAAACGGGAACAGCCCTGGCTGAGGGAGCT
GCAGCGCAGCAGAGTATCTGACGGCGCCAGGTTGCGTAGGTGCGGCACGAGGAGTTTTCC
CGGCAGCGAGGAGGTCCTGAGCAGCATGGCCCCGGAGGAGCGCCTTCCCTGCCGCCGCGCT
CTGGCTCTGGAGCATCCTCCTGTGCCTGCTGGCACTGCGGGCGGAGGCCGGGCCGCCGCA
GGAGGAGAGCCTGTACCTATGGATCGATGCTCACCAGGCAAGAGTACTCATAGGATTTGA
AGAAGATATCCTGATTGTTTCAGAGGGGAAAATGGCACCTTTTACACATGATTTTCAGAAA
AGCGCAACAGAGAATGCCAGCTATTCTGTCAATATCCATTCCATGAATTTTACCTGGCA
AGCTGCAGGGCAGGCAGAATACTTCTATGAATTCCTGTCCTTGCCTCCCTGGATAAAGG
CATCATGGCAGATCCAACCGTCAATGTCCCTCTGCTGGGAACAGTGCCTCACAAGGCATC
AGTTGTTCAAGTTGGTTTCCCATGTCTTGGAACACAGGATGGGGTGGCAGCATTTTGAAGT
GGATGTGATTGTTATGAATTCTGAAGGCAACACCATTCTCCAAACACCTCAAATGCTAT
CTTCTTTAAACATGTCAACAAGCTGAGTGCCCAGGCGGGTGCCGAAATGGAGGCTTTTG
TAATGAAAGACGCATCTGCGAGTGTCCTGATGGGTTCACGGACCTCACTGTGAGAAAGC
CCTTTGTACCCACGATGTATGAATGGTGGACTTTGTGTGACTCCTGGTTTCTGCATCTG
CCCACCTGGATTCTATGGAGTGAAGTGTGACAAAGCAAACCTGCTCAACCACCTGCTTTAA
TGGAGGGACCTGTTTCTACCCTGGAAAATGTATTTGCCCTCCAGGACTAGAGGGAGAGCA
GTGTGAAATCAGCAAATGCCACAACCCTGTGCAAATGGAGGTAAATGCATTGGTAAAAG
CAAATGTAAGTGTTCCAAAGGTTACCAGGGAGACCTCTGTTCAAAGCCTGTCTGCGAGCC
TGGCTGTGGTGACATGGAACCTGCCATGAACCCAAACAAATGCCAATGTCAAGAAGGTTG
GCATGGAAGACACTGCAATAAAAGGTACGAAGCCAGCCTCATAATGCCCTGAGGCCAGC
AGGCGCCCAGCTCAGGCAGCACACGCCTTCACTTAAAAAGGCCGAGGAGCGGCGGGATCC
ACCTGAATCCAATTACATCTGGTGAACTCCGACATCTGAAACGTTTTAAGTTACACCAAG
TTCATAGCCTTTGTTAACCTTTTCATGTGTTGAATGTTCAAATAATGTTTCATTACACTTAA
GAATACTGGCCTGAATTTTATTAGCTTCATTATAAATCACTGAGCTGATATTTACTCTTC
CTTTTAAGTTTTCTAAGTACGTCTGTAGCATGATGGTATAGATTTTCTTGTTTCAGTGCT
TTGGGACAGATTTTATATTATGTCAATTGATCAGGTAAAATTTTCAGTGTGTAGTTGGC
AGATATTTTCAAATTTACAATGCATTTATGGTGTCTGGGGGCAGGGGAACATCAGAAAGG
TTAAATTGGGCAAAAATGCGTAAGTCACAAGAATTTGGATGGTGCAGTTAATGTTGAAGT
TACAGCATTTTCAGATTTTATTGTGAGATATTTAGATGTTTGTACATTTTAAAAAATTGC
TCTTAATTTTAAACTCTCAATAACAATATATTTTGACCTTACCATTATTCCAGAGATTCA
GTATTAAAAAAAAAAAAAATTACACTGTGGTAGTGGCATTTAACAATATAATATATTCTA
AACACAATGAAATAGGGAATATAATGTATGAACTTTTGCATTGGCTTGAAGCAATATAA
TATATTGTAAACAAAACACAGCTCTTACCTAATAAACATTTTATACTGTTTGTATGTATA
AAATAAAGGTGCTGCTTTTAGTTTTTTTGGAATAAAAAAAAAAAAAAAAAAAAAAA
AA

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Figure 110

MARRSAFPAAALWLWSILLCLLALRAEAGPPQEESLYLWIDAHQARVLIGFEEDILIVSE
GKMAPFTHDFRKAQQORMPAIPVNIHSMNFTWQAAGQAEYFYEFSLRSLDKGIMADPTVN
VPLLGTVPHKASVVQVGFPCLGKQDGVAAFEVDVIVMNSEGNTILQTPQNAIFFKTCQQA
ECPGGCRNGGFCNERRICECPDGFHGPHEKALCTPRCMNGGLCVTPGFCICPPGFYGVN
CDKANCSTTCFNGGTCTFYPGKCI CPPGLEGEQCEISKCPQPCRNGGKCI GSKCKCSKGY
QGDLCSPVCEPGCGAHGTCHEPNKCQCQEGWHGRHCNKRYEASLIHALRPAGAQLRQHT
PSLKKAEEERRDPPESNYIW

Signal sequence

1-28

Transmembrane domain

none

N-glycosylation site

88-91

245-248

Tyrosine kinase phosphorylation site.

370-376

N-myristoylation site.

184-189

185-190

189-194

315-320

ATP/GTP-binding site motif A (P-loop).

285-292

EGF-like domain cysteine pattern signature.

198-209

230-241

262-273

294-305

326-337

WIF domain

38-173

EGF-like domain

177-209

214-241

246-273

278-305

310-337

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Figure 111

CCCACGCGTCCGCCCACGCGTCCGCCCACGGGTCCGCCCACGCGTCCGGGCCACCAGAAG
TTTGAGCCTCTTTGGTAGCAGGAGGCTGGAAGAAAGGACAGAAGTAGCTCTGGCTGTG **AT**
GGGGATCTTACTGGGCCTGCTACTCCTGGGGCACCTAACAGTGGACACTTATGGCCGTCC
CATCCTGGAAGTGCCAGAGAGTGTAACAGGACCTTGGAAGGGGATGTGAATCTTCCCTG
CACCTATGACCCCCCTGCAAGGCTACACCCAAGTCTTGGTGAAGTGGCTGGTACAACGTGG
CTCAGACCCTGTCAACCATCTTTCTACGTGACTCTTCTGGAGACCATATCCAGCAGGCAAA
GTACCAGGGCCGCTGCATGTGAGCCACAAGGTTCCAGGAGATGTATCCCTCCAATTGAG
CACCTGGAGATGGATGACCGGAGCCACTACACGTGTGAAGTCACCTGGCAGACTCCTGA
TGGCAACCAAGTCGTGAGAGATAAGATTACTGAGCTCCGTGTCCAGAACTCTCTGTCTC
CAAGCCCACAGTGACAACCTGGCAGCGGTTATGGCTTCACGGTGCCCCAGGGAATGAGGAT
TAGCCTTCAATGCCAGGCTCGGGGTTCTCCTCCCATCAGTTATATTTGGTATAAGCAACA
GACTAATAACCAGGAACCCATCAAAGTAGCAACCCTAAGTACCTTACTCTTCAAGCCTGC
GGTGATAGCCGACTCAGGCTCCTATTTCTGCACTGCCAAGGGCCAGGTTGGCTCTGAGCA
GCACAGCGACATTGTGAAGTTTGTGGTCAAAGACTCCTCAAAGCTACTCAAGACCAAGAC
TGAGGCACCTACAACCATGACATACCCCCTTGAAGCAACATCTACAGTGAAGCAGTCCTG
GGACTGGACCACTGACATGGATGGCTACCTTGGAGAGACCAGTGCTGGGCCAGGAAAGAG
CCTGCCTGTCTTTGCCATCATCCTCATCATCTCCTTGTGCTGTATGGTGGTTTTTACCAT
GGCCTATATCATGCTCTGTCTGGAAGACATCCCAACAAGAGCATGTCTACGAAGCAGCCAG
GTAAGAAAGTCTCTCCTCTTCCATTTTTGACCCCGTCCCTGCCCTCAATTTTGATTACTG
GCAGGAAATGTGGAGGAAGGGGGGTGTGGCACAGACCCAATCCTAAGGCCGAGGCCTTC
AGGGTCAGGACATAGCTGCCTTCCCTCTCTCAGGCACCTTCTGAGGTTGTTTTGGCCCTC
TGAACACAAAGGATAATTTAGATCCATCTGCCTTCTGCTTCCAGAATCCCTGGGTGGTAG
GATCCTGATAATTAATTGGCAAGAATTGAGGCAGAAGGGTGGGAAACCAGGACCACAGCC
CCAAGTCCCTTCTTATGGGTGGTGGGCTCTTGGGCCATAGGGCACATGCCAGAGAGGCCA
ACGACTCTGGAGAAACCATGAGGGTGGCCATCTTCGCAAGTGGCTGCTCCAGTGATGAGC
CAACTTCCCAGAATCTGGGCAACAACACTACTCTGATGAGCCCTGCATAGGACAGGAGTACC
AGATCATCGCCAGATCAATGGCAACTACGCCCGCCTGCTGGACACAGTTCCCTCTGGATT
ATGAGTTTCTGGCCACTGAGGGCAAAGTGTCTGTTAAAAATGCCCCATTAGGCCAGGAT
CTGCTGACATAATTGCCTAGTCAGTCCTTGCCTTCTGCATGGCCTTCTTCCCTGCTACCT
CTCTTCCCTGGATAGCCCAAAGTGTCCGCCTACCAACACTGGAGCCGCTGGGAGTCACTGG
CTTTGCCCTGGAATTTGCCAGATGCATCTCAAGTAAGCCAGCTGCTGGATTTGGCTCTGG
GCCCTTCTAGTATCTCTGCCGGGGGCTTCTGGTACTCCTCTCTAAATACCAGAGGGAAGA
TGCCCATAGCACTAGGACTTGGTCATCATGCCTACAGACACTATTCAACTTTGGCATCTT
GCCACCAGAAGACCCGAGGGAGGCTCAGCTCTGCCAGCTCAGAGGACCAGCTATATCCAG
GATCATTTTCTCTTTCTTCAGGGCCAGACAGCTTTTAATTGAAATTGTTATTTACAGGCC
AGGGTTCAGTTCTGCTCCTCCACTATAAGTCTAATGTTCTGACTCTCTCCTGGTGCTCAA
TAAATATCTAATCATAACAGC

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Figure 112

MGILLGLLLLGHLLTVDTYGRPILEVPESVTGPWKGDVNLPCITYDPLQGYTQVLVKWLVQR
GSDPVTIFLRDSSGDHIQQAKYQGRLHVSHKVPGDVSLQLSTLEMDDRSHYTCEVTWQTP
DGNQVVRDKITELRVQKLSVSKPTVTTGSGYGFTVPQGMRLSLQCQARGSPPISYIWYKQ
QTNNQEPIKVATLSTLLFKPAVIADSGSYFCTAKGQVGSEQHSDIVKFVVKDSSKLLKTK
TEAPTTMTYPLKATSTVKQSWDWTTDMDGYLGETSAGPGKSLPVFAIILIIISLCCMVVFT
MAYIMLCRKTSQQEHVYEAAR

Signal sequence
1-19

Transmembrane domain
281-301

Glycosaminoglycan attachment site.
149-152

cAMP- and cGMP-dependent protein kinase phosphorylation site.
308-311

N-myristoylation site.
2-7
148-153
158-163
207-212
215-220

Immunoglobulin domain
34-115
158-213

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Figure 113

AGCCGCTGCCCCGGGCGGGCGCCCGCGGCGGCACCATGAGTCCCCGCTCGTGCCCTGCGT
TCGCTGCGCCTCCTCGTCTTCGCCGTCTTCTCAGCCGCCGCGAGCAACTGGCTGTACCTG
GCCAAGCTGTCTCGTCGGTGGGGAGCATCTCAGAGGAGGAGACGTGCGAGAACTCAAGGGC
CTGATCCAGAGGCAGGTGCAGATGTGCAAGCGGAACCTGGAAGTCATGGACTCGGTGCGC
CGCGGTGCCCAGCTGGCCATTGAGGAGTGCCAGTACCAGTTCCGGAACCGGCGCTGGAAC
TGCTCCACACTCGACTCCTTGCCCGTCTTCGGCAAGGTGGTGACGCAAGGGACTCGGGAG
GCGGCCTTCGTGTACGCCATCTCTTCGGCAGGTGTGGCCTTTGCAGTGACGCGGGCGTGC
AGCAGTGGGGAGCTGGAGAAGTGCGGCTGTGACAGGACAGTGTCATGGGGTCAGCCACAG
GGCTTCCAGTGGTCAGGATGCTCTGACAACATCGCCTACGGTGTGGCCTTCTCACAGTCG
TTTGTGGATGTGCGGGAGAGAAGCAAGGGGGCCTCGTCCAGCAGAGCCCTCATGAACCTC
CACAACAATGAGGCCGGCAGGAAGGCCATCCTGACACACATGCGGGTGGAATGCAAGTGC
CACGGGGTGTGAGGCTCCTGTGAGGTAAAGACGTGCTGGCGAGCCGTGCCGCCCTTCCGC
CAGGTGGGTACGCACTGAAGGAGAAGTTTGATGGTGCCACTGAGGTGGAGCCACGCCGC
GTGGGCTCCTCCAGGGCACTGGTACCACGCAACGCACAGTTCAAGCCGCACACAGATGAG
GACCTGGTGTACTTGGAGCCTAGCCCCGACTTCTGTGAGCAGGACATGCGCAGCGGCGTG
CTGGGCACGAGGGGGCCGCACATGCAACAAGACGTCCAAGGCCATCGACGGCTGTGAGCTG
CTGTGCTGTGGCCGCGGCTTCCACACGGCGCAGGTGGAGCTGGCTGAACGCTGCAGCTGC
AAATTCCACTGGTGCTGCTTCGTCAAGTGCCGGCAGTGCCAGCGGCTCGTGGAGTTGCAC
ACGTGCCGATGACCGCCTGCCTAGCCCTGCGCCGGCAACCACCTAGTGGCCCAGGGAAGG
CCGATAATTTAAACAGTCTCCCAACACCTACCCCAAGAGATACTGGTTGTATTTTTTGT
CTGGTTTGGTTTTTTGGGTCCTCATGTTATTTATTTGCCGAAACCAGGCAGGCAACCCCAAG
GGCACCACAGGGCCTCCCCAAGCCTGGGCCTTTGTGGCTGCCACTGACCAAAGGGAC
CTTGCTCGTGCCGCTGGCTGCCCGCATGTGGCTGCCACTGACCACTCAGTTGTTATCTGT
GTCCGTTTTTCTACTTGCAGACCTAAGGTGGAGTAACAAGGAGTATTACCACCACATGGC
TACTGACCGTGTGTCATCGGGGAAGAGGGGGCCTTATGGCAGGGAAAATAGGTACCGACTTG
ATGGAAGTCACACCCTCTGGAAAAAAGAACTCTTAACCTCTCCAGCACACATACACATGGA
CTCCTGGCAGCTTGAGCCTAGAAGCCATGTCTCTCAAATGCCCTGAGAAAGGGAACAAGC
AGATAACAGGTCAAGGGCACCAGGTTCAATTTAGCCCTTACATGGACAGCTAGAGGTTCG
ATATCTGTGGGTCTTCCAGGCAAGAAGAGGGAGATGAGAGCAAGAGACGACTGAAGTCC
CACCTTAGAACCCAGCCTGCCCCAGCCTGCCCCCTGGGAAGAGGAACTTAACCACTCCCC
AGACCCACCTAGGCAGGCATATAGGCTGCCATCCTGGACCAGGGATCCCGGCTGTGCCTT
TGCAGTCATGCCCGAGTCACCTTTCACAGCGCTGTTCTCCATGAAACTGAAAAACACAC
ACACACACACACACACACACACACACACACACACACACACACACACACACACACCTGC
GAGAGAGAGGGAGGAAAGGGCTGTGCCTTTGCAGTCATGCCCGAGTCACCTTTCACAGCA
CTGTTCTC

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Figure 114

MSPRSCLRSLRLLVFAVFSAAASNWLYLAKLSSVGSISEEETCEKLKGLIQRQVQMCKRN
LEVMDSVRRGAQLAIEECQYQFRNRRWNCSTLDSL PVFGKVVTQGTREAAFVYAISSAGV
AFAVTRACSSGELEKCGCDRTVHGVSPQGFQWSGCSDNIAYGVAFSQS FVDVRERSKGAS
SSRALMNLHNNEAGRKAILTHMRVECKCHGVSGSCEVKT CWRAVPPFRQVGHALKEKFDG
ATEVEPRRVGSSRALVPRNAQFKPHTDEDLVYLEPSPDFCEQDMRSGVLGTRGRTC NKTS
KAIDGCELLCCGRGFHTAQVELAERCSCKFHWCCFVKCRQCQRLVELHTCR

Signal sequence
1-22

Transmembrane domain
none

N-glycosylation site.
88-91
297-300

N-myristoylation site.
70-75
105-110
119-124
137-142
154-159
162-167
178-183
210-215
250-255
287-292

Amidation site.
193-196

Wnt-1 family signature.
206-215

wnt family
42-351

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Figure 115

CTTAGATATTAACTGATAGGATAAGATATAAAATAATTTAAGATTGCTGATATATGTTT
TAAAATTAATTATTTGCTCAAGCATTGTGACAATTTACAGTTCTAATTGAGGTTTTTAAA
TTTAGTAGTTTGTAGGTATTTTAAGTTTTTGCCCCTGAATTCTTTATAGGTGCTGATAAGC
CTTTGGTTAAGTTTTACTCCATGAAAGACTATTACTGAAAAAATGTAATCTCAATAAAA
GAACTTTAATAAGCTTGACTAAATATTTAGAAAGCACATTGTGTTTCAGTGAACTTTGTA
TATAATGAATAGAATAATAAAAGATTATGTTGGATGACTAGTCTGTAATTGCCTCAAGGA
AAGCATACAATGAATAAGTTATTTTGGTACTTCCTCAAAATAGCCAACACAATAGGGAAA
TGGAGAAAATGTACTCTGAACACCATGAAAAGGGAACCTGAAAATCTAATGTGTAAACTT
GGAGAAATGACATTAGAAAACGAAAGCAACAAAAGAGAACACTCTCCAAAATAATCTGAG
ATGCATGAAAGGCAAACATTCCTAGAGCTGGAATTTCCCTAAGTCTATGCAGGGATAAG
TAGCATATTTGACCTTCACCATGATTATCAAGCACTTCTTTGGAAGTGTGTTGGTGCTGC
TGGCCTCTACCCTATCTTCTCTCTAGATTTGAACTGATTATCTTCCAGCAAAGACAAG
TGAATCAAGAAAGTTTAAACTCTTGAATAAGTTGCAAACCTTGTCAATTCAGCAGTGTC
TACCACACAGGAAAACTTTCTGCTTCCTCAGAAGTCTTTGAGTCCTCAGCAGTACCAA
AAGGACACACTCTGGCCATTCTCCATGAGATGCTTCAGCAGATCTTCAGCCTCTTCAGGG
CAAATATTTCTCTGGATGGTTGGGAGGAAAACACACGGAGAAATTCCTCATTCAACTTC
ATCAACAGCTAGAATACCTAGAAGCACTCATGGGACTGGAAGCAGAGAAGCTAAGTGGTA
CTTTGGGTAGTGATAACCTTAGATTACAAGTTAAAATGTACTTCCGAAGGATCCATGATT
ACCTGGAAAACAGGACTACAGCACCTGTGCCTGGGCCATTGTCCAAGTAGAAATCAGCC
GATGTCTGTTCTTTGTGTTTCAGTCTCACAGAAAACTGAGCAAACAAGGAAGACCTTGA
ACGACATGAAGCAAGAGCTTACTACAGAGTTTAGAAGCCCGAGG TAGGTGGAGGGACTAG
AGGACTTCTCCAGACATGATTCTTCATAGAGTGGTAATACAATTTATAGTACAATCACAT
TGCTTTGATTTTGTGTATATATATATTTATCTGAGTTTTAAGATTGTGCATATTGACCAC
AATTGTTTTTATTTTGTAATGTGGCTTTATATATTCTATCCATTTTAAATTGTTTGTATG
TCAAAATAAATTCATTAATATGGTTGATTCTTCAAAAAAAAAAAAAAAAAAAAAAAAAAA
AA

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Figure 116

MIKHFFGTVLVLLASTTIFSLDLKLIIFQQRQVNQESLKLLNKLQTLSTIQQCLPHRKNF
LLPQKSLSPQQYQKGHTLAILHEMLQQIFSLFRANISLDGWEENHTEKFLIQLHQQLEYL
EALMGLEAEKLSGTLGSDNLRLOVKMYFRRIDYLENQDYSTCAWAI VQVEISRCLFFVF
SLTEKLSKQGRPLNDMKQELTTEFRSPR

signal sequence
1-21

transmembrane domain
none

N-glycosylation site.
95-98
104-107

N-myristoylation site.
133-138

Interferon alpha, beta and delta family signature.
147-165

Interferon alpha/beta domain
1-190

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Figure 117

GACCCGGCCATGCGCGGCCTCGGGCTCTGGCTGCTGGGCGCGATGATGCTGCCTGCGATT
GCCCCAGCCGGCCCTGGGCCCCTCATGGAGCAGTATGAGGTCGTGTTGCCGCGGCGTCTG
CCAGGCCCCCGAGTCCGCGGAGCTCTGCCCTCCCACCTTGGGCCTGCACCCAGAGAGGGTG
AGCTACGTCCTTGGGGCCACAGGGCACAACTTCACCCTCCACCTGCGGAAGAACAGGGAC
CTGCTGGGTTCGGGCTACACAGAGACCTATACGGCTGCCAATGGCTCCGAGGTGACGGAG
CAGCCTCGCGGGCAGGACCACTGCTTATACCAGGGCCACGTAGAGGGGTACCCGGACTCA
GCCGCCAGCCTCAGCACCTGTGCCGGCCCTCAGGGGTTTCTTCCAGGTGGGGTCAGACCTG
CACCTGATCGAGCCCCTGGATGAAGGTGGCGAGGGCGGACGGCACGCCGTGTACCAGGCT
GAGCACCTGCTGCAGACGGCCGGGACCTGCGGGGTGACGCGACGACAGCCTGGGCAGCCTC
CTGGGACCCCGGACGGCAGCCGTCTTCAGGCCTCGGCCCGGGGACTCTCTGCCATCCCGA
GAGACCCGCTACGTGGAGCTGTATGTGGTCGTGGACAATGCAGAGTTCCAGATGCTGGGG
AGCGAAGCAGCCGTGCGTCATCGGGTGCTGGAGGTGGTGAATCACGTGGACAAGCTATAT
CAGAACTCAACTTCCGTGTGGTCTGGTGGGCCTGGAGATTTGGAATAGTCAGGACAGG
TTCCACGTCAGCCCCGACCCAGTGTCACTGGAGAACCTCCTGACCTGGCAGGCACGG
CAACGGACACGGCGGCACCTGCATGACAACGTACAGCTCATCACGGGTGTCGACTTCACC
GGGACTACTGTGGGGTTTGCCAGGGTGTCCGCCATGTGCTCCCACAGCTCAGGGGCTGTG
AACCAGGACCACAGCAAGAACCCCGTGGGCGTGGCCTGCACCATGGCCCATGAGATGGGC
CACAACCTGGGCATGGACCATGATGAGAACGTCCAGGGCTGCCGCTGCCAGGAACGCTTC
GAGGCCGGCCGCTGCATCATGGCAGGCAGCATTGGCTCCAGTTTCCCCAGGATGTTCACT
GACTGCAGCCAGGCCTACCTGGAGAGCTTTTTGGAGCGGCCGAGTCGGTGTGCTCGCC
AACGCCCTGACCTCAGCCACCTGGTGGGCGGCCCGTGTGTGGGAACCTGTTTGTGGAG
CGTGGGGAGCAGTGCGACTGCGGCCCCCGAGGACTGCCGGAACCGCTGCTGCAACTCT
ACCACCTGCCAGCTGGCTGAGGGGGCCAGTGTGCGCACGGTACCTGCTGCCAGGAGTGC
AAGGTGAAGCCGGCTGGTGAGCTGTGCCGTCCCAAGAAGGACATGTGTGACCTCGAGGAG
TTCTGTGACGGCCGGCACCCCTGAGTGCCCGGAAGACGCCTTCCAGGAGAACGGCACGCCC
TGCTCCGGGGGCTACTGCTACAACGGGGCCTGTCCCACTGGCCCAGCAGTGCCAGGCC
TTCTGGGGGGCCAGGTGGGCAGGCTGCCGAGGAGTCCTGCTTCTCCTATGACATCCTACCA
GGCTGCAAGGCCAGCCGGTACAGGGCTGACATGTGTGGCGTTCTGCAGTGCAAGGGTGGG
CAGCAGCCCCCTGGGGCGTGCCATCTGCATCGTGGATGTGTGCCACGCGCTCACCACAGAG
GATGGCACTGCGTATGAACAGTGCCCCGAGGGCACCCGGTGTGGACCAGAGAAGGTTTGC
TGGAAGGACGTTGCCAGGACTTACACGTTTACAGATCCAGCAACTGCTCTGCCCAGTGC
CACAACCATGGGGTGTGCAACCACAAGCAGGAGTGCCACTGCCACGCGGGCTGGGCCCCG
CCCCACTGCGCGAAGCTGCTGACTGAGGTGCACGCAGCGTCCGGGAGCCTCCCCGTCTC
GTGGTGGTGGTTCTGGTGCTCCTGGCAGTTGTGCTGGTCAACCTGGCAGGCATCATCGTC
TACCGCAAAGCCCGGAGCCGCATCCTGAGCAGGAACGTGGCTCCCAAGACCACAATGGGG
CGCTCCAACCCCTGTTCCACCAGGCTGCCAGCCGCGTGCCGGCCAAGGGCGGGGCTCCA
GCCCCATCCAGGGGCCCCCAAGAGCTGGTCCCCACCACCCACCCGGGCCAGCCCGCCCGA
CACCCGGCCTCCTCGGTGGCTCTGAAGAGGCCGCCCCCTGCTCCTCCGGTCACTGTGTCC
AGCCACCCCTTCCCAGTTCTGTCTACACCCGGCAGGCACCAAGCAGGTCAATCAAGCCA
ACGTTTCGCACCCCCAGTGCCCCCAGTCAAACCCGGGGCTGGTGGGCCAACCCTGGTCCA
GCTGAGGGTGCTGTTGGCCCCAAGGTTGCCCTGAAGCCCCCATCCAGAGGAAGCAAGGA
GCCGGAGCTCCACAGCACCCTAGGGGGGCACCTGCGCCTGTGTGGAAATTTGGAGAAGT
TGCGGCAGAGAAGCCATGCGTTCCAGCCTTCCACGGTCCAGCTAGTGCCGCTCAGCCCTA
GACCCTGACTTTGCAGGCTCAGCTGCTGTTCTAACCTCAGTAATGCATCTACCTGAGAGG
CTCCTGCTGTCCACGCCCTCAGCCAATTCTTCTCCCCGCCTTGGCCACGTGTAGCCCCA
GCTGTCTGCAGGCACCAAGGCTGGGATGAGCTGTGTGCTTGCGGGTGCGTGTGTGTGTACG
TGTCTCCAGGTGGCCGCTGGTCTCCCGCTGTGTTTCCAGGAGGCCACATATACAGCCCCCTCC
CAGCCACACCTGCCCCCTGCTCTGGGGCCTGCTGAGCCGGCTGCCCTGGGCACCCGGTTCC
AGGCAGCACAGACGTGGGGCATCCCCAGAAAGACTCCATCCCAGGACCAGGTTCCTCCCTCC
GTGCTCTTCGAGAGGGTGTGAGTGAGCAGACTGCACCCCAAGCTCCCGACTCCAGGTCCC
CTGATCTTGGGCCTGTTTCCCATGGGATTCAAGAGGGACAGCCCCAGCTTTGTGTGTGTT
TAAGCTTAGGAATGCCCTTTATGGAAAGGGCTATGTGGGAGAGTCAGCTATCTTGTCTGG
TTTTCTTGAGACCTCAGATGTGTGTTTACGAGGGCTGAAAGCTTTTATTCTTTAATAATG
AGAAATGTATATTTTACTAATAAATTATTGACCGAGTTCTGTAGATTCTTGTTAGA

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Figure 118

MRGLGLWLLGAMMLPAIAPSRPWALMEQYEVVLPRRLPGPRVRRALPSHLGLHPERSYV
LGATGHNFTLHLRKNRDLLGSGYTETTYTAANGSEVTEQPRGQDHCLYQGHVEGYPDSAAS
LSTCAGLRGFFQVGSDLHLIEPLDEGGEGGRHAVYQAEHLLQTAGTCGVSDDSLGSLLGP
RTAAVFRPRPGDSLPSRETRYVELYVVVDNAEFQMLGSEA AVRHRVLEVNVHVDKLYQKL
NFRVVLVGLEIWNSQDRFHVSPDPSVTLENLLTWQARQRTRRHLHDNVQLITGVDFGTGT
VGFARVSAMCSHSSGAVNQDHSKNPVG VACTMAHEMGNLGMHDENVQGCRCQERFEAG
RCIMAGSIGSSFPRMFSDCSQAYLESFLERPQSVCLANAPDL SHLVGGPVCGNLFVERGE
QCDCGPPEDCRNRCCNSTTCQLAEGAQCAHGTCCQECKVKPAGELCRPPKKDMCDLEEFCD
GRHPECPEDAFQENGTPCSGGYCYNGACPTLAQQCQAFWGP GGQAAEESCF SYDILPGCK
ASRYRADMCGVLQCKGGQQPLGRAICIVDVCHALT TEDGTAYEPVPEGTRCGPEKVCWKG
RCQDLHVYRSSNCSAQCHNHGVCNHKQECHCHAGWAPPHCAKLLTEVHAASGSLPVLVVV
VLVLLAVVLVTLAGIIVYRKARSRLSRNVAPKTTMGRSNPLFHQAASRVPAKGGAPAPS
RGPQELVPTTHPGQPARHPASSVALKRPPAPPVTVSSPPFPVPVYTRQAPKQVIKPTFA
PPVPPVKPGAGAAPNGPAEGAVGPKVALKPPIQRKQGAGAPTAP

Signal sequence

1-19

Transmembrane domain

653-673

N-glycosylation site.

67-70

91-94

436-439

612-615

Tyrosine kinase phosphorylation site.

100-107

601-608

N-myristoylation site.

80-85

92-97

101-106

146-151

149-154

217-222

293-298

298-303

327-332

366-371

407-412

445-450

495-500

506-511

522-527

538-543

550-555

789-794

Neutral zinc metalloproteinases, zinc-binding region signature.

331-340

Reprolysin (M12B) family zinc metalloprotease

200-400

Reprolysin family propeptide

71-185

Disintegrin

417-492

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Figure 120

MNLWLLACL VAGFLGAWAPAVHTQGVFEDCCLAYHYPIGWAVLRRRAWTYRIQEVS GSCNL
PAAIFYLPKRHRKVC GNP KSREVQ RAMKLLDARNKVFAKLHHNTQTFQGPHAVKKLSSGN
SKLSSSKFSNPISSSKRNVSLLISANSGL

signal sequence
1-15

Transmembrane domain
none

N-glycosylation site.
138-141

cAMP- and cGMP-dependent protein kinase phosphorylation site.
114-117

N-myristoylation site.
76-81

Small cytokines (intecrine/chemokine)
22-90

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Figure 121

GAGCTATTTATCCCTAGGTCCTTTTCCTCCTGCACGTCAGCTTTGAGCCCCGAGCTGGTGCT
TTCTGCTCTCTGAGACATGGCAGGCCTGATGACCATAGTAACCAGCCTTCTGTTCCCTTGG
TGTCTGTGCCCACCACATCATCCCTACGGGCTCTGTGGTCATCCCCCTCTCCCTGCTGCAT
GTTCTTTGTTTCCAAGAGAATTCCTGAGAACCGAGTGGTCAGCTACCAGCTGTCCAGCAG
GAGCACATGCCTCAAGGCAGGAGTGATCTTCACCACCAAGAAGGGCCAGCAGTTCTGTGG
CGACCCCAAGCAGGAGTGGGTCCAGAGGTACATGAAGAACCTGGACGCCAAGCAGAAGAA
GGCTTCCCCTAGGGCCAGGGCAGTGGCTGTCAAGGGCCCTGTCCAGAGATATCCTGGCAA
CCAAACCACCTGCTAAATCCCCGCCAGCCCTCCAGCCCTGAGTTTGGGCCTGAGCTGCTT
GGCGGGCTACTCGGGGCCTGGAGAAGCCACAGTGATGGGGGGAAGAGCTAATTTTCTGT
TTCTTAGCAACACTCTCCAGGGATGTGTCTTCTATGAAAAACCCGAGGGAGCAGGTGA
TGTGGTTCCCGGGGGCTGAGCAATGGCTCCAAGCATCCAAGGCCCTTGCCTTCTCCTCCTGACCT
CTGGGTGAGAAGATCCCAGAAGGAGAGCAGTGGCAACTCTTTGCCTTCTCCTCCTGACCT
GGTTCTGATGCTTTTTTCTTTTTTTTTTTTTCTGAGACGGAGTCTCGCTCTGTCACCCAG
GCTGGAGTGCAGTGGCACAATCTCGGTTCACTGCAACCTCCGCCTCCTGGGTTCAGTGA
TTCTCGTGCCTCAGCCTCCCGAGTACCTGGGACTACAGGTGTGTACCACCACACCCAACT
AACTTTTGTATTTTGTAGTAGAGATGAGGTTTCACCATGTTGGCCAGGCTGGTCTCAAAC
CCTGGCCTCAAGTGATCTACCTGCCTCGGCCTCCCAAAGTGCTGGGATTACAGGCATGAG
CCACCACACCCAGCCTACTCAAACCTTTTATGTTGAAAAAAAAAATCATAATTTTTTTTTT
TTTTAAAGGAAATGAACGTGGAGGACTGGGGTGAAGGGCCAGCCTGGGTAGTTTAATCTT
TTTGGGAAGACATGACTTTAAGGAGATTCCCTGCTTTGTGACAGGTTGCTCCATGCTGTC
TTGGGGACAAGGGCCTGTACTGCCTTCAAATCTGGGCTCACCCACATTTTGGTGAGGGG
AAGATAGGGTGGGGGATTAGGGGGAGAAAAGACTCTAGCTTTTTTTTTTCTATGCATGAT
ATACTGTGTGGGTTTATCAAGAGTGTAGACACAGTTGCTGTTCTCAAATAATAGGCCAAA
TAAAATGCGATTCTTTTTTTCTTTGA

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Figure 122

MAGLMTIVTSLLFLGVCAHHIIPTGSVVIPSPCCMFFVSKRIPENRVVSYQLSSRSTCLK
AGVIFTTKKGQQFCGDPKQEWVQRYMKNLDAKQKKASPRARAVAVKGPVQRYPGNQTTTC

signal sequence
1-18

Transmembrane domain
none

N-glycosylation site.
115-118

cAMP- and cGMP-dependent protein kinase phosphorylation site.
94-97

N-myristoylation site.
62-67
70-75
114-119

Small cytokines (intecrine/chemokine)
25-89

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Figure 123

CAGGAGTGACTTGGA~~ACT~~CCATTCTATCACTATGAAGAAAAGTGGTGTTCCTTTCTCTT
GGGCATCATCTTGCTGGTTCTGATTGGAGTGCAAGGAACCCAGTAGTGAGAAAGGGTCG
CTGTTCTTGCAATCAGCACCAACCAAGGGACTATCCACCTACAATCCTTGAAAGACCTTAA
ACAATTTGCCCCAAGCCCTTCCTGCGAGAAAATTGAAATCATTGCTACACTGAAGAATGG
AGTTCAAACATGTCTAAACCCAGATTCAGCAGATGTGAAGGAAGTGAATTTAAAGTGGGA
GAAACAGGTCAGCCAAAAGAAAAAGCAAAAGAATGGGAAAAAACATCAAAAAAGAAAGT
TCTGAAAGTTCGAAAATCTCAACGTTCTCGTCAAAAGAAGACTACATAAGAGACCACTTC
ACCAATAAGTATTCTGTGTTAAAAATGTTCTATTTTAATTATAACCGCTATCATTCCAAAG
GAGGATGGCATATAATACAAAGGCTTATTAATTTGACTAGAAAATTTAAACATTACTCT
GAAATTGTA~~ACT~~TAAAGTTAGAAAGTTGATTTTAAGAATCCAAACGTTAAGAATTGTTAA
GGCTAA

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Figure 124

MKKSGVLFLLGIILLVLIGVQGTPVVRKGRCSCISTNQGTIHLQSLKDLKQFAPSPSCEK
IEIIATLKNGVQTCLNPDSADVKELIKKEKQVSQKKKQKNGKKHQQKKVLKVRKSQSR
QKKT

Signal sequence
1-22

Transmembrane domain
none

cAMP- and cGMP-dependent protein kinase phosphorylation site.
122-125

N-myristoylation site.
70-75

Amidation site.
101-104

Small cytokines (intecrine/chemokine)
23-89

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Figure 125

GTAGGCAGCAACTCACCCCTCACTCAGAGGTCTTCTGGTTCTGGAAACAACCTCTAGCTCAG
CCTTCTCCACCATGAGCCTCAGACTTGATACCACCCCTTCCTGTAAACAGTGCGAGACCAC
TTCATGCCTTGCAGGTGCTGCTGCTTCTGTTCATTGCTGCTGACTGCTCTGGCTTCCTCCA
CCAAAGGACAACTAAGAGAACTTGGCGAAAGGCAAAGAGGAAAGTCTAGACAGTGACT
TGTATGCTGAACTCCGCTGCATGTGTATAAAGACAACCTCTGGAATTCATCCCAAAAACA
TCCAAAGTTTGGAAAGTGATCGGGAAAGGAACCCATTGCAACCAAGTCGAAGTGATAGCCA
CACTGAAGGATGGGAGGAAAATCTGCCTGGACCCAGATGCTCCCAGAATCAAGAAAATTG
TACAGAAAAAATTGGCAGGTGATGAATCTGCTGATTAATTTGTCTGTTTCTGCCAACT
TCTTTAACTCCCAGGAAGGGTAGAATTTTGAAACCTTGATTTTCTAGAGTTCTCATTTAT
TCAGGATACCTATTCTTACTGTATTAAAATTTGGATATGTGTTTCATTCTGTCTCAAAAA
TCACATTTTATTCTGAGAAGGTGGTTAAAAGATGGCAGAAAGAAGATGAAAATAAATAA
GCCTGGTTTCAACCCTCTAATTCTTGCCA

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Figure 126

MSLRLDTPSCNSARPLHALQVLLLLSLLLTALASSTKGQTKRNLAKGKEESLDSPLYAE
LRCMCIKTTSGIHPKNIQSLEVIGKGTHCNQVEVIATLKDGRKICLDPDAPRIKKIVQKK
LAGDESAD

Signal sequence
1-34

Transmembrane domain
none

N-myristoylation site.
86-91

Amidation site.
100-103

Small cytokines (intecrine/chemokine)
54-121

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Figure 127

AAAACAAAACATTTGAGAAACACGGCTCTAACTCATGTAAAGAGTGCATGAAGGAAAGC
AAAAACAGAAATGGAAAGTGGCCCAGAAGCATTAAAGAAAGTGGAAATCAGTATGTTCCCT
ATTTAAGGCATTTGCAGGAAGCAAGGCCTTCAGAGAACCTAGAGCCCAAGGTTTCAGAGTC
ACCCATCTCAGCAAGCCCAGAAGTATCTGCAATATCTACGATGGCCTCGCCCTTTGCTTT
ACTGATGGTCCTGGTGGTGCTCAGCTGCAAGTCAAGCTGCTCTCTGGGCTGTGATCTCCC
TGAGACCCACAGCCTGGATAACAGGAGGACCTTGATGCTCCTGGCACAAATGAGCAGAAT
CTCTCCTTCCTCCTGTCTGATGGACAGACATGACTTTGGATTTCCTCCAGGAGGAGTTTGA
TGGCAACCAGTTCCAGAAGGCTCCAGCCATCTCTGTCCTCCATGAGCTGATCCAGCAGAT
CTTCAACCTCTTTACCACAAAAGATTCATCTGCTGCTTGGGATGAGGACCTCCTAGACAA
ATTCTGCACCGAACTCTACCAGCAGCTGAATGACTTGGAAGCCTGTGTGATGCAGGAGGA
GAGGGTGGGAGAACTCCCCTGATGAATGCGGACTCCATCTTGGCTGTGAAGAAATACTT
CCGAAGAATCACTCTCTATCTGACAGAGAAGAAATACAGCCCTTGTGCCTGGGAGGTGT
CAGAGCAGAAATCATGAGATCCCTCTCTTTATCAACAACTTGCAAGAAAGATTAAGGAG
GAAGGAATTAACATCTGGTCCAACATGAAAACAATTCTTATTGACTCATACACCAGGTCAC
GCTTTCATGAATTCTGTCATTTCAAAGACTCTCACCCTGCTATAACTATGACCATGCTG
ATAAACTGATTTATCTATTTAAATATTTATTTAACTATTCATAAGATTTAAATTATTTTT
GTTCAATAACGTCATGTGCACCTTTACACTGTGGTTAGTGTAATAAAACATGTTCCCTTA
TATTTACTCAATCCATTATTTTGTGTTGTTCAATAACTTTTACTATAGGAACTTCCTGT
ATGTGTTCAATCTTTAATATGAAATTCCTAGCCTGACTGTGCAACCTGATTAGAGAATAA
AGGGTATATTTTATTTGCTTATCATTATTATATGTAAGA

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Figure 128

MASPFALLMVLVVLSCKSSCSLGCDLPETHSLDNRRTLMLLAQMSRISPSSCLMDRHDFG
FPQEEFDGNQFQKAPAI SVLHELIQQIFNLFTTKDSSAAWDEDLLDKFCTELYQQLNDLE
ACVMQEERVGETPLMNADSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTN
LQERLRRKE

Signal sequence
1-23

Transmembrane domain
none

cAMP- and cGMP-dependent protein kinase phosphorylation site.
148-151
157-160

Interferon alpha, beta and delta family signature.
146-164

interferon Interferon alpha/beta domain
1-189

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Figure 129

GATGGCGCAGCCACAGCTTCTGTGAGATTTCGATTTCTCCCCAGTTCCCCTGTGGGTCTGA
GGGGACCAGAAGGGTGAGCTACGTTGGCTTTCTGGAAGGGGAGGCTATATGCGTCAATTC
CCCAAACAAGTTTTGACATTTCCCCTGAAATGTCATTCTCTATCTATTTCACTGCAAGTG
CCTGCTGTTCCAGGCCTTACCTGCTGGGCACTAACGGCGGAGCCAGGATGGGGACAGAAT
AAAGGAGCCACGACCTGTGCCACCAACTCGCACTCAGACTCTGAACTCAGACCTGAAATC
TTCTCTTCACGGGAGGCTTGGCAGTTTTTCTTACTCCTGTGGTCTCCAGATTTTCAGGCCT
AAGATGAAAGCCTCTAGTCTTGCCTTCAGCCTTCTCTCTGCTGCGTTTTATCTCCTATGG
ACTCCTTCCACTGGACTGAAGACACTCAATTTGGGAAGCTGTGTGATCGCCACAAACCTT
CAGGAAATACGAAATGGATTTTCTGAGATACGGGGCAGTGTGCAAGCCAAAGATGGAAAC
ATTGACATCAGAATCTTAAGGAGGACTGAGTCTTTGCAAGACACAAAGCCTGCGAATCGA
TGCTGCCTCCTGCGCCATTTGCTAAGACTCTATCTGGACAGGGTATTTAAAAACTACCAG
ACCCCTGACCATTATACTCTCCGGAAGATCAGCAGCCTCGCCAATTCCTTTCTTACCATC
AAGAAGGACCTCCGGCTCTCTCATGCCACATGACATGCCATTGTGGGGAGGAAGCAATG
AAGAAATACAGCCAGATTCTGAGTCACTTTGAAAAGCTGGAACCTCAGGCAGCAGTTGTG
AAGGCTTTGGGGGAAGTAGACATTTCTTCTGCAATGGATGGAGGAGACAGAA TAGGAGGAA
AGTGATGCTGCTGCTAAGAATATTCGAGGTCAAGAGCTCCAGTCTTCAATACCTGCAGAG
GAGGCATGACCCCAAACCATCTCTTTACTGTACTAGTCTTGTGCTGGTTCACAGTGTA
TCTTATTTATGCATTACTTGCTTCCTTGCAATGATTGTCTTTATGCATCCCCAATCTTAAT
TGAGACCATACTTGTATAAGATTTTGTAAATATCTTTCTGCTATTGGATATATTTATTAG
TTAATATATTTATTTATTTTTTGCTATTTAATGTATTTATTTTTTTTACTTGGACATGAAA
CTTTAAAAAAATTCACAGATTATATTTATAACCTGACTAGAGCAGGTGATGTATTTTTAT
ACAGTAAAAAAAACCTTGTAATTTCTAGAAGAGTGGCTAGGGGGGTATTTCATTTG
TATTCAACTAAGGACATATTTACTCATGCTGATGCTCTGTGAGATATTTGAAATTGAACC
AATGACTACTTAGGATGGGTGTGGAATAAGTTTTGATGTGGAATTGCACATCTACCTTA
CAATTACTGACCATCCCCAGTAGACTCCCCAGTCCCATAATTGTGTATCTTCCAGCCAGG
AATCCTACACGGCCAGCATGTATTTCTACAAATAAAGTTTTCTTTGCATACCACAAAAAAA
AAAAAAAAAAAA

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Figure 130

MKASSLAFSLLSAAFYLLWTPSTGLKTLNLGSCVIATNLQEIRNGFSEIRGSVQAKDGN
DIRILRRTESLQDTKPANRCCLLRHLLRLYLDRVFKNYQTPDHYTLRKISSLANSTLIK
KDLRLSHAHMTCHCGEEAMKKYSQILSHFEKLEPQAAVVKALGELDILLQWMEETE

signal sequence
1-24

Transmembrane domain
none

cAMP- and cGMP-dependent protein kinase phosphorylation site.
107-110
140-143

N-myristoylation site.
51-56

Interleukin 10
9-176

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Figure 131

TGAAATGACTTCCACGGCTGGGACGGGAACCTTCCACCCACAGCTATGCCTCTGATTGGT
GAATGGTGAAGGTGCCTGTCTAACTTTTCTGTAAAAAGAACCAGCTGCCTCCAGGCAGCC
AGCCCTCAAGCATCACTTACAGGACCAGAGGGACAAGACATGACTGTGATGAGGAGCTGC
TTTCGCCAATTTAACACCAAGAAGAATTGAGGCTGCTTGGGAGGAAGGCCAGGAGGAACA
CGAGACTGAGAGATGAATTTTCAACAGAGGCTGCAAAGCCTGTGGACTTTAGCCAGACCC
TTCTGCCCTCCTTTGCTGGCGACAGCCTCTCAAATGCAGATGGTTGTGCTCCCTTGCCTG
GGTTTTACCTTGCTTCTCTGGAGCCAGGTATCAGGGGCCCAGGGCCAAGAATTCCTTTT
GGGCCCTGCCAAGTGAAGGGGGTTGTTCCCCAGAACTGTGGGAAGCCTTCTGGGCTGTG
AAAGACACTATGCAAGCTCAGGATAACATCACGAGTGCCCGGCTGCTGCAGCAGGAGGTT
CTGCAGAACGTCTCGGATGCTGAGAGCTGTTACCTTGTCCACACCCTGCTGGAGTTCTAC
TTGAAAACGTGTTTTCAAAAACCACCACAATAGAACAGTTGAAGTCAGGACTCTGAAGTCA
TTCTCTACTCTGGCCAACAACCTTTGTTCTCATCGTGTCACTGCAACCCAGTCAAGAA
AATGAGATGTTTTCCATCAGAGACAGTGCACACAGGCGGTTTTCTGCTATTCCGGAGAGCA
TTCAAACAGTTGGACGTAGAAGCAGCTCTGACCAAAGCCCTTGGGGAAGTGGACATTCTT
CTGACCTGGATGCAGAAATTCTACAAGCTCTGAATGTCTAGACCAGGACCTCCCTCCCC
TGGCACTGGTTTTGTTCCCTGTGTCAATTTCAAACAGTCTCCCTTCCTATGCTGTTCACTGG
ACACTTCACGCCCTTGGCCATGGGTCCCATTCTTGGCCCAGGATTATTGTCAAAGAAGTC
ATTCTTTAAGCAGCGCCAGTGACAGTCAGGGAAGGTGCCTCTGGATGCTGTGAAGAGTCT
ACAGAGAAGATTCTTGTATTTATTACAACCTCTATTTAATTAATGTCAGTATTTCAACTGA
AGTTCTATTTATTTGTGAGACTGTAAGTTACATGAAGGCAGCAGAATATTGTGCCCCATG
CTTCTTTACCCCTCACAATCCTTGCCACAGTGTGGGGCAGTGGATGGGTGCTTAGTAAGT
ACTTAATAAACTGTGGTGCTTTTTTTTGGCCTGTCTTTGGATTGTTAAAAAACAGAGAGGG
ATGCTTGGATGTAAACTGAACTTCAGAGCATGAAAATCACACTGTCTTCTGATATCTGC
AGGGACAGAGCATTGGGGTGGGGGTAAAGGTGCATCTGTTTGAAAAGTAAACGATAAAATG
TGGATTAAAGTGCCCAAGCAGATCCTCAATAAACATTTTCAATTTCCACCCACAC
TCGCCAGCTCACCCCATCATCCCTTTCCCTTGGTGCCCTCCTTTTTTTTTTATCCTAGTC
ATTCTTCCCTAATCTTCCACTTGAGTGTCAAGCTGACCTTGCTGATGGTGACATTGCACC
TGGATGTACTATCCAATCTGTGATGACATTCCCTGCTAATAAAAGACAACATAACTCCAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAA

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Figure 132

MNFQQRLQSLWTLARPFPCPLLATASQMQMVVLPCLGFTLLLWSQVSGAQGGQEFHFGPCQ
VKGVPQKLWEAFWAVKDTMQAQDNITSARLLQQEVLQNVSDAESCYLEVHTLLEFYLKTV
FKNHHNRTVEVRTLKSFSTLANNFVLIVSQLQPSQENEMFSIRDSAHRRFLLFRRRAFKQL
DVEAALTKALGEVDILLTWMQKFYKL

signal sequence
1-48

Transmembrane domain
none

N-glycosylation site.
85-88
99-102
126-129

Interleukin 10
31-206

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Figure 133

AAGGAGCAGCCCGCAAGCACCAAGTGAGAGGCATGAAGTTACAGTGTGTTTCCCTTTGGC
TCCTGGGTACAATACTGATATTGTGCTCAGTAGACAACCACGGTCTCAGGAGATGTCTGA
TTTCCACAGACATGCACCATATAGAAGAGAGTTTCCAAGAAATCAAAAGAGCCATCCAAG
CTAAGGACACCTTCCCAAATGTCACCTATCCTGTCCACATTGGAGACTCTGCAGATCATTA
AGCCCTTAGATGTGTGCTGCGTGACCAAGAACCTCCTGGCGTTCTACGTGGACAGGGTGT
TCAAGGATCATCAGGAGCCAAACCCCAAATCTTGAGAAAAATCAGCAGCATTGCCAACT
CTTTCCTCTACATGCAGAAAACCTCTGCGGCAATGTCAGGAACAGAGGCAGTGTCACTGCA
GGCAGGAAGCCACCAATGCCACCAGAGTCATCCATGACAACCTATGATCAGCTGGAGGTCC
ACGCTGCTGCCATTAAATCCCTGGGAGAGCTCGACGTCTTCTAGCCTGGATTAATAAGA
ATCATGAAGTAATGTTCTCAGCTTGATGACAAGGAACCTGTATAGTGATCCAGGGATGAA
CACCCCTGTGCGGTTTACTGTGGGAGACAGCCCACCTTGAAGGGGAAGGAGATGGGGAA
GGCCCTTGCAGCTGAAAGTCCCACTGGCTGGCCTCAGGCTGTCTTATTCCGCTTGAAAA
TAGGCAAAAAGTCTACTGTGGTATTTGTAATAAACTCTATCTGCTGAAAGGCCTGCAGG
CCATCCTGGGAGTAAAGGGCTGCCTTCCCATCTAATTTATTGTAAAGTCATATAGTCCAT
GTCTGTGATGTGAGCCAAGTGATATCCTGTAGTACACATTGTACTGAGTGGTTTTTCTGA
ATAAATTCCATATTTTACCTATGA

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Figure 134

MKLQCVSLWLLGTILILCSVDNHGLRRCLISTDMHHIEESFQEIKRAIQAKDTFFPNVTIL
STLETLQIIKPLDVCCVTKNLLAFYVDRVFKDHQEPNPKILRKISSIANSFLYMQKTLRQ
CQEQRQCHCRQEATNATRVIHNYDQLEVHAAAIKSLGELDVFLAWINKNHEVMFSA

Signal sequence
1-18

Transmembrane domain
none

N-glycosylation site.
56-59
135-138

cAMP- and cGMP-dependent protein kinase phosphorylation site.
102-105

N-myristoylation site.
24-29

Actinin-type actin-binding domain signature 1.
159-169

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Figure 135

CCTTTCGAAGCCTTTGCTCTGGCACAAACAGGTAAGTAGGCGACACTGTTTCGTGTTGTCAAC
ATGACCAACAAGTGTCTCCTCCAAATTGCTCTCCTGTTGTGCTTCTCCACTACAGCTCTT
TCCATGAGCTACAACCTTGCTTGGATTCCCTACAAAGAAGCAGCAATTTTCAGTGTGAGAAG
CTCCTGTGGCAATTGAATGGGAGGCTTGAATACTGCCTCAAGGACAGGATGAACTTTGAC
ATCCCTGAGGAGATTAAGCAGCTGCAGCAGTTCCAGAAGGAGGACGCCGCATTGACCATC
TATGAGATGCTCCAGAACATCTTTGCTATTTTCAGACAAGATTCATCTAGCACTGGCTGG
AATGAGACTATTGTTGAGAACCCTCCTGGCTAATGTCTATCATCAGATAAACCATCTGAAG
ACAGTCCTGGAAGAAAACTGGAGAAAGAAGATTTACCCAGGGGAAAACTCATGAGCAGT
CTGCACCTGAAAAGATATTATGGGAGGATTCTGCATTACCTGAAGGCCAAGGAGTACAGT
CACTGTGCCTGGACCATAGTCAGAGTGGAAATCCTAAGGAACCTTTTACTTCATTAACAGA
CTTACAGGTTACCTCCGAAACTTGAAGATCTCCTAGCCTGTGCCTCTGGGACTGGACAATT
GCTTCAAGCATTCTTCAACCAGCAGATGCTGTTTAAAGTGACTGATGGCTAATGTACTGCA
TATGAAAGGACACTAGAAGATTTTGAAATTTTATTAAATTATGAGTTATTTTTATTTAT
TTAAATTTTATTTTGGAATAAATTATTTTGGTGCAAAAGTCAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAGA

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Figure 136

MTNKCLLQIALLLCFSTTALSMSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFD
IPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSSTGWNETIVENLLANVYHQINHLK
TVLEEKLEKEDFTRGKLMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINR
LTGYLRN

signal sequence
1-21

Transmembrane domain
none

N-glycosylation site.
101-104

Leucine zipper pattern.
6-27

Interferon alpha, beta and delta family signature.
146-164

Interferon alpha/beta domain
1-187

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Figure 137

GAAAGATCAGTTAAGTCCTTTGGACCTGATCAGCTTGATACAAGAACTACTGATTTCAAC
TTCTTTGGCTTAATTCTCTCGGAAACGATGAAATATACAAGTTATATCTTGGCTTTTCAG
CTCTGCATCGTTTTGGGTTCTCTTGGCTGTTACTGCCAGGACCCATATGTAAAAGAAGCA
GAAAACCTTAAGAAATATTTTAATGCAGGTCATTCAGATGTAGCGGATAATGGAACTCTT
TTCTTAGGCATTTTGAAGAATTGGAAAGAGGAGAGTGACAGAAAAATAATGCAGAGCCAA
ATTGTCTCCTTTTACTTCAAACTTTTTAAAAACTTTAAAGATGACCAGAGCATCCAAAAG
AGTGTGGAGACCATCAAGGAAGACATGAATGTCAAGTTTTTCAATAGCAACAAAAAGAAA
CGAGATGACTTCGAAAAGCTGACTAATTATTTCGGTAACTGACTTGAATGTCCAACGCAAA
GCAATACATGAACTCATCCAAGTGATGGCTGAACTGTCGCCAGCAGCTAAAACAGGGAAG
CGAAAAAGGAGTCAGATGCTGTTTCGAGGTCGAAGAGCATCCCAGTAATGGTTGTCCTGC
CTGCAATATTTGAATTTTAAATCTAAATCTATTTATTAATATTTAACATTATTTATATGG
GGAATATATTTTTAGACTCATCAATCAAATAAGTATTTATAATAGCAACTTTTGTGTAAT
GAAAATGAATATCTATTAATATATGTATTATTTATAATTCCTATATCCTGTGACTGTCTC
ACTTAATCCTTTGTTTTCTGACTAATTAGGCAAGGCTATGTGATTACAAGGCTTTATCTC
AGGGGCCAACTAGGCAGCCAACCTAAGCAAGATCCCATGGGTGTGTGTTTATTTCACTT
GATGATACAATGAACACTTATAAGTGAAGTGATACTATCCAGTTACTGCCGGTTTGAAAA
TATGCCTGCAATCTGAGCCAGTGCTTTAATGGCATGTCAGACAGAACTTGAATGTGTCAG
GTGACCCTGATGAAAACATAGCATCTCAGGAGATTTTCATGCCTGGTGCTTCCAAATATTG
TTGACAACTGTGACTGTACCCAAATGGAAAGTAACTCATTTGTTAAAATTATCAATATCT
AATATATATGAATAAAGTGTAAGTTCACAACCTAA

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Figure 138

MKYTSYILAFQLCIVLGSLGICYCQDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWK
EESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTN
YSVTDLNVQRKAIHELIQVMAELSPAAGTGKRKRSQMLFRGRRASQ

signal sequence
1-20

Transmembrane domain
none

N-glycosylation site.
48-51
120-123

cAMP- and cGMP-dependent protein kinase phosphorylation site.
152-155
162-165

N-myristoylation site.
17-22
54-59

Amidation site.
149-152
160-163

IFN-gamma Interferon gamma
15-152

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Figure 139

GCTAGACCGAGCCCTGGGAGGCTACGGGCTCCCCCGGAAACCCTGCCAGGGGAGCCGGGT
TTTGAGCTCAGGCGCCTCTAGCGGCGGCCCCCAGAAATCTGACTCGCGAGGCCAGAGTTG
CAGGGACTGAATAGCAAACCTGAGGCTGAGTAGGGAACAGACCATGAGGTCAGTGCAGATC
TTCTCTCCCAATGCCGTTTGCTCCTTCTACTAGTTCCGACAATGCTCCTTAAAGTCTCTT
GGCGAAGATGTAAATTTTTCACCCTGAAGGGGAGTTTGACTCGTATGAAGTCACCATTCCT
GAGAAGCTGAGCTTCCGGGGAGAGGTGCAGGGTGTGGTCAGTCCCGTGTCTTACCTACTG
CAGTTAAAAGGCAAGAAGCACGTCTCCATTTGTGGCCCAAGAGACTTCTGTTGCCCCGA
CATCTGCGCGTTTTCTCCTTCACAGAACATGGGGAACTGCTGGAGGATCATCCTTACATA
CCAAAGGACTGCAACTACATGGGCTCCGTGAAAGAGTCTCTGGACTCTAAAGCTACTATA
AGCACATGCATGGGGGGTCTCCGAGGTGTATTTAACATTGATGCCAAACATTACCAAATT
GAGCCCCCTCAAGGCCTCTCCAGTTTTTGAACATGTCGTCTATCTCCTGAAGAAAGAGCAG
TTTGGAATCAGGTTTGTGGCTTAAGTGATGATGAAATAGAATGGCAGATGGCCCCTTAT
GAGAATAAGGCGAGGCTAAGGGACTTTCCTGGATCCTATAAACACCCAAAGTACTTGGA
TTGATCCTACTCTTTGATCAAAGTAGGTATAGGTTTGTGAACAACAATCTTTCTCAAGTC
ATACATGATGCCATTCTTTGACTGGGATTATGGACACCTACTTTCAAGATGTTTCTGATG
AGGATACACTTAAAGGCTCTTGAAGTATGGACAGATTTTAAACAAAATACGCGTTGGATAT
CCAGAGTTAGCTGAAGTTTTAGGCAGATTTGTAATATATAAAAAAAGTGTATTAATGCT
CGCTGTGCATCAGATTGGGCACATTTATATCTTCAAAGAAAATATAATGATGCTCTTGCA
TGGTCGTTTGGAAGAGTGTGTTCTCTAGAATATGCTGGATCAGTGAGTACTTTACTAGAT
ACAAATATCCTTGCCCCCTGCTACCTGGTCTGCTCATGAGCTGGGTGCTGCTGTAGGAATG
TCACATGATGAACAATACTGCCAATGTAGGGGTAGGCTTAATTGCATCATGGGCTCAGGA
CGCACTGGGTTTAGCAATTGCAGTTATATCTCTTTTTTTTAAACATATCTCTTCGGGAGCA
ACATGTCTAAATAATATCCCAGGACTAGGTTATGTGCTTAAGAGATGTGGAAACAAAATT
GTGGAGGACAATGAGGAATGTGACTGTGGTTCCACAGAGGAGTGTGAGAAAGATCGGTGT
TGCCAATCAAATTGTAAGTTGCAACCAGGTGCCAACTGTAGCATTGGACTTTGCTGTCAT
GATTGTGCGTTTTCGTCCATCTGGATACGTGTGTAGGCAGGAAGGAAATGAATGTGACCTT
GCAGAGTACTGCGACGGGAATTCAAGTTCCTGCCCAAATGACGTTTATAAGCAGGATGGA
ACCCCTTGCAAGTATGAAGGCCGTTGTTTCAGGAAGGGGTGCAGATCCAGATATATGCAG
TGCCAAAGCATTTTTTGACCTGATGCCATGGAGGCTCCTAGTGAGTGCTATGATGCAGTT
AACTTAATAGGTGATCAATTTGGTAACTGTGAGATTACAGGAATTCGAAATTTTAAAAAG
TGTGAAAGTGCAAATTCAATATGTGGCAGGCTACAGTGTATAAATGTTGAAACCATCCCT
GATTTGCCAGAGCATACGACTATAATTTCTACTCATTTACAGGCAGAAAATCTCATGTGC
TGGGGCACAGGCTATCATCTATCCATGAAACCCATGGGAATACCTGACCTAGGTATGATA
AATGATGGCACCTCCTGTGGAGAAGGCCGGGTATGTTTTAAAAAAATTGCGTCAATAGC
TCAGTCCTGCAGTTTGACTGTTTGCCCTGAGAAATGCAATACCCGGGGTGTGTTGCAACAAC
AGAAAAAACTGCCACTGCATGTATGGGTGGGCACCTCCATTCTGTGAGGAAGTGGGGTAT
GGAGGAAGCATTGACAGTGGGCCTCCAGGACTGCTCAGAGGGGCGATTCCCTCGTCAATT
TGGGTTGTGTCCATCATAATGTTTCGCCCTTATTTTATTAATCCTTTTCAAGTGGTTTTTGTG
TTTTTCCGGCAAGTGATAGGAAACCACTTAAAACCCAAACAGGAAAAAATGCCACTATCC
AAAGCAAAAACCTGAACAGGAAGAATCTAAAACAAAACCTGTACAGGAAGAATCTAAAACA
AAAACCTGGACAGGAAGAATCTGAAGCAAAAACCTGGACAGGAAGAATCTAAAGCAAAAACCT
GGACAGGAAGAATCTAAAGCAAACATTGAAAGTAAACGACCCAAAGCAAAGAGTGTCAAG
AAACAAAAAAAGTAAACCGGGCAATCCATACTCATTCAGTAACACAGGCTCATTTATTTAA
CCAGCTAATCATTTATCCAAAGGCTTTCCATTCTTCTCCCAATATTTTCTTACTTTAATT
TTTCCCACAAGTTTTTGATCAGCAAATAAACAGCATTCCTTGTTTTTGGAAC
AAAAA

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Figure 140

MRSVQIFLSQCRLLLLLLVPTMLLKSLGEDVIFHPEGEFDSYEVTIPEKLSFRGEVQGVVS
PVSYLLQLKGKKHVLHLWPKRLLLPRLRVFSFTEHGELLEHPYIPKDCNYMGSVKESL
DSKATISTCMGGLRGVFNIDAKHYQIEPLKASPSFEHVVYLLKKEQFGNQVCGLSDDEIE
WQMAPYENKARLRDFPGSYKHPKYLELILLLFDQSRVRFVNNNLSQVIHDAILLTGIMDTY
FQDVRMRIHLKALEVWTDENKIRVGYPELAEVLGRFVIYKKSVLNARLSSDWAHLYLQRK
YNDALAWSFGKVCSEYAGSVSTLLDTNILAPATWSAHELGHAVGMSHDEQYCQCRGRLN
CIMGSGRTGFSNCSYISFFKHISSGATCLNNIPGLGYVLKRCGNKIVEDNEECDGSGSTEE
CQKDRCCQSNCKLQPGANCSIGLCCHDCRFRPSGYVCRQEGNECDLAEYCDGNSSSCPND
VYKQDGTFCYEGRCFRKGCRSRYMOCQSI FGP DAMEAPSECYDAVNLI GDQFGNCEITG
IRNFKKCESANSICGRLQCINVTIPDLPEHTTIIISTHLQAENLMCWGTGYHLSMKPMGI
PDLGMINDGTSCGEGRVCFKKNCVNSSVLQFDCLPEKCNTRGVCNNRKNCHCMYGWAPPF
CEEVGYGGSIDSGPPGLLRGAIPSSIWVVSIIIMFRLILLILSVVFVFFRQVIGNHLKPKQ
EKMPLSKAKTEQEESKTKTVQEESKTKTGQEESEAKTGQEESKAKTGQEESKANIESKRP
KAKSVKKQKK

Signal sequence
1-27

Transmembrane domain
688-708

N-glycosylation site.
222-225
372-375
438-441
473-476
625-628

N-myristoylation site.
131-136
168-173
235-240
319-324
364-369
436-441
472-477
609-614
642-647
668-673
676-681
680-685
749-754
758-763
767-772

Amidation site.
69-72

Reprolysin family propeptide
76-193

Reprolysin (M12B) family zinc metalloprotease
203-393

Disintegrin
408-483

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Figure 141

AGGAGTTGTGAGTTTCCAAGCCCCAGCTCACTCTGACCACTTCTCTGCCTGCCCAGCATC
ATGAAGGGCCTTGCAGCTGCCCTCCTTGTCTCGTCTGCACCATGGCCCTCTGCTCCTGT
GCACAAGTTGGTACCAACAAAGAGCTCTGCTGCCTCGTCTATACCTCCTGGCAGATTCCA
CAAAAGTTCATAGTTGACTATTCTGAAACCAGCCCCAGTGCCCCAAGCCAGGTGTCATC
CTCCTAACCAAGAGAGGGCCGGCAGATCTGTGCTGACCCAATAAGAAGTGGGTCCAGAAA
TACATCAGCGACCTGAAGCTGAATGCCTGAAGGGGCCTGGAAGCTGCGAGGGCCCAGTGAA
CTTGGTGGGCCCAGGAGGGAACAGGAGCCTGAGCCAGGGCAATGGCCCTGCCACCCTGGA
GGCCACCTCTTCTAAGAGTCCCATCTGCTATGCCCAGCCACATTAACCTTTAATCTT
AGTTTATGCATCATATTTTCATTTTGAAATTGATTTCTATTGTTGAGCTGCATTATGAAAT
TAGTATTTTCTCTGACATCTCATGACATTGTCTTTATCATCCTTTCCCCTTTCCCTTCAA
CTCTTCGTACATTCAATGCATGGATCAATCAGTGTGATTAGCTTTCTCAGCAGACATTGT
GCCATATGTATCAAATGACAAATCTTTATTGAATGGTTTTGCTCAGCACCACCTTTTAAT
ATATTGGCAGTACTTATTATATAAAAGGTA

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Figure 142

MKGLAAALLVLVCTMALCSCAQVGTNKELCCLVYTSWQIPQKFIVDYSETSPQCPKPGVI
LLTKRGRQICADPNKKWVQKYISDLKLNA

Signal sequence
1-20

Transmembrane domain
none

N-myristoylation site.
3-8

Small cytokines (intecrine/chemokine)
21-85

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Figure 143

AAACCAGAAACCTCCAATTCTCATGTGGAAGCCCATGCCCTCACCTCCAAC ATGAAAGC
CTCTGCAGCACTTCTGTGTCTGCTGCTCACAGCAGCTGCTTTCAGCCCCCAGGGGCTTGC
TCAGCCAGTTGGGATTAATACTTCAACTACCTGCTGCTACAGATTTATCAATAAGAAAAT
CCCTAAGCAGAGGCTGGAGAGCTACAGAAGGACCACCAGTAGCCACTGTCCCCGGGAAGC
TGTAATCTTCAAGACCAAACCTGGACAAGGAGATCTGTGCTGACCCACACAGAAGTGGGT
CCAGGACTTTATGAAGCACCTGGACAAGAAAACCCAAACTCCAAAGCTT TGAACATTCAT
GACTGAACTGAAAACAAGCCATGACTTGAGAAACAAATAATTTGTATACCCTGTCCTTTC
TCAGAGTGGTTCTGAGATTATTTTAATCTAATTCTAAGGAATATGAGCTTTATGTAATAA
TGTGAATCATGGTTTTTCTTAGTAGATTTTAAAAGTTATTAATATTTTAATTTAATCTTC
CATGGATTTTGGTGGGTTTTGAACATAAAGCCTTGGATGTATATGTCATCTCAGTGCTGT
AAAACTGTGGGATGCTCCTCCCTTCTNTACCTCATGGGGGTATTGTATAAGTCCTTGCA
AGAATCAGTGCAAAGATTTGCTTTAATTGTTAAGATATGATGTCCCTATGGAAGCATATT
GTTATTATATAATTACATATTTGCATATGTATGACTCCCAAATTTTCACATAAAATAGAT
TTTTGTATAAAAAAAAAAAAAAAAAA

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Figure 144

MKASAALLCLLLTAAAFSPQGLAQPVGINSTTCCYRFINKKIPKQRLESYRRTTSSHCP
REAVIFKTKLDKEICADPTQKWVQDFMKHLDKKTQTPKL

signal sequence
1-18

transmembrane domain
none

N-glycosylation site.
29-32

cAMP- and cGMP-dependent protein kinase phosphorylation site.
52-55

N-myristoylation site.
27-32

Small cytokines (intecrine/chemokine)
24-90

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Figure 145

GGGAAGAGAAGCTGAGAGGAACTCCTCACTCAGCTAGCTTCAGGAGCATGACGTCATCTC
TACCATGGAAATTCCACTCACTCTCCTGTGCCCCCACATTTGTCCTAGGCCTCAGAGTCC
CTATAAAGAGAGATTCCCAAGTCAGTATCAGCACAGGACACAGCTGGGTTCTGAAGCTTC
TGAGTTCTGCAGCCTCACCTCTGAGAAAACCTCTTTTCCACCAATACCATGAAGCTCTGC
GTGACTGTCCTGTCTCTCCTCATGCTAGTAGCTGCCTTCTGCTCTCCAGCGCTCTCAGCA
CCAATGGGCTCAGACCCTCCCACCGCCTGCTGCTTTTCTTACACCGCGAGGAAGCTTCCT
CGCAACTTTGTGGTAGATTACTATGAGACCAGCAGCCTCTGCTCCCAGCCAGCTGTGGTA
TTCCAAACCAAAAGAAGCAAGCAAGTCTGTGCTGATCCCAGTGAATCCTGGGTCCAGGAG
TACGTGTATGACCTGGAAGTGAAGTGAAGCTGCTCAGAGACAGGAAGTCTTCAGGGAAGGT
CACCTGAGCCCCGGATGCTTCTCCATGAGACACATCTCCTCCATACTCAGGACTCCTCTCC
GCAGTTCCTGTCCCTTCTCTTAATTTAATCTTTTTTATGTGCCGTGTTATTGTATTAGGT
GTCATTTCCATTATTTATATTAGTTTAGCCAAAGGATAAGTGTCCCCTATGGGGATGGTC
CACTGTCACTGTTTCTCTGCTGTTGCAAATACATGGATAACACATTTGATTCTGTGTGTT
TTCATAATAAACTTTAAAATAA

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Figure 146

MKLCVTVLSLLMLVAAFCSALSAPMGSDPPTACCFSTARKLPNRFVVDYYETSSLCSQ
PAVVFQTKRSKQVCADPSESQVQYVYDLELN

Signal sequence
1-23

Transmembrane domain

none

Small cytokines (intecrine/chemokine)
24-89

153/169

Figure 147

CGGCTCGAGCCAGGCTCATCAAAGCTGCTCCAGGAAGGCCCAAGCCAGACCAGAAGAC AT
GCCAGATCATCACACAGCCCTGGTGTGCTTGCTGCTAGCTGGGATGTGGCCGGAAGATGT
GGACAGCAAGAGCATGCAGGTACCCTTCTCCAGATGTTGCTTCTCATTTGCGGAGCAAGA
GATTCCCCTGAGGGCAATCCTGTGTTACAGAAATACCAGCTCCATCTGCTCCAATGAGGG
CTTAATATTCAAGCTGAAGAGAGGCAAAGAGGCCTGCGCCTTGGACACAGTTGGATGGGT
TCAGAGGCACAGAAAAATGCTGAGGCACTGCCCGTCAAAAAGAAAA TGAGCAGATTTCCT
TCCATTGTGGGCTCTGGAAACCACATGGCTTCACCTGTCCCCGAAACTACCAGCCCTACA
CCATTCCTTCTGCCCTGCTTTTGCTAGGTCACAGAGGATCTGCTTGGTCTTGATAAGCTA
TGTTGTTGCACTTTAAACATTTAAATTATACAATCATCAACCCCC

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Figure 148

MQIITTALVCLLLAGMWPEVDVDSKSMQVPFSSRCCFSFAEQEIPLRAILCYRNTSSICSNE
GLIFKLKRGKEACALDTVGVVQRHRKMLRHCP SKRK

signal sequence
1-23

transmembrane domain
none

N-glycosylation site.
52-55

Small cytokines (intecrine/chemokine)
23-88

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Figure 149

AGAAGCCATTGTTTCATAATGGTAGGGATACAGGGTCCTTCGTAACAGATTATCAGTATGG
CCTATGCTGGAAAGTCTGGTGACCTCTGATTTTTTTTGGCTTCCAGGTCTTTGGCCTTGGC
ACTCTTTGTCATATTAGAGTTCCTGGGTCTAGGCCTGGGCAGGATTCATAGGTGCAGCTG
CTTCTGCTGGAGGTAGACTGCATCCAACAAAGTAAGGGTGCTGGGTGAGTTCTGGGAGTA
TAGATTCTGACTGGGGTCACTGCTGGGCTGGCCGCCAGTCTTTCATCTGACCCAGGGTTA
AACTGTGGCTTGGGACTGACTCAGGTCCTCTCTTGGGGTCGGTCTGCACATAAAAGGACT
CCTATCCTTGGCAGTTCTGAAACAACACCACCACA ATGGAAAAAGCATTGAAAATTGACA
CACCTCAGCGGGGGAGCATTTCAGGATATCAATCATCGGGTGTGGGTTCCTTCAGGACCAGA
CGCTCATAGCAGTCCCGAGGAAGGACCGTATGTCTCCAGTCACTATTGCCTTAATCTCAT
GCCGACATGTGGAGACCCTTGAGAAAGACAGAGGGAACCCCATCTACCTGGGCCTGAATG
GACTCAATCTCTGCCTGATGTGTGCTAAAGTCGGGGACCAGCCACACTGCAGCTGAAGG
AAAAGGATATAATGGATTTGTACAACCAACCCGAGCCTGTGAAGTCCTTTCTCTTCTACC
ACAGCCAGAGTGGCAGGAACCTCCACCTTCGAGTCTGTGGCTTTCCCTGGCTGGTTCATCG
CTGTCAGCTCTGAAGGAGGCTGTCTCTCATCCTTACCCAAGAACTGGGGAAAGCCAACA
CTACTGACTTTGGGTAACTATGCTGTTT TAAGATAGATTCTCTGTGATGGAGTATCAA
GACCTTTTGGATTCTGACAAGGAGAAGCAGATATAAATGTTCCATCAGAAAGAGGAGACC
AAAAAGAAAACCTGCGCCACTCCTGGGCTTGGCTTATGTCTCAGTGAAGTTACATATGCTG
GTGCTGGTTTGGGTGAAGAACTGCTGTGGTTTATGAAGCTTTCTTTTTTTTTTTTAAATTT
TATTATTATTATACTTTAAGTTTCAGGGTACATGTGCATGACATGCAGGTTGGTTACATA
TGCATACATGTGCCATGCTGGTATGCTGCACCCATTAACCTCGTCATTTAGCATTAGGTAT
ATCTCCTAATGCTATCCCTCCCCCTCCCCCACCACCAACAGTCCCCGGTGTGTGATG
TTCCCCTTCTGTGTCCATGTGTTCTCATTTGTTCAATTTCCACCTATGAGTGAGAAGATG
CGGTGTTTGGTTTTTTTGTCTTGCGATAGTGTGCTGAGAATAATGGTTTCCAGCTTCATC
CATGTCCCTACAAAGGACATGAACTCATCATTTTTTATGGCTGCTTAGTATTCCATGATG
TATATGTGGCACATTTTCTTAATCCAGTCTATCGTTGTTGGACATTTAGGTTGGTCGTCA
GTGTGGCGATTTCTCAGGGATCTAGAAGTAGAAATACCATTTTACCTAGCCATCCCATTA
CTGGGTATATAACCAAAAGACTATAAATCATGCTGCTATAAAGACACATGCACACGTATG
TTTATAGCAGCACTATTCACAATAGCAAAGACTTGGAACCAACCTAAATGTCCAACAACG
ATAGACTGGATTAAGAAAATGAAGCTTTCACCTAAAGTGTTATCACTGGACCTCAAAAGC
ATTAAATTTGTGAAATAAAAATTTTGACATCTAAAAAAAAAAAAAAAAAAAA

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Figure 150

MEKALKIDTPQRGSIQDINHRVWVLQDQTLIAVPRKDRMSPVTIALISCRHVETLEKDRG
NPIYLGLNGLNLCLMCAKVGDPQPTLQLKEKDIMDLYNQPEPVKSFLFYHSQSGRNSTFES
VAFPGWFIAVSSEGGCPLILTQELGKANTTDFGLTMLF

Signal sequence
none

transmembrane domain
60-80

N-glycosylation site.
115-118
148-151

N-myristoylation site.
69-74

Interleukin-1/18
15-158

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Figure 151

GGTGCAGCTGCAGGCAAGCCTGGCCACTGTTGGCTGCAGCAGGACATCCCAGGCACAGCC
CCTAGGGCTCTGAGCAGACATCCCTCGCCATTGACACATCTTCAG**ATG**CTCTCCCAACTA
GCCATGCTGCAGGGCAGCCTCCTCCTTGTGGTTGCCACCATGTCTGTGGCTCAACAGACA
AGGCAGGAGGCGGATAGGGGCTGCGAGACACTTGTAGTCCAGCACGGCCACTGTAGCTAC
ACCTTCTTGCTGCCCAAGTCTGAGCCCTGCCCTCCGGGGCCTGAGGTCTCCAGGGACTCC
AACACCCTCCAGAGAGAATCACTGGCCAACCCACTGCACCTGGGGAAGTTGCCACCCAG
CAGGTGAAACAGCTGGAGCAGGCACTGCAGAACAACACGCAGTGGCTGAAGAAGCTAGAG
AGGGCCATCAAGACGATCTTGAGGTGGAAGCTGGAGCAGGTCCAGCAGCAAATGGCCCAG
AATCAGACGGCCCCCATGCTAGAGCTGGGCACCAGCCTCCTGAACCAGACCACTGCCAG
ATCCGCAAGCTGACCGACATGGAGGCTCAGCTCCTGAACCAGACATCAAGAATGGATGCC
CAGATGCCAGAGACCTTTCTGTCCACCAACAAGCTGGAGAACCAGCTGCTGCTACAGAGG
CAGAAGCTCCAGCAGCTTCAGGGCCAAAACAGCGCGCTCGAGAAGCGGTTGCAGGCCCTG
GAGACCAAGCAGCAGGAGGAGCTGGCCAGCATCCTCAGCAAGAAGGCGAAGCTGCTGAAC
ACGCTGAGCCGCCAGAGCGCCGCCCTCACCAACATCGAGCGCGGCCTGCGCGGTGTCAGG
CACAACCTCCAGCCTCCTGCAGGACCAGCAGCACAGCCTGCGCCAGCTGCTGGTGTGTTG
CGGCACCTGGTGCAAGAAAGGGCTAACGCCTCGGCCCGGCCTTCATAATGGCAGGTGAG
CAGGTGTTCCAGGACTGTGCAGAGATCCAGCGCTCTGGGGCCAGTGCCAGTGGTGTGTAC
ACCATCCAGGTGTCCAATGCAACGAAGCCCAGGAAGGTGTTCTGTGACCTGCAGAGCAGT
GGAGGCAGGTGGACCCTCATCCAGCGCCGTGAGAATGGCACCGTGAATTTTCAGCGGAAC
TGGAAGGATTACAAACAGGGCTTCGGAGACCCAGCTGGGGAGCACTGGCTGGGCAATGAA
GTGGTGCACCAGCTCACCAGAAGGGCAGCCTACTCTCTGCGTGTGGAGCTGCAAGACTGG
GAAGGCCACGAGGCCTATGCCCAGTACGAACATTTCCACCTGGGCAGTGAGAACCAGCTA
TACAGGCTTTCTGTGGTTCGGGTACAGCGGCTCAGCAGGGCGCCAGAGCAGCCTGGTCCTG
CAGAACACCAGCTTTAGCACCTTTGACTCAGACAACGACCACTGTCTCTGCAAGTGTGCC
CAAGTGATGTCTGGAGGGTGGTGGTTTGACGCCTGTGGCCTGTCAAACCTCAACGGXGTC
TACTACCACGCTCCCGACAACAAGTACAAGATGGACGGCATCCGCTGGCACTACTTCAAG
GGCCCCAGCTACTCACTGCGTGCCTCTCGCATGATGATACGGCCTTTGGACATC**TAA**CGA
GCAGCTGTGCCAGAGGCTGGACCACACAGGAGAAGCTCGGACTTGGCACTCCTGGACAAC
CTGGACCCAGATGCAAGACACTGTGCCACCGCCTTCCCTGACACCCTGGGCTTCCTGAGC
CAGCCCTCCTTGACCCAGAAGTCCAGAAGGGTCATCTGCCCCCCCCACTCCCCTCCGTCTG
TGACATGGAGGGTGTTCGGGGCCCATCCCTCTGATGTAGTCTCGCCCCCTCTTCTCTCCC
TCCCCCTTCAGGGGCTCCCTGCCTGAGGGTCACAGTACCTTGAATGGGCTGAGAACAGAC
CAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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Figure 152

MLSQLAMLQGSLLLIVVATMSVAQQTRQEADRGCE TLVVQHGHC SYTFLLPKSEPCPPGPE
VSRDSNTLQRES LANPLHLGKLPTQQVKQLEQALQNN TQWLKKLERAIKTILRSKLEQVQ
QQMAQNQTAPMLELGTSLLNQTTAQIRKLTDM EAQLLNQTSRMDAQMPETFLSTNKLENQ
LLLQRQKLQQ LQGQNSALEKRLQALET KQQEELASILSKKAKLLNTLSRQSAALTNI ERG
LRGVRHNSSLQDQQHSLRQLLVLLRHLVQERANASAPAFIM AGEQVFQDCAEIQRSGAS
ASGVYTIQVSNATKPRKVFCDLQSSGGRWT LIQRRENGTVNFQRNWKDYKQGF GDPAGEH
WLGNEVVHQLTRRAAYSLRVELQDWE GHEAYAQYEHFHLGSENQLYRLSVVGYS GSAGRQ
SSLVLQNTSFSTLDSNDHCLCKCAQVM SGGWWFDACGLSNLNGVYYHAPDNKYKMDGIR
WHYFKGPSYSLRASRMMIRPLDI

Signal sequence
1-24

Transmembrane domain
none

N-glycosylation site.
96-99
126-129
140-143
158-161
247-250
274-277
311-314
337-340
427-430

cAMP- and cGMP-dependent protein kinase phosphorylation site.
147-150

N-myristoylation site.
193-198
243-248
298-303
326-331

Fibrinogen beta and gamma chains C-terminal domain signature.
452-464

Fibrinogen beta and gamma chains, C-term
287-501

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Figure 153

AAGCCACCCAGCCTATGCATCCGCTCCTCAATCCTCTCCTGTTGGCACTGGGCCTC **ATGG**
CGCTTTTGTGTTGACCACGGTCATTGCTCTCACTTGCCTTGGCGGCTTTGCCTCCCCAGGCC
CTGTGCCTCCCTCTACAGCCCTCAGGGAGCTCATTGAGGAGCTGGTCAACATCACCCAGA
ACCAGAAGGCTCCGCTCTGCAATGGCAGCATGGTATGGAGCATCAACCTGACAGCTGGCA
TGTA CTGTGCAGCCCTGGAATCCCTGATCAACGTGTCAGGCTGCAGTGCCATCGAGAAGA
CCCAGAGGATGCTGAGCGGATTCTGCCCCGCACAAGGTCTCAGCTGGGCAGTTTTCCAGCT
TGCATGTCCGAGACACCAAAATCGAGGTGGCCAGTTTGTAAAGGACCTGCTCTTACATT
TAAAGAACTTTTTTCGCGAGGGACGGTTCAAC **TGA**AACTTCGAAAGCATCATTATTTGCA
GAGACAGGACCTGACTATTGAAGTTGCAGATTCATTTTTCTTTCTGATGTCAAAAATGTC
TTGGGTAGGCGGGAAGGAGGGTTAGGGAGGGGTAAAATTCCTTAGCTTAGACCTCAGCCT
GTGCTGCCCGTCTTCAGCCTAGCCGACCTCAGCCTTCCCCTTGCCCAGGGCTCAGCCTGG
TGGGCCTCCTCTGTCCAGGGCCCTGAGCTCGGTGGACCCAGGGATGACATGTCCCTACAC
CCCTCCCCTGCCCTAGAGCACACTGTAGCATTACAGTGGGTGCCCCCTTGCCAGACATG
TGGTGGGACAGGGACCCACTTCACACACAGGCAACTGAGGCAGACAGCAGCTCAGGCACA
CTTCTTCTTGGTCTTATTTATTATTGTGTGTTATTTAAATGAGTGTGTTTGTACCGTTG
GGGATTGGGGAAGACTGTGGCTGCTGGCACTTGGAGCCAAGGGTTCAGAGACTCAGGGCC
CCAGCACTAAAGCAGTGGACCCAGGAGTCCCTGGTAATAAGTACTGTGTACAGAATTCT
GCTACCTCACTGGGGTCCTGGGGCCTCGGAGCCTCATCCGAGGCAGGGTCAGGAGAGGGG
CAGAACAGCCGCTCCTGTCTGCCAGCCAGCAGCCAGCTCTCAGCCAACGAGTAATTTATT
GTTTTTCCTCGTATTTAAATATTAAATATGTTAGCAAAGAGTTAATATATAGAAGGGTAC
CTTGAACACTGGGGGAGGGGACATTGAACAAGTTGTTTCATTGACTATCAAACCTGAAGCC
AGAAATAAAGTTGGTGACAGATA

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Figure 154

MALLLTTVIALTCLGGFASPGVPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTA
GMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLL
HLKKLRFREGRFN

signal sequence
1-15

Transmembrane domain
none

N-glycosylation site.
38-41
49-52
57-60
72-75

N-myristoylation site.
61-66
97-102

Interleukins -4 and -13 signature.
29-56

Interleukin-13
1-43

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Figure 155

TTCCTTTTCATGTTTCAGCATTCTCTACTCCTTCCAAGAAGAGCAGCAAAGCTGAAGTAGCAG
CAACAGCACCAGCAGCAACAGCAAAAAACAAACATGAGTGTGAAGGGCATGGCTATAGCC
TTGGCTGTGATATTGTGTGCTACAGTTGTTCAAGGCTTCCCCATGTTCAAAAGAGGACGC
TGTCTTTGCATAGGCCCTGGGGTAAAAGCAGTGAAAGTGGCAGATATTGAGAAAGCCTCC
ATAATGTACCCAAGTAACAACCTGTGACAAAAATAGAAGTGATTATTACCCTGAAAGAAAAT
AAAGGACAACGATGCCTAAATCCCAAATCGAAGCAAGCAAGGCTTATAATCAAAAAAGTT
GAAAGAAAGAATTTTTTAAAAATATCAAAACATATGAAGTCCTGGAAAAGGGCATCTGAAA
AACCTAGAACAAGTTTAACTGTGACTACTGAAATGACAAGAATTCTACAGTAGGAACTG
AGACTTTTCTATGGTTTTGTGACTTTCAACTTTTGTACAGTTATGTGAAGGATGAAAGGT
GGGTGAAAGGACCAAAAACAGAAATACAGTCTTCCTGAATGAATGACAATCAGAATTCCA
CTGCCCAAAGGAGTCCAGCAATTAAATGGATTTCTAGGAAAAGCTACCTTAAGAAAGGCT
GGTTACCATCGGAGTTTACAAAGTGCTTTCACGTTCTTACTTGTTGTATTATACATTCAT
GCATTTCTAGGCTAGAGAACCTTCTAGATTTGATGCTTACAACCTATTCTGTTGTGACTAT
GAGAACATTTCTGTCTCTAGAAGTTATCTGTCTGTATTGATCTTTATGCTATATTACTAT
CTGTGGTTACAGTGGAGACATTGACATTATTACTGGAGTCAAGCCCTTATAAGTCAAAAG
CATCTATGTGTCTGTAAAGCATTCCCTCAAACATTTTTTTCATGCAAATACACAYTTCTTTCC
CCAAATATCATGTAGCACATCAATATGTAGGGAAACATTCTTATGCATCATTGTTGTTGT
TTTATAACCAATTCAATTAAATGTAATTCATAAAATGTACTATGAAAAAATTATACGCTA
TGGGATACTGGCAACAGTGCACATATTTCATAACCAAATTAGCAGCACCGGTCTTAATTT
GATGTTTTTCAACTTTTATTCAATTGAGATGTTTTGAAGCAATTAGGATATGTGTGTTTAC
TGTACTTTTTTGTTTTGATCCGTTTGTATAAATGATAGCAATATCTTGGACACATTTGAAA
TACAAAATGTTTTTGTCTACCAAAGAAAAATGTTGAAAAATAAGCAAATGTATACCTAGC
AATCACTTTTACTTTTTGTAAATCTGTCTCTTAGAAAAATACATAATCTAATCAATTTCT
TTGTTTCATGCCTATATACTGTAAATTTAGGTATACTCAAGACTAGTTTAAAGAATCAA
GTCATTTTTTTCTCTAATAAACTACCACAACCTTTCTTTTTTAAAAA

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Figure 156

MSVKGMAIALAVILCATVVQGFPMFKRGRCLCIGPGVKAVKVADIEKASIMYPSNNCDKI
EVIITLKENKGQRCLNPKSKQARLIKKVERKNF

Signal sequence
1-21

Transmembrane domain
none

N-myristoylation site.
5-10

Small cytokines (intecrine/chemokine)
22-89

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Figure 157

GGACCACAGCTCCTCCCGTGCATCCACTCGGCCTGGGAGGTTCTGGATTTTGGCTGTCTGA
GGGAGTTTGCCTGCCTCTCCAGAGAAAAGATGGTCATGAGGCCCTGTGGAGTCTGCTTCT
CTGGGAAGCCCTACTTCCCATTACAGTTACTGGTGCCCAAGTGCTGAGCAAAGTCGGGGG
CTCGGTGCTGCTGGTGGCAGCGCGTCCCCCTGGCTTCCAAGTCCGTGAGGCTATCTGGCG
ATCTCTCTGGCCTTCAGAAGAGCTCCTGGCCACGTTTTTCCGAGGCTCCCTGGAGACTCT
GTACCATTTCCCGCTTCTGGGCCGAGCCCAGCTACACAGCAACCTCAGCCTGGAGCTCGG
GCCGCTGGAGTCTGGAGACAGCGGCAACTTCTCCGTGTTGATGGTGGACACAAGGGGCCA
GCCCTGGACCCAGACCCCTCCAGCTCAAGGTGTACGATGCAGTGCCCGAGGCCCTGGTACA
AGTGTTTCATTGCTGTAGAAAGGGATGCTCAGCCCTCCAAGACCTGCCAGGTTTTCTTGTC
CTGTTGGGCCCCCAACATCAGCGAAATAACCTATAGCTGGCGACGGGAGACAACCATGGA
CTTTGGTATGGAACCACACAGCCTCTTTCACAGACGGACAGGTGCTGAGCATTTCCTGGG
ACCAGGAGACAGAGATGTGGCCTATTCTGCATTGTCTCCAACCCTGTCAGCTGGGACTT
GGCCACAGTCACGCCCTGGGATAGCTGTCATCATGAGGCAGCACCAGGGAAGGCCTCCTA
CAAAGATGTGCTGCTGGTGGTGGTGCCTGTCTCGCTGCTCCTGATGCTGGTTACTCTCTT
CTCTGCCTGGCACTGGTGGCCCTGCTCAGGGAAAAAGAAAAAGGATGTCCATGCTGACAG
AGTGGGTCCAGAGACAGAGAACCCCCCTTGTGCAGGATCTGCCA TAAAGGACAATATGAAC
TGATGCCTGGACTATCAGTAACCCCACTGCACAGGCACACGATGCTCTGGGACATAACTG
GTGCCTGGAAATCACCATGGTCTCATATCTCCCATGGGAATCCTGTCCTGCCTCGAAGG
AGCAGCCTGGGCAGCCATCACACCACGAGGACAGGAAGCACCAGCACGTTTCACACCTCC
CCCTTCCCTCTCCCATCTTCTCATATCCTGGCTCTTCTCTGGGCAAGATGAGCCAAGCAG
AACATTTCCATCCAGGACACTGGAAGTTCTCCAGGATCCAGATCCATGGGGACATTAATAG
TCCAAGGCATTTCCCTCCCCCACTATTTCAATAAGTATTAACCAACTGGCACCAAGGAA
TTGCCTCCAGCCTGAGTCCTAGGCTCTAAAAGATATTACATATTTGAACATAATAGAGGAA
CTCTGAGTCACCCATGCCAGCATCAGCTTCAGCCCCAGACCCCTGCAGTTTGAGATCTGAT
GCTTCTGAGGGCCAAGGCATTGCTGTAAGAAAAGGTCTAGAAATAGGTGAAAGTGAGAG
GTGGGGGACAGGGGTTTTCTTTCTGGCCTAAGGACTTTCAGGTAATCAGAGTTCATGGG
CCCTCAAAGGTAAATTGCAGTTGTAGACACCGAGGATGGTTGACAACCCATGGTTGAGAT
GGGCACCGTTTTTGAGGAAACACCATATTAATAGACATCCTCACCATCTCCATCCGCTCT
CACGCCTCCTGCAGGATCTGGGAGTGAGGGTGGAGAGTCTTTCCTCACGCTCCAGCACAG
TGGCCAGGAAAAGAAATACTGAATTTGCCCCAGCCAACAGGACGTTCTTGACAACTTCA
AGAAAAGCAGCTCAGCTCAGGATGAGTCTTCTGCTGAAACTGAGAGAGTGAAGAACCA
TAAAACGCTATGCAGAAGGAACATTATGGAGAGAAAGGGTACTGAGGCACTCTAGAATCT
GCCACATTCATTTTCAAATGCAAATGCAGAAGACTTACCTTAGTTCAAGGGGAGGGGACA
AAGACCCACAGCCCAACAGCAGGACTGTAGAGGTCACTCTGACTCCATCAAACCTTTTAA
TTGTGGCCATCTTAGGAAAATACATTCTGCCCCCTGAATGATTCTGTCTAGAAAAGCTCTG
GAGTATTGATCACTACTGGAAAAACACTTAAGGAGCTAACTTACCTTCGGGGATTATTA
GCTGATAAGGTTTACAGTTTCTCTACCCAGGTGTAACCTGGATTTTTTCTGGGGCCTCAA
TCCAGTCTTGATAACAGCGAGGAAAGAGGTATTGAAGAAACAGGGGTGGGTTTGAAGTAC
TATTTTCCCCAGGGTGGCTTCAATCTCCCCACCTAGGATGTCAGCCCTGTCCAAGGACCT
TCCCTCTTCTCCCCCAGTTCCCTGGGCAATCACTTCACCTTGGACAAAGGATCAGCACAG
CTGGCCTCCAGATCCACATCACCCTCTTCCACTCGATTGTTCCAGATCCTCCCTGCCT
GGCCTGCTCAGAGGTTCCCTGTTGGTAACCTGGCTTTATCAAATTCTCATCCCTTTCCCA
CACCCACTTCTCTCCTATCACCTTCCCCCAAGATTACCTGAACAGGGTCCATGGCCACTC
AACCTGTCAGCTTGCACCATCCCCACCTGCCACCTACAGTCAGGCCACATGCCTGGTCAC
TGAATCATGCAAACTGGCCTCAGTCCCTAAAAATGATGTGGAAAGGAAAGCCCAGGATC
TGACAATGAGCCCTGGTGGATTTGTGGGGAAAAAATACACAGCACTCCCCACCTTTCTTT
CGTTCATCTCCAGGGCCCCACCTCAGATCAAAGCAGCTCTGGATGAGATGGGACCTGCAG
CTCTCCCTCCACAAGGTGACTCTTAGCAACCTCATTTTCGACAGTGGTTTGTAGCGTGGTG
CACCAGGGCCTTGTTGAACAGATCCACACTGCTCTAATAAAGTTCCCATCCTTAATGACT
CACTTGTCAACTAGTGGACTAATTAACCTCCACCAAAAAACACAAAGTGCTTCTGTGA
GACCAATTTTGTGCTAATGAGCATTGAGACTGATGCTTTGTAAAGTCACACCACAACAAAT
ATTGATTGAGGGCGCTGCATGTGCTGGGTACATTTCTTGGCACTTGGGAATCAGTAGTCA
AGCGAAACCCCTTGCCCTTGAGAGTTTATGGTCTGGATAATATAAATAAACAAGTAAGCAT
AAAAAAAAAAAAAAAAAA

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Figure 158

MVMRPLWSLLLWEALLPITVTGAQVLSKVGGSVLLVAARPPGFQVREAIWRS LWPSEELL
ATFFRGSLETLYHSRFLGRAQLHSNLSLELGPLESGDSGNFSVLMVDTRGQPWTQTLQLK
VYDAVPRPVVQVFIAVERDAQPSKTCQVFLSCWAPNISEITYSWRRETTMDFGMEPHSLF
TDGQVLSISLGPGRDVAAYSCIVSNPVS WDLATVTPWDSCHHEAAPGKASYKDVLLVVVP
VSLLLMLVTLFSAWHWCPCSGK KKKDVHADRVGPETENPLVQDLP

Signal sequence
1-22

transmembrane domain

233-253

N-glycosylation site.
85-88
100-103
156-159

cAMP- and cGMP-dependent protein kinase phosphorylation site.
165-168

Tyrosine kinase phosphorylation site.
65-72

N-myristoylation site.
66-71
110-115
183-188

Amidation site.
260-263

Immunoglobulin domain
145-203

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Figure 159

GAATTCGTGTCTCGGCACTCACTCCCGGCCGCGCCGGACAGGGAGCTTTTCGCTGGCGCGCT
TGGCCGGCGACAGGACAGGTTTCGGGACGTCCATCTGTCCATCCGTCCGGAGAGAAATTAC
AGATCCGCAGCCCCGGGATG~~GGGG~~CCGCGCCCGCTGCCGCTGCTGCTGGGCCTCTTCCTCC
CCGCGCTCTGGCGTAGAGCTATCACTGAGGCAAGGGAAGAAGCCAAGCCTTACCCGCTAT
TCCCGGGACCTTTTCCAGGGAGCCTGCAAACCTGACCACACACCGCTGTTATCCCTTCCTC
ACGCCAGTGGGTACCAGCCTGCCTTGATGTTTTTACCAACCCAGCCTGGAAGACCACATA
CAGGAAACGTAGCCATTCCCCAGGTGACCTCTGTGCAATCAAAGCCCCCTACCGCCTCTTG
CCTTCAAACACACAGTTGGACACATAATACTTTCTGAACATAAAGGTGTCAAATTTAATT
GCTCAATCAATGTACCTAATATATACCAGGACACCACAATTTCTTGGTGGAAGATGGGA
AGGAATTGCTTGGGGGACATCATCGAATTACACAGTTTTATCCAGATGATGAAGTTACAG
CAATAATCGCTTCCTTCAGCATAACCAGTGTGCAGCGTTTACAGACAATGGGTCTATATCT
GTAAGATGAAAATAAACAATGAAGAGATCGTGTCTGATCCCATCTACATCGAAGTACAAG
GACTTCCTCACTTTACTAAGCAGCCTGAGAGCATGAATGTCACCAGAAACACAGCCTTCA
ACCTCACCTGTGAGGCTGTGGGCCCCGCTGAGCCCGTCAACATTTTCTGGGTTCAAAACA
GTAGCCGTGTAAACGAACAGCCTGAAAAATCCCCCGCGTGCTAACTGTTCCAGGCCTGA
CGGAGATGGCGGTCTTCAGTTGTGAGGCCCAATGACAAAGGGCTGACCGTGTCCCAGG
GAGTGCAGATCAACATCAAAGCAATTCCTCCCCACCAACTGAAGTCAGCATCCGTAACA
GCACTGCACACAGCATTTCTGATCTCCTGGGTTCCTGGTTTTGATGGATACTCCCCGTTCA
GGAATTGCAGCATTCAGGTCAAGGAAGCTGATCCGCTGGGTAATGGCTCAGTCATGATTT
TTAACACCTCTGCCTTACCACATCTGTACCAAATCAAGCAGCTGCAAGCCCTGGCTAATT
ACAGCATTTGGTGTTCCTGTCATGAATGAAATAGGCTGGTCTGCAGTGAGCCCTTGGATTC
TAGCAAGCACGACTGAAGGAGCCCCATCAGTAGCACCTTTAAATGTCACTGTGTTTCTGA
ATGAATCTAGTGATAATGTGGACATCAGATGGATGAAGCCTCCGACTAAGCAGCAGGATG
GAGAACTGGTGGGCTACCGGATATCCCACGTGTGGCAGAGTGCAGGGATTTCCAAAGAGC
TCTTGGAGGAAGTTGGCCAGAATGGCAGCCGAGCTCGGATCTCTGTTCAAGTCCACAATG
CTACGTGCACAGTGAGGATTGCAGCCGTCAACAGAGGGGGAGTTGGGCCCTTCAGTGATC
CAGTGAATAATTTATCCCTGCACACGGTTGGGTAGATTATGCCCCCTCTTCAACTCCGG
CGCCTGGCAACGCAGATCCTGTGCTCATCATCTTTGGCTGCTTTTGTGGATTTATTTTGA
TTGGGTTGATTTTATACATCTCCTTGGCCATCAGAAAAAGAGTCCAGGAGACAAAGTTTG
GGAATGCATTCACAGAGGAGGATTCTGAATTAGTGGTGAATTATATAGCAAAGAAATCCT
TCTGTGCGCGAGCCATTGAACTTACCTTACATAGCTTGGGAGTCAGTGAGGAACTACAAA
ATAAACTAGAAGATGTTGTGATTGACAGGAATCTTCTAATTCTTGGAATAATCTGGGTG
AAGGAGAGTTTGGGTCTGTAATGGAAGGAAATCTTAAGCAGGAAGATGGGACCTCTCTGA
AAGTGGCAGTGAAGACCATGAAGTTGGACAACCTCTTCACATCGGGAGATCGAGGAGTTTC
TCAGTGAGGCAGCGTGCATGAAAGACTTCAGCCACCCAAATGTCATTCGACTTCTAGGTG
TGTGTATAGAAATGAGCTCTCAAGGCATCCCAAAGCCCATGGTAATTTTACCCTTCATGA
AATACGGGGACCTGCATACTTACTTACTTTATTCCCGATTGGAGACAGGACCAAAGCATA
TTCCTCTGCAGACACTATTGAAGTTCATGGTGGATATTGCCCTGGGAATGGAGTATCTGA
GCAACAGGAATTTTCTTCATCGAGATTTAGCTGCTCGAAACTGCATGTTGCGAGATGACA
TGACTGTCTGTGTTGCGGACTTCGGCCTCTCTAAGAAGATTTACAGTGGCGATTATTACC
GCCAAGGCCGCATTGCTAAGATGCCTGTTAAATGGATCGCCATAGAAAGTCTTGCAGACC
GAGTCTACACAAGTAAAAGTGATGTGTGGGCATTTGGCGTGACCATGTGGGAAATACGTA
CGCGGGGAATGACTCCCTATCCTGGGGTCCAGAACCATGAGATGTATGACTATCTTCTCC
ATGGCCACAGGTTGAAGCAGCCCGAAGACTGCCTGGATGAACTGTATGAAATAATGTACT
CTTGCTGGAGAACCGATCCCTTAGACCGCCCCACCTTTTCAGTATTGAGGCTGCAGCTAG
AAAACTCTTAGAAAGTTTGCCTGACGTTCCGAACCAAGCAGACGTTATTTACGTCAATA
CACAGTTGCTGGAGAGCTCTGAGGGCCTGGCCCAGGGCCCCACCCTTGCTCCACTGGACT
TGAACATCGACCCTGACTCTATAATTGCCTCCTGCACTCCCCGCGCTGCCATCAGTGTGG
TCACAGCAGAAGTTCATGACAGCAAACCTCATGAAGGACGGTACATCCTGAATGGGGGCA
GTGAGGAATGGGAAGATCTGACTTCTGCCCCCTCTGCTGCAGTCACAGCTGAAAAGAACA
GTGTTTTTACCGGGGGAGAGACTTGTAGGAATGGGGTCTCCTGGTCCCATTTCGAGCATGC
TGCCCTTGGGAAGCTCATTGCCCGATGAACTTTTGTGTTGCTGACGACTCCTCAGAAGGCT
CAGAAGTCTGATG~~TG~~AGGAGAGGTGCGGGGAGACATTCAAAAATCAAGCCAATTCTTC
TGCTGTAGGAGAATCCAATTGTACCTGATGTTTTTGGTATTTGTCTTCCTTACCAAGTGA
ACTCCATGGCCCCAAAGCACCAGATGAATGTTGTTAAGGAAGCTGTCATTAATAATACAT
AATATATATTTATTTAAAGAGAAAAATATGTGTATATCATGAAAAAGACAAGGATATTT
TAATAAAACATTACTTATTTCAATTCATTTACTTATCTTGCATATCTTAAATTAAGCTTCAGC
TGCTCCTTGATATTAACCTTTGTACAGAGTTGAAGTTGTTTTTTCAACTTCTTTTCTTTT
TCATTACTATTAATGTAAAAATATTTGTAAAAATGAAATGCCATATTTGACTTGGCTTCT
GGTCTTGATGTATTTGATAAGAATGATTAATTTTCTGATATGGCTTCCATAATAAAATTG
AAATAGGA

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Figure 160A

MGPAPLPLLLGLFLPALWRRRAITEAREEAKPYPLFPGPFPGLQTDHTPLLSLPHASGYQ
PALMFSPTQPGRPHTGNVAIPQVTSVESKPLPPLAFKHTVGHIILSEHKGVKFNC SINVP
NIYQDTTISWWKD GKELLGGHHRITQFYPDDEVTAIIASF SITSVQRS DNGSYICKMKIN
NEEIVSDPIYIEVQGLPHFTKQPESMNVTRNTAFNLTCQAVGPPEPVNIFWVQNSSRVNE
QPEKSPGVLTVPGLT MAVFSCEAHNDKGLTVSQGVQINIKAI P SPPT EVSIRNSTAHSI
LISWVPGFDGYSPFRNC SIQVKEADPLGNGSVMIFNTSALPHLYQIKQLQALANYSIGVS
CMNEIGWSAVSPWILASTTEGAPSVAPLNVTVFLNESSDNVDIRWMKPPTKQODGELVGY
RISHVWQSAGISKELLE EVGQNGSRARISVQVHNATCTVRIAAVTRGGVGPFS DPVKIFI
PAHGWDYAPSS TPAPGNADPVLIIIFGCFCGFILIGLILYISLAIRKRVQETKFGNAFTE
EDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILGKILGEGEFGS
VMEGNLKQEDGTSLKVAVKTMKLDNSSHREIEEFLSEAACMKDFSHPNVIRLLGVCIEMS
SQGIPKPMVILPFMKYGDLHTYLLYSRLETGPKHIP LQTLLKFMVDIALGMEYLSNRNFL
HRDLAARNCMLRDDMTVCVADFGLSKKIYSGDYRQGR IAKMPVKWIAIESLADRVYTSK
SDVWAFGVMTWEIRTRGMT PYPGVQNH EMYDYLLHGHRLKQPEDCLDELYEIMYSCWRD
PLDRPTFSVLRLQLEKLLES LPDVRNQADV IYVNTQLLESSEGLAQGP TLAPLDLNIDPD
SIIASCTPRAAISVVTA EVHDSKPHEGRYILNNGGSEEWEDLTSAPSAAVTA EKNSVLPGE
RLVRNGVSWSHSSMLPLGSSLPDELLFADDSSEGSEVLM

Signal sequence
1-18

Transmembrane domain
503-523

N-glycosylation site.
114-117
170-173
207-210
215-218
234-237
294-297
316-319
329-332
336-339
354-357
389-392
395-398
442-445
454-457
625-628

Tyrosine kinase phosphorylation site.
675-682
865-872
923-929

N-myristoylation site.
41-46
110-115
171-176
269-274
275-280
440-445
507-512
535-540
966-971

Tyrosine protein kinases specific active-site signature.
719-731

Protein kinase domain
587-854

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Figure 160B

Immunoglobulin domain

108-177

211-264

Fibronectin type III domain

284-368

383-473

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Figure 161

TACTGAGTGGGGTGAAGGGAAATGCTGGTGAATTTCAATTTGAGGTGTGGGTTGCTGTTA
GTCACCTCTGTCTCTTGCCATTGCCAAGCACAAAGCAATCTTCCTTCACCAAAGTTGTTAC
CCAAGGGGAACATTGTCCCAAGCTGTTGACGCTCTCTATATCAAAGCAGCATGGCTCAAA
GCAACGATTCCAGAAGACCGCATAAAAAATATACGATTATTAAGAAACAAAAAG
CAGTTTATGAAAACTGTCAATTTCAAGAACAGCTTCTGTCCTTCTTCATGGAAGACGTT
TTTGGTCAACTGCAATTGCAAGGCTGCAAGAAAATACGCTTTGTGGAGGACTTTCATAGC
CTTAGGCAGAAATTGAGCCACTGTATTTCTGTGCTTCATCAGCTAGAGAGATGAAATCC
ATTACCAGGATGAAAAGAATATTTTATAGGATTGGAAACAAAGGAATCTACAAAGCCATC
AGTGAACCTGGATATTCTTCTTCTTCTGGATTAAAAATTATTGGAAAGCAGTCAGGGGCGC
GCCCATCACCATCACCATCACTAGTTA

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Figure 162

MLVNFILRCGLLLVTLSLAIAKHKQSSFTKSCYPRGTL SQAVDALYIKA AAWLKATIPEDR
IKNIRLLKKKTKKQFMKNCQFQEQLLSFFMEDVFGQLQLQGCKKIRFVEDFHSLRQKLSH
CISCASSAREMKSITRMKRIFYRIGNKGIYKAISELDILLSWIKKLLESSQGRAHHHHHH

Signal sequence
1-21

Transmembrane domain
none

cAMP- and cGMP-dependent protein kinase phosphorylation site.
68-71

N-myristoylation site.
148-153

Interleukin 10
5-169