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(71) Applicants *(for all designated States except US)*: **CURAGEN CORPORATION** [US/US]; 322 East Main Street, Branford, CT 06405 (US). **ABGENIX, INC.** [US/US]; 6701 Kaiser Drive, Fremont, CA 94555 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KANG, Jaspal** [CA/CA]; 16727 109 Avenue, Surrey, British Columbia V4N 5H6 (CA). **ETTENBERG, Seth** [US/US]; 39 Mather Street, Hamden, CT 06517 (US). **HERRMANN, John** [US/US]; 2201 192nd Street S.E. #C4, (W) 3830 Monte Villa PKWY, Suite 200, Bothell, WA 98012 (US). **RASTELLI, Luca** [IT/US]; 52 Pepperbush Lane, Guilford, CT 06437 (US). **JEFFERS, Michael, E.** [US/US]; 14 Flax Mill Hollow, Branford, CT 06405 (US). **LAROCHELLE, William** [US/US]; 15 Devonshire Lane, Madison, CT 06443 (US).

(74) Agent: **ELRIFI, Ivor, R.**; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo PC, One Financial Center, Boston, MA 02111 (US).

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(54) Title: ANTIBODIES DIRECTED TO TEN-M PROTEINS AND USES THEREOF

(57) Abstract: The present invention is related to fully human antibodies directed to Ten-M4 and uses of such antibodies. Provided are human monoclonal antibodies directed to Ten-M4. Isolated polynucleotide sequences encoding, and amino acid sequences comprising, heavy and light chain immunoglobulin molecules, particularly sequences corresponding to contiguous heavy and light chain sequences spanning the framework regions (FR's) and/or complementarity determining regions (CDR's), are provided. Hybridomas or other cell lines expressing such immunoglobulin molecules and monoclonal antibodies are also provided. Some of the antibodies can inhibit the metastasis of tumors. Some of the antibodies can be used for delivering an agent, such as a toxin, to a particular target.

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ANTIBODIES DIRECTED TO TEN-M PROTEINS AND USES THEREOF

FIELD OF INVENTION

[0001] The present invention relates generally to antibodies that bind to Ten-M proteins. More specifically, the invention relates to fully human antibodies that specifically bind to Ten-M4 proteins.

BACKGROUND OF THE INVENTION

[0002] The human Ten-M family of genes, also known as teneurins or hOdz, are a class of type II transmembrane proteins containing a short intracellular N-terminus followed by a transmembrane region, which is followed by eight EGF-like repeats, which are followed by a large globular domain on the extracellular side. The EGF-like repeats of Ten-M proteins are thought to mediate dimerization. The expression patterns of mouse and chicken homologues of Ten-M proteins, as well as *in vitro* models of cell migration, such as neurite outgrowth, have suggested a role in neural development. This may also involve binding to extracellular matrix proteins such as heparin, indicating a role as a cell adhesion molecule.

[0003] The structure and function of the Ten-M protein has previously been examined (*e.g.*, Oohashi et al., J. Cell Biol., 145:563-577 (1999)). The various forms of the protein (*e.g.*, m1, m2, m3, and m4) are generally 2700 to 2800 amino acids in length.

[0004] The Ten-M4 protein appears to lack a signal peptide at the NH_2 terminus. Ten-M4 contains a short hydrophobic domain, similar to those in transmembrane proteins, of 300-400 amino acids after the NH_2 terminus. This section of the protein is then followed by eight consecutive EGF-like domains.

SUMMARY OF THE INVENTION

[0005] In one aspect, a fully human antibody that selectively binds to a Ten-M4 protein on a cell is provided. In one embodiment, the fully human antibody, when administered to a patient, reduces the metastasis of a cancer in a patient. In one embodiment, the fully human antibody binds to a Ten-M4 protein at least five, ten, thirty, or forty fold more strongly than the antibody binds to a Ten-M2 protein on a cell. In one aspect, a fully human antibody that selectively binds to a Ten-M4 protein that is not connected to a cell is provided. In one

embodiment the antibody binds to a Ten-M4 protein at least five fold more strongly than the antibody binds to a Ten-M2 protein.

[0006] In another aspect, the antibody that binds to Ten-M4 comprises a human heavy chain immunoglobulin molecule having an amino acid sequence shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, and 38. In another aspect, the antibody that binds to Ten-M4 comprises a human kappa light chain immunoglobulin molecule having an amino acid sequence of SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 36, and 40. In some embodiments, the antibody molecules are formed by combinations comprising the above recited heavy chain immunoglobulin molecules with the above recited light chain immunoglobulin molecules, such as the kappa light chain immunoglobulin molecules, and vice versa, as well as fragments and analogs thereof. In some embodiments, the antibody has a sequence from the heavy chain CDR1, CDR2, CDR3, FR1, FR2, FR3, and/or FR4 or any of the sequences listed in FIG. 12. In some embodiments, the antibody has a sequence from the light chain CDR1, CDR2, CDR3, FR1, FR2, FR3, and/or FR4 or any of the sequences listed FIG. 13.

[0007] Yet another aspect of the invention is a fully human antibody that binds to Ten-M4 and has a heavy chain variable gene derived from the VH3-33 germline.

[0008] In another aspect, a conjugated fully human antibody that binds to a Ten-M4 protein is provided. Attached to the antibody is an agent, and the binding of the antibody to a cell results in the delivery of the agent to the cell. In one embodiment, the above conjugated fully human antibody binds to an extracellular section of the Ten-M4 protein. In another embodiment, the antibody binds to an EGF-like repeat of the Ten-M4 protein. In another embodiment, the antibody and conjugated toxin are internalized by a cell that expresses a Ten-M4 protein. In another embodiment, the agent is a cytotoxic agent. In another embodiment, the agent is saporin. In another embodiment, the conjugated fully human antibody has an IC_{50} of no more than about 1300 pM for PC-3 cells. In another embodiment, the conjugated fully human antibody has an IC_{50} of no more than about 250 or 121 pM for PC-3 cells.

[0009] In another aspect, a composition comprising a monoclonal antibody or antigen-binding portion described herein and a pharmaceutically acceptable carrier is provided.

[0010] In another aspect, a kit for treating Ten-M4 related disorders comprising a Ten-M4 antibody and instructions for administering the Ten-M4 antibody to a subject is provided.

[0011] In another aspect, a method of reducing the metastasis of a cancer in a patient is provided. The method comprises administering a fully human antibody to a patient. The antibody binds to a Ten-M4 protein so as to prevent the Ten-M4 protein from binding to and thereby forming a duplex with a second Ten-M4 protein. The antibody thereby reduces the metastasis of a cancer in a patient.

[0012] In another aspect, a method of reducing the risk of metastasis of a cancer in a patient is provided. The method comprises administering a fully human antibody to a patient. The antibody binds to a first Ten-M4 protein in a manner so as to prevent the Ten-M4 protein from forming an active Ten-M4/Ten-M4 duplex with a second Ten-M4 protein. The antibody binds so as to still allow the first Ten-M4 protein to bind to the second Ten-M4 protein. The antibody thereby reduces the risk of metastasis of a cancer in a patient.

[0013] In another aspect, a method of selectively killing a cancerous cell in a patient is provided. The method comprises administering a fully human antibody conjugate to a patient. The fully human antibody conjugate comprises an antibody that can bind to a Ten-M4 protein and an agent. The agent is either a toxin or another substance that will kill a cancer cell. The antibody conjugate thereby selectively kills the cancer cell. The agent can be saporin. In one embodiment, the antibody conjugate has an IC_{50} of no more than about 130 pM.

[0014] In another aspect, a method of diagnosing a risk of cancer metastasis in a patient is provided. The method comprises administering to a patient a fully human antibody conjugate that selectively binds to a ten-M4 protein on a cell. The antibody conjugate comprises an antibody that selectively binds to ten-M4 and a label. The method further comprises observing the presence of the label in the patient. A relatively high amount of the label will indicate a relatively high risk of cancer metastasis and a relatively low amount of the label will indicate a relatively low risk of cancer metastasis. In one embodiment, the label is a green fluorescent protein.

[0015] Further embodiments include an isolated antibody, or fragment thereof, that comprises a heavy chain amino acid sequence. Other embodiments include an isolated antibody, or fragment thereof, that comprises a heavy chain nucleic acid sequence.

[0016] It will be appreciated that in these embodiments the isolated antibodies can be monoclonal antibodies, chimeric antibodies and/or human or humanized antibodies. Preferably, the antibodies are human antibodies.

[0017] It will also be appreciated that embodiments of the invention are not limited to any particular form of an antibody. For example, the antibodies provided may be a full length antibody (*e.g.* having an intact human Fc region) or an antibody fragment (*e.g.* a Fab, Fab' or $F(ab')_2$). In addition, the antibodies may be manufactured from a hybridoma that secretes the antibody, or from a recombinantly produced cell that has been transformed or transfected with a gene or genes encoding the antibody.

[0018] Other embodiments include isolated nucleic acid molecules encoding any of the antibodies described herein.

[0019] In yet further embodiments, the invention provides an isolated polynucleotide molecule described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The invention will be better understood from the Detailed Description and from the appended drawings, which are meant to illustrate and not to limit the invention.

[0021] FIG. 1A is an amino acid sequence of the Ten-m4 protein.

[0022] FIG. 1B is a nucleic acid sequence encoding the Ten-M4 protein.

[0023] FIG. 1C is an amino acid sequence of the antigen from the Ten-M4 protein that was used to create the discussed antibodies.

[0024] FIG. 1D is a diagram of the various structures in the Ten-M4 protein and the antigen that was used to create the current antibodies.

[0025] FIG. 2A is the nucleotide sequence of the heavy chain variable region of antibody 1.16.

[0026] FIG. 2B is the amino acid sequence of the heavy chain variable region of antibody 1.16.

[0027] FIG. 2C is the nucleotide sequence of the light chain variable region of antibody 1.16.

[0028] FIG. 2D is the amino acid sequence of the light chain variable region of antibody 1.16.

[0029] FIG. 3A is the nucleotide sequence of the heavy chain variable region of antibody 1.20.

[0030] FIG. 3B is the 1.20 amino acid sequence of the heavy chain variable region of antibody 1.20.

[0031] FIG. 3C is the nucleotide sequence of the light chain variable region of antibody 1.20.

[0032] FIG. 3D is the amino acid sequence of the light chain variable region of antibody 1.20.

[0033] FIG. 4A is the nucleotide sequence of the heavy chain variable region of antibody 1.44.

[0034] FIG. 4B is the amino acid sequence of the heavy chain variable region of antibody 1.44.

[0035] FIG. 4C is the nucleotide sequence of the light chain variable region of antibody 1.44.

[0036] FIG. 4D is the amino acid sequence of the light chain variable region of antibody 1.44.

[0037] FIG. 5A is the nucleotide sequence of the heavy chain variable region of antibody 1.47.

[0038] FIG. 5B is the amino acid sequence of the heavy chain variable region of antibody 1.47.

[0039] FIG. 5C is the nucleotide sequence of the light chain variable region of antibody 1.47.

[0040] FIG. 5D is the amino acid sequence of the light chain variable region of antibody 1.47.

[0041] FIG. 6A is the nucleotide sequence of the heavy chain variable region of antibody 1.48.

[0042] FIG. 6B is the amino acid sequence of the heavy chain variable region of antibody 1.48.

[0043] FIG. 6C is the nucleotide sequence of the light chain variable region of antibody 1.48.

[0044] FIG. 6D is the amino acid sequence of the light chain variable region of antibody 1.48.

[0045] FIG. 7A is the nucleotide sequence of the heavy chain variable region of antibody 1.58.

[0046] FIG. 7B is the amino acid sequence of the heavy chain variable region of antibody 1.58.

[0047] FIG. 7C is the nucleotide sequence of the light chain variable region of antibody 1.58.

[0048] FIG. 7D is the amino acid sequence of the light chain variable region of antibody 1.58.

[0049] FIG. 8A is the nucleotide sequence of the heavy chain variable region of antibody 2.13.

[0050] FIG. 8B is the amino acid sequence of the heavy chain variable region of antibody 2.13.

[0051] FIG. 8C is the nucleotide sequence of the light chain variable region of antibody 2.13.

[0052] FIG. 8D is the amino acid sequence of the light chain variable region of antibody 2.13.

[0053] FIG. 9A is the nucleotide sequence of the heavy chain variable region of antibody 2.15.

[0054] FIG. 9B is the amino acid sequence of the heavy chain variable region of antibody 2.15.

[0055] FIG. 9C is the nucleotide sequence of the light chain variable region of antibody 2.15.

[0056] FIG. 9D is the amino acid sequence of the light chain variable region of antibody 2.15.

[0057] FIG. 10A is the nucleotide sequence of the heavy chain variable region of antibody 2.36.

[0058] FIG. 10B is the amino acid sequence of the heavy chain variable region of antibody 2.36.

[0059] FIG. 10C is the nucleotide sequence of the light chain variable region of antibody 2.36.

[0060] FIG. 10D is the amino acid sequence of the light chain variable region of antibody 2.36.

[0061] FIG. 11A is the nucleotide sequence of the heavy chain variable region of antibody 2.59.

[0062] FIG. 11B is the amino acid sequence of the heavy chain variable region of antibody 2.59.

[0063] FIG. 11C is the nucleotide sequence of the light chain variable region of antibody 2.59.

[0064] FIG. 11D is the amino acid sequence of the light chain variable region of antibody 2.59.

[0065] FIG. 12 is a comparison of the heavy chain amino acid sequences of the various antibodies generated towards Ten-M4.

[0066] FIG. 13 is a comparison of the light chain amino acid sequences of the various antibodies generated towards Ten-M4.

[0067] FIG. 14 is a graph displaying the effectiveness of the various antibodies conjugated to a toxin on the inhibition of cancer cell proliferation.

DETAILED DESCRIPTION

[0068] Messenger RNA levels of human Ten-M proteins may be upregulated in certain cancers. Thus, Ten-M4 proteins may have a role in cell migration during cancer metastasis. Given the developmental studies suggesting a role in cell migration and the Ten-M proteins' expression in human cancer, it is possible that therapies designed towards Ten-M may inhibit metastasis of primary tumors. The administration of antibodies to the duplex forming regions of ten-M4 proteins can thereby result in the inhibition of cancer metastasis.

[0069] Additionally, the Ten-M proteins appear to be involved in neuron growth and guidance. As such, the present compositions and methods can be applied to promote or inhibit neuron growth and development in situations where such needs arise. For example, the presently disclosed antibodies that promote neuron growth through the binding of the antibody to the Ten-M protein can be used in situations such as nerve regeneration in damaged tissues.

[0070] Some embodiments of the invention relate to the generation and identification of isolated, preferably fully human, monoclonal antibodies that bind to the Ten-M4 protein. In some embodiments, these antibodies can bind to Ten-M4 with high affinity, high potency, or both.

[0071] In some embodiments, these antibodies are associated with a toxin or similar compound and be used to associate the toxin to a particular location or cell type to promote the killing of the cell type or cells in a desired location. In some embodiments the antibodies are internalized with a high degree of efficiency.

[0072] In some embodiments, the antibody will prevent effective functioning (*e.g.*, signaling) of the Ten-M4 protein. For example, the antibody may prevent dimerization of the Ten-M4 protein with another Ten-M4 protein by binding to a dimerization domain (*e.g.*, EGF-like repeats) of the protein. Accordingly, some of the present embodiments provide isolated antibodies, or fragments of those antibodies, that bind to the EGF-like repeat domain of the ten-M4 protein.

[0073] Embodiments of the invention also provide cells for producing these antibodies. In addition, embodiments provide for using these antibodies as a diagnostic or treatment for diseases related to the under or over expression of the Ten-m4 protein.

[0074] The nucleic acids described herein, and fragments and variants thereof, may be used, by way of nonlimiting example, (a) to direct the biosynthesis of the corresponding encoded proteins, polypeptides, fragments and variants as recombinant or heterologous gene products, (b) as probes for detection and quantification of the nucleic acids disclosed herein, (c) as sequence templates. Such uses are described more fully below.

Definitions:

[0075] Unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The definitions provided herein control over definitions from external sources, including definitions provided in references which are incorporated by reference.

[0076] Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well known and commonly used in the art, as described in various general and more specific references such as those that are cited and discussed throughout the present specification. See *e.g.* Singleton *et al., Dictionary of Microbiology and Molecular Biology 2nd ed.,* J. Wiley & Sons (New York, NY 1994); Sambrook et al. Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (*e.g.*, electroporation, lipofection). Enzymatic reactions and purification techniques are performed

according to manufacturer's specifications or as commonly accomplished in the art or as described herein. Standard techniques are also used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0077] As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0078] "Polymerase chain reaction" or "PCR" refers to a procedure or technique in which minute amounts of a specific piece of nucleic acid, RNA and/or DNA, are amplified as described in U.S. Patent No. 4,683,195 issued July 28, 1987. Generally, sequence information from the ends of the region of interest or beyond needs to be available, such that oligonucleotide primers can be designed; these primers will be identical or similar in sequence to opposite strands of the template to be amplified. The 5' terminal nucleotides of the two primers can coincide with the ends of the amplified material. PCR can be used to amplify specific RNA sequences, specific DNA sequences from total genomic DNA, and cDNA transcribed from total cellular RNA, bacteriophage or plasmid sequences, etc. See generally Mullis *et al., Cold Spring Harbor Symp. Quant. Biol.* 51:263 (1987); Erlich, ed., *PCR Technology* (Stockton Pres, NY, 1989). A used herein, PCR is considered to be one, but not the only, example of a nucleic acid polymerase reaction method for amplifying a nucleic acid test sample comprising the use of a known nucleic acid as a primer and a nucleic acid polymerase to amplify or generate a specific piece of nucleic acid.

[0079] "Antibodies" (Abs) and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules which lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas.

[0080] "Native antibodies and immunoglobulins" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end; the constant domain of the light chain is aligned with the first

constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light- and heavy-chain variable domains (Chothia *et al. J. Mol. Biol.* 186:651 (1985; Novotny and Haber, *Proc. Natl. Acad. Sci. U.S.A.* 82:4592 (1985); Chothia *et al., Nature* 342:877-883 (1989)).

[0081] The term "antibody" herein is used in the broadest sense and specifically covers intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.* bispecific antibodies) formed from at least two intact antibodies, and antibody fragments including Fab and F(ab)'2, so long as they exhibit the desired biological activity. The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called κ and λ, based on the amino acid sequences of their constant domains. Binding fragments are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies. Binding fragments include Fab, Fab', $F(ab')_2$, Fv, and single-chain antibodies, as described in more detail below. An antibody other than a "bispecific" or "bifunctional" antibody is understood to have each of its binding sites identical.

[0082] Depending on the amino acid sequence of the constant domain of their heavy chains, intact antibodies can be assigned to different "classes." There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into "subclasses" (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of antibodies are called α, δ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

[0083] 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" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is

not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.*, *Nature*, 256:495 (1975), or may be made by recombinant DNA methods (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.

[0084] An "isolated" antibody is one 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 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 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.

[0085] A "neutralizing antibody" is an antibody molecule that is able to eliminate or significantly reduce an effector function of a target antigen to which it binds. Accordingly, a "neutralizing" Ten-M4 antibody is capable of eliminating or significantly reducing an effector function, such as ten-M4 activity. In one embodiment, a neutralizing antibody will reduce an effector function by 1-10, 10-20, 20-30, 30-50, 50-70, 70-80, 80-90, 90-95, 95-99, 99-100%. In one embodiment, the Ten-M4 antibody inhibits function by inhibiting, to some extent, the dimerization of two Ten-M4 proteins. In another embodiment, the Ten-M4 antibody inhibits function by inhibiting, to some extent, the association of the dimerized Ten-M4 protein duplex with another protein. In one embodiment, the neutralizing antibody inhibits dimmer formation by directly binding to the location on the Ten-M4 protein that binds to a second ten-M4 protein. In another embodiment, the neutralizing antibody binds to one part of the Ten-M4 protein, while a part of the antibody, or something associated with the antibody, blocks the dimerzation of the Ten-M4 proteins. In another embodiment, the antibody binds to the Ten-M4 protein and induces a conformational change in the protein which prevents dimerization from occurring.

[0086] In another embodiment, the Ten-M4 antibody actually increases the likelihood of dimerization occurring. In another embodiment, the antibodies are activating antibodies and binding of the antibody functions to effectively cause the Ten-M4 protein to act as if it had dimerized with another ten-M4 protein.

[0087] "Antibody-dependent cell-mediated cytotoxicity" and "ADCC" refer to a cell-mediated reaction in which non-specific cytotoxic cells that express Ig Fc receptors (FcRs) (*e.g.* Natural Killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and subsequently cause lysis of the target cell. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcRs 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. PNAS (USA)* 95:652-656 (1988).

[0088] The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the Ig light-chain and heavy-chain variable domains. The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat *et al.* (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 toxicity.

[0089] Digestion of antibodies with the enzyme, papain, results in two identical antigen-binding fragments, known also as "Fab" fragments, and a "Fc" fragment, having no

antigen-binding activity but having the ability to crystallize. Digestion of antibodies with the enzyme, pepsin, results in the a $F(ab')_2$ fragment in which the two arms of the antibody molecule remain linked and comprise two-antigen binding sites. The $F(ab')_2$ fragment has the ability to crosslink antigen.

[0090] "Fv" when used herein refers to the minimum fragment of an antibody that retains both antigen-recognition and antigen-binding sites.

[0091] "Fab" when used herein refers to a fragment of an antibody which comprises the constant domain of the light chain and the CH1 domain of the heavy chain.

[0092] "Fv" is the minimum antibody fragment which contains a complete antigen-recognition and binding site. In a two-chain Fv species, this region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. In a single-chain Fv species, one heavy- and one light-chain variable domain can be covalently linked by a flexible peptide linker such that the light and heavy chains can associate in a "dimeric" structure analogous to that in a two-chain Fv species. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six CDRs 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.

[0093] 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.* residues 24-34 (L1), 50-62 (L2), and 89-97 (L3) in the light chain variable domain and 31-55 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain; 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 light chain variable domain and 26-32 ((H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain; Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). "Framework Region" or "FR" residues are those variable domain residues other than the hypervariable region residues as herein defined.

[0094] The term "complementarity determining regions" or "CDRs" when used herein refers to parts of immunological receptors that make contact with a specific ligand and

determine its specificity. The CDRs of immunological receptors are the most variable part of the receptor protein, giving receptors their diversity, and are carried on six loops at the distal end of the receptor's variable domains, three loops coming from each of the two variable domains of the receptor.

[0095] The term "epitope" is used to refer to binding sites for antibodies on protein antigens. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to bind an antigen when the dissociation constant is ≤ 1 μM, preferably ≤ 100 nM and most preferably $\leq$ 10 nM. An increased or greater dissociation constant ("K_D") means that there is less affinity between the epitope and the antibody. In other words, that the antibody and the epitope are less favorable to bind or stay bound together. A decrease of lower dissociation constant means that there is a higher affinity between the epitope and the antibody. In other words, it is more likely that the antibody and the epitope will bind or stay bound together. An antibody with a K_D of "no more than" a certain amount means that the antibody will bind to the epitope with the given affinity, or more strongly (or tightly).

[0096] While K_D describes the binding characteristics of an epitope and an antibody, "potency" describes the effectiveness of the antibody itself for a function of the antibody. A relatively low K_D does not automatically mean a high potency. Thus, antibodies can have a relatively low K_D and a high potency (*e.g.*, they bind well and alter the function strongly), a relatively high K_D and a high potency (*e.g.*, they don't bind well but have a strong impact on function), a relatively low K_D and a low potency (*e.g.*, they bind well, but not in a manner effective to alter a particular function) or a relatively high K_D and a low potency (*e.g.*, they simply do not bind to the target well). In one embodiment, high potency means that there is a high level of inhibition with a low concentration of antibody. In one embodiment, an antibody is potent or has a high potency when its IC_{50} is a small value, for example, 1300-600, 600-200, 200-130, 130-120, 12-50, 50-10, 10-1 or less pM.

[0097] "Substantially," unless otherwise specified in conjunction with another term, means that the value can vary within the any amount that is contributable to errors in measurement that may occur during the creation or practice of the embodiments. "Significant" means that the value can vary as long as it is sufficient to allow the claimed invention to function for its intended use.

[0098] The term "selectively bind" in reference to an antibody does not mean that the antibody only binds to a single substance. Rather, it denotes that the K_D of the antibody to a first substance is less than the K_D of the antibody to a second substance. Antibodies that exclusively bind to an epitope only bind to that single epitope.

[0099] The term "amino acid" or "amino acid residue," as used herein, refers to naturally occurring L amino acids or to D amino acids as described further below with respect to variants. The commonly used one and three-letter abbreviations for amino acids are used herein (Bruce Alberts *et al., Molecular Biology of the Cell*, Garland Publishing, Inc., New York (3d ed. 1994)).

[0100] The term "mAb" refers to monoclonal antibody.

[0101] The term "XENOMOUSE® refers to strains of mice which have been engineered to contain 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus, as described in Green et al. *Nature Genetics* 7:13-21 (1994), incorporated herein by reference. The XENOMOUSE® strains are available from Abgenix, Inc. (Fremont, CA).

[0102] The term "XENOMAX®" refers use of to the use of the "Selected Lymphocyte Antibody Method" (Babcook et al., *Proc. Natl. Acad. Sci. USA,* i93:7843-7848 (1996)), when used with XENOMOUSE® animals.

[0103] The term "SLAM®" refers to the "Selected Lymphocyte Antibody Method" (Babcook et al., *Proc. Natl. Acad. Sci. USA,* i93:7843-7848 (1996), and Schrader, US Patent No. 5,627,052), both of which are incorporated by reference in their entireties.

[0104] The terms "disease," "disease state" and "disorder" refer to a physiological state of a cell or of a whole mammal in which an interruption, cessation, or disorder of cellular or body functions, systems, or organs has occurred.

[0105] The term "symptom" means any physical or observable manifestation of a disorder, whether it is generally characteristic of that disorder or not. The term "symptoms" can mean all such manifestations or any subset thereof.

[0106] The term "treat" or "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state

of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented. The term "inhibit," when used in conjunction with a disease or symptom can mean that the antibody can reduce or eliminate the disease or symptom.

[0107] The term "patient" includes human and veterinary subjects.

[0108] "Administer," for purposes of treatment, means to deliver to a patient. For example and without limitation, such delivery can be intravenous, intraperitoneal, by inhalation, intramuscular, subcutaneous, oral, topical, transdermal, or surgical.

[0109] "Therapeutically effective amount," for purposes of treatment, means an amount such that an observable change in the patient's condition and/or symptoms could result from its administration, either alone or in combination with other treatment.

[0110] A "pharmaceutically acceptable vehicle," for the purposes of treatment, is a physical embodiment that can be administered to a patient. Pharmaceutically acceptable vehicles can be, but are not limited to, pills, capsules, caplets, tablets, orally administered fluids, injectable fluids, sprays, aerosols, lozenges, neutraceuticals, creams, lotions, oils, solutions, pastes, powders, vapors, or liquids. One example of a pharmaceutically acceptable vehicle is a buffered isotonic solution, such as phosphate buffered saline (PBS).

[0111] "Neutralize," for purposes of treatment, means to partially or completely suppress chemical and/or biological activity.

[0112] "Down-regulate," for purposes of treatment, means to lower the level of a particular target composition.

[0113] "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as monkeys, dogs, horses, cats, cows, etc.

[0114] The term "polynucleotide" as referred to herein means a polymeric form of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA.

[0115] The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the "isolated polynucleotide" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence.

[0116] The term "oligonucleotide" referred to herein includes naturally occurring, and modified nucleotides linked together by naturally occurring, and non-naturally occurring oligonucleotide linkages. Oligonucleotides are a polynucleotide subset generally comprising a length of 200 bases or fewer. Preferably, oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 bases in length. Oligonucleotides are usually single stranded, *e.g.*, for probes; although oligonucleotides may be double stranded, *e.g.*, for use in the construction of a gene mutant. Oligonucleotides can be either sense or antisense oligonucleotides.

[0117] The term "naturally occurring nucleotide" as used herein includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" referred to herein includes oligonucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoroamidate, and the like. *See e.g.,* LaPlanche et al. *Nucl. Acids Res.* 14:9081 (1986); Stec et al. *J. Am. Chem. Soc.* 106:6077 (1984); Stein et al. *Nucl. Acids Res.* 16:3209 (1988); Zon et al. *Anti-Cancer Drug Design* 6:539 (1991); Zon et al. *Oligonucleotides and Analogues: A Practical Approach,* pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec et al. U.S. Patent No. 5,151,510; Uhlmann and Peyman *Chemical Reviews* 90:543 (1990), the disclosures of which are hereby incorporated by reference. An oligonucleotide can include a label for detection, if desired.

[0118] The term "selectively hybridize" referred to herein means to detectably and specifically bind. Polynucleotides, oligonucleotides and fragments thereof selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. High stringency conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic acid sequence homology between the polynucleotides, oligonucleotides,

or antibody fragments and a nucleic acid sequence of interest will be at least 80%, and more typically with preferably increasing homologies of at least 85%, 90%, 95%, 99%, and 100%.

[0119] The term "control sequence" as used herein refers to polynucleotide sequences which are necessary to effect the expression and processing of coding sequences to which they are connected. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence; in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

[0120] The term "operably linked" as used herein refers to positions of components so described that are in a relationship permitting them to function in their intended manner. For example, a control sequence "operably linked" to a coding sequence is connected in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences.

[0121] The term "isolated protein" referred to herein means a protein of cDNA, recombinant RNA, or synthetic origin or some combination thereof, which by virtue of its origin, or source of derivation, the "isolated protein" (1) is not associated with proteins found in nature, (2) is free of other proteins from the same source, *e.g.*, free of murine proteins, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

[0122] The term "polypeptide" is used herein as a generic term to refer to native protein, fragments, or analogs of a polypeptide sequence. Hence, native protein, fragments, and analogs are species of the polypeptide genus. Preferred polypeptides in accordance with the invention comprise the human heavy chain immunoglobulin molecules represented by SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, and 38, for example, and the human kappa light chain immunoglobulin molecules represented by SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 36, and 40, for example, as well as antibody molecules formed by combinations comprising the heavy chain immunoglobulin molecules with light chain immunoglobulin molecules, such as the kappa light chain immunoglobulin molecules, and vice versa, as well as fragments and analogs thereof. In some embodiments, the antibody has a sequence from the heavy chain CDR1, CDR2, CDR3, FR1, FR2, FR3, and/or FR4 or any of the sequences listed in FIG. 12. In some embodiments, the

antibody has a sequence from the light chain CDR1, CDR2, CDR3, FR1, FR2, FR3, and/or FR4 or any of the sequences listed FIG. 13.

[0123] Unless specified otherwise, the left-hand end of single-stranded polynucleotide sequences is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA and which are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences"; sequence regions on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences".

[0124] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See Immunology--A Synthesis (2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as alpha-, alpha-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the lefthand direction is the amino terminal direction and the righthand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0125] The term "corresponds to" is used herein to mean that a polynucleotide sequence is homologous (*i.e.*, is identical, not strictly evolutionarily related) to all or a portion of a reference polynucleotide sequence, or that a polypeptide sequence is identical to a reference polypeptide sequence.

[0126] In contradistinction, the term "complementary to" is used herein to mean that the complementary sequence is homologous to all or a portion of a reference polynucleotide sequence. For illustration, the nucleotide sequence "TATAC" corresponds to a reference sequence "TATAC" and is complementary to a reference sequence "GTATA".

[0127] The following terms are among those used to describe the sequence relationships between two or more polynucleotide or amino acid sequences: "reference

sequence", "comparison window", "sequence identity", "percentage of sequence identity", "substantial identity", and "homology." A "reference sequence" is a defined sequence used as a basis for a sequence comparison. A reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length cDNA or gene sequence given in a sequence listing or may comprise a complete cDNA or gene sequence. Generally, a reference sequence is at least 18 nucleotides or 6 amino acids in length, frequently at least 24 nucleotides or 8 amino acids in length, and often at least 48 nucleotides or 16 amino acids in length. Since two polynucleotides or amino acid sequences may each (1) comprise a sequence (*i.e.*, a portion of the complete polynucleotide or amino acid sequence) that is similar between the two molecules, and (2) may further comprise a sequence that is divergent between the two polynucleotides or amino acid sequences, sequence comparisons between two (or more) molecules are typically performed by comparing sequences of the two molecules over a "comparison window" to identify and compare local regions of sequence similarity.

[0128] A "comparison window", as used herein, refers to a conceptual segment of at least about 18 contiguous nucleotide positions or about 6 amino acids wherein the polynucleotide sequence or amino acid sequence is compared to a reference sequence of at least 18 contiguous nucleotides or 6 amino acid sequences and wherein the portion of the polynucleotide sequence in the comparison window may include additions, deletions, substitutions, and the like (*i.e.*, gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman and Wunsch *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson and Lipman *Proc. Natl. Acad. Sci. (U.S.A.)* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, (Genetics Computer Group, 575 Science Dr., Madison, Wis.), GENEWORKS™, or MACVECTOR® software packages), or by inspection, and the best alignment (*i.e.*, resulting in the highest percentage of homology over the comparison window) generated by the various methods is selected.

[0129] The term "sequence identity" means that two polynucleotide or amino acid sequences are identical (i.e., on a nucleotide-by-nucleotide or residue-by-residue basis) over the comparison window. The term "percentage of sequence identity" is calculated by comparing

two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (*e.g.*, A, T, C, G, U, or I) or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the comparison window (*i.e.*, the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The terms "substantial identity" as used herein denotes a characteristic of a polynucleotide or amino acid sequence, wherein the polynucleotide or amino acid comprises a sequence that has at least 85 percent sequence identity, preferably at least 90 to 95 percent sequence identity, more preferably at least 99 percent sequence identity, as compared to a reference sequence over a comparison window of at least 18 nucleotide (6 amino acid) positions, frequently over a window of at least 24-48 nucleotide (8-16 amino acid) positions, wherein the percentage of sequence identity is calculated by comparing the reference sequence to the sequence which may include deletions or additions which total 20 percent or less of the reference sequence over the comparison window. The reference sequence may be a subset of a larger sequence.

[0130] Two amino acid sequences or polynucleotide sequences are "homologous" if there is a partial or complete identity between their sequences. For example, 85% homology means that 85% of the amino acids are identical when the two sequences are aligned for maximum matching. Gaps (in either of the two sequences being matched) are allowed in maximizing matching; gap lengths of 5 or less are preferred with 2 or less being more preferred. Alternatively and preferably, two protein sequences (or polypeptide sequences derived from them of at least about 30 amino acids in length) are homologous, as this term is used herein, if they have an alignment score of at more than 5 (in standard deviation units) using the program ALIGN with the mutation data matrix and a gap penalty of 6 or greater. *See* Dayhoff, M.O., in *Atlas of Protein Sequence and Structure*, pp. 101-110 (Volume 5, National Biomedical Research Foundation (1972)) and Supplement 2 to this volume, pp. 1-10. The two sequences or parts thereof are more preferably homologous if their amino acids are greater than or equal to 50% identical when optimally aligned using the ALIGN program.

[0131] As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80 percent sequence identity, preferably at least 90 percent sequence identity, more preferably at least 95 percent sequence identity, and most preferably at least 99 percent sequence identity. Preferably, residue positions which are not identical differ by

conservative amino acid substitutions. Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine; a group of amino acids having amide-containing side chains is asparagine and glutamine; a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side chains is lysine, arginine, and histidine; and a group of amino acids having sulfur-containing side chains is cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamic-aspartic, and asparagine-glutamine.

[0132] As discussed herein, minor variations in the amino acid sequences of antibodies or immunoglobulin molecules are contemplated as being encompassed by the present invention, providing that the variations in the amino acid sequence maintain at least 75%, more preferably at least 80%, 90%, 95%, and most preferably 99%. In particular, conservative amino acid replacements are contemplated. Conservative replacements are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids are generally divided into families: (1) acidic=aspartate, glutamate; (2) basic=lysine, arginine, histidine; (3) non-polar=alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar=glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. More preferred families are: serine and threonine are aliphatic-hydroxy family; asparagine and glutamine are an amide-containing family; alanine, valine, leucine and isoleucine are an aliphatic family; and phenylalanine, tryptophan, and tyrosine are an aromatic family. For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the binding or properties of the resulting molecule, especially if the replacement does not involve an amino acid within a framework site. Whether an amino acid change results in a functional peptide can readily be determined by assaying the specific activity of the polypeptide derivative. Assays are described in detail herein. Fragments or analogs of antibodies or immunoglobulin molecules can be readily prepared by those of ordinary skill in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to

public or proprietary sequence databases. Preferably, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. Bowie et al. Science 253:164 (1991). The foregoing examples demonstrate that those of skill in the art can recognize sequence motifs and structural conformations that may be used to define structural and functional domains in accordance with the invention.

[0133] Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (5) confer or modify other physiocochemical or functional properties of such analogs. Analogs can include various muteins of a sequence other than the naturally-occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally-occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in Proteins, Structures and Molecular Principles (Creighton, Ed., W. H. Freeman and Company, New York (1984)); Introduction to Protein Structure (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et at. Nature 354:105 (1991), which are each incorporated herein by reference.

[0134] The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally-occurring sequence deduced, for example, from a full-length cDNA sequence. Fragments typically are at least 5, 6, 8 or 10 amino acids long, preferably at least 14 amino acids long, more preferably at least 20 amino acids long. In other embodiments polypeptide fragments are at least 25 amino acids long, more preferably at least 50 amino acids long, and even more preferably at least 70 amino acids long.

[0135] Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics". Fauchere, *J. Adv. Drug*

Res. 15:29 (1986); Veber and Freidinger *TINS* p.392 (1985); and Evans et al. *J. Med. Chem.* 30:1229 (1987), which are incorporated herein by reference. Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a biochemical property or pharmacological activity), such as human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH_2NH--, --CH_2S--, --CH_2-CH_2--, --CH=CH-- (cis and trans), --$COCH_2$--, --$CH(OH)CH_2$--, and –CH_2SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch *Ann. Rev. Biochem.* 61:387 (1992), incorporated herein by reference); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

[0136] As used herein, the terms "label" or "labeled" refers to incorporation of a detectable marker, *e.g.,* by incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In certain situations, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[0137] The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly

administered to a patient. Other chemistry terms herein are used according to conventional usage in the art, as exemplified by The McGraw-Hill Dictionary of Chemical Terms (Parker, S., Ed., McGraw-Hill, San Francisco (1985)), incorporated herein by reference).

[0138] An "agent" refers to a substance that is useful in the treatment of active disease, prophylactic treatment, or diagnosis of a mammal including, but not restricted to, a human, bovine, equine, porcine, murine, canine, feline, or any other warm-blooded animal. For example, the agent is selected from the group of radioisotope, toxin, pharmaceutical agent, oligonucleotide, cytotoxic agents, recombinant protein, antibody fragment, anti-cancer agents, anti-adhesion agents, anti-thrombosis agents, anti-restenosis agents, anti-autoimmune agents, anti-aggregation agents, anti-bacterial agents, anti-viral agents, and anti-inflammatory agents. Other examples of such agents include, but are not limited to anti-viral agents including acyclovir, ganciclovir, and zidovudine; anti-thrombosis/resteno- sis agents including cilostazol, dalteparin sodium, reviparin sodium, and aspirin; anti-inflammatory agents including zaltoprofen, pranoprofen, droxicam, acetyl salicylic 17, diclofenac, ibuprofen, dexibuprofen, sulindac, naproxen, amtolmetin, celecoxib, indomethacin, rofecoxib, and nimesulid; anti-autoimmune agents including leflunomide, denileukin diftitox, subreum, WinRho SDF, defibrotide, and cyclophosphamide; and anti-adhesion/anti-aggregation agents including limaprost, clorcromene, and hyaluronic acid. The term "agent" is meant to encompass any of the compounds known to one of skill in the art or disclosed herein that can influence a target cell or target area in a desired way. Agents can include labels and various therapeutics as well.

[0139] As used herein, "substantially pure" means an object species is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition), and preferably a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species present. Generally, a substantially pure composition will comprise more than about 80 percent of all macromolecular species present in the composition, more preferably more than about 85%, 90%, 95%, and 99%. Most preferably, the object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

[0140] The term "Ten-M protein," denotes a protein from the Ten-M family of genes, also known as teneurins, , or hOdz. The Ten-M proteins are a class of type IItransmembrane

proteins containing a short intracellular N-terminus, which is followed by a transmembrane region, which is followed by 8 EGF-like repeats (Epidermal Growth Factor-like repeats), which is followed by a large globular domain on the extracellular side. Ten-M4 denotes a particular member of that family of proteins. Ten-M4 is also known as CR105 or curagen 105. Ten-M4 cDNA can be highly similar if not identical to DOC4 cDNA. The amino acid sequence of a human Ten-M4 protein is shown in FIG. 1A, SEQ ID NO: 41. The highlighted section represents the antigen used for the present antibodies. A nucleic acid sequence is displayed in FIG. 1B, SEQ ID NO: 42. The isolated section of the Ten-M4 protein used in the present application is displayed in FIG. 1C, SEQ ID NO: 43. The general layout of the Ten-M4 protein and its various components (*e.g.*, TM, intracellular, extracellular, EGF-like repeat, and C terminal globular region) are shown in FIG. 1D. FIG. 1D also depicts the actual modified (V5-6xHis) peptide used as the antigen to generate the present antibodies. As will be appreciated by one of skill in the art, and as described in more detail below, other sections of the Ten-M4 protein can be used to generate antibodies in the same manner as described herein.

[0141] Additionally, as will be appreciated by one of skill in the art, the present written description and enabling disclosure can readily be applied to create and use antibodies directed to the various members of the ten-M family; however, for simplicity's sake, the ten-M4 protein will be discussed as the example herein. Members of the ten-M protein family have been described in rat (Otaki et al., *Dev. Biol.* 212, 165-1813 (1999)); chicken (Minet et al., *J. Cell Sci.* 112, 2019-2032 (1999); Rubin et al., R., *Dev. Biol.* 216, 195-209 (1999); Tucker et al., *Mech. Dev.* 98, 187-191 (2000); Tucker et al., *Dev. Dyn.* 220, 27-39 (2001)), human (Brandau et al., *Hum. Mol. Genet.* 8, 2407-2413 (1999); Minet et al., *Gene* 257, 87-97 (2000)), zebrafish (Mieda et al., *Mech. Dev.* 87, 223-227 (1999)), and *Caenorhabditis elegans* (Wilson et al., *Nature* 368, 32-38 (1994)).

Ten-M4 Antibodies

[0142] In some embodiments, the present antibodies can prevent the formation of a ten-M4/Ten-M4 duplex on a cancerous cell and thereby reduce the likelihood that a cancer will spread to another location. As will be appreciated by one of skill in the art, the antibody can prevent or reduce the formation of the Ten-M4/Ten-M4 duplex formation in a number of ways. For example, the antibody can directly bind to the section of the Ten-M4 protein that is involved in binding for Ten-M4/Ten-M4 duplex formation (*e.g.*, an EGF-like repeat) and thus prevent the

two Ten-M4 proteins from effectively binding together. In some embodiments, the antibody directly binds to the EGF-like repeat or repeats that are involved in duplex formation. The antibody can be created to bind to any one or multiple EGF-like repeats, including, for example, the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, and 8th repeat. Thus, in one embodiment, the antibody can bind to the second and fourth EGF-like repeats. Fully human antibodies that bind to these particular sections can be generated by the methods disclosed herein and the knowledge of one of skill in the art. Alternatively, the antibody can bind at another location and the nonbonding section of the antibody can sterically interfere with the binding of the two halves of the protein. Alternatively, the antibody can bind to a location on the Ten-M4 proteins and induce a conformational change in the protein that will prevent duplex formation.

[0143] In some embodiments, the antibody binds in such a way as to allow for the binding of the two Ten-M4 proteins, but so as to prevent any functional signaling from occurring. In some embodiments, this involves the antibody binding to only a part of the section of the Ten-M4 protein directly involved in duplex formation (*e.g.*, one EGF-like repeat), while the antibody does not interfere with the binding of the two Ten-M4 proteins otherwise (*e.g.*, the other EGF-like repeat will still bind together). This particular antibody has the advantage of reducing the number of Ten-M4 proteins available to form duplexes, as each antibody can bind to two Ten-M4 proteins. Similarly, antibodies that bind to two Ten-M4 proteins at once can also have this advantage in some embodiments.

[0144] In some embodiments, the antibody actually promotes the dissociation of the Ten-M4/Ten-M4 duplex. In other embodiments, the antibody promotes the formation of the Ten-M4/Ten-M4 duplex. Such antibodies can be created by raising antibodies against particular locations of the Ten-M4 protein or duplex thereof, so that the antibody, when bound to the Ten-M4 protein or duplex thereof, will help stabilize the other state (individual or duplexed) of the Ten-M4 protein.

[0145] One of skill in the art will appreciate that with the combination of 1) the present teachings, 2) logical selection of the antigen from the Ten-M4 protein (*e.g.*, one, some or all of the EGF-like repeats), 3) a standard antibody binding assay (*e.g.*, surface plasmon resonance in a BIACORE™ device), and 4) a functional duplex formation assay (*e.g.*, a cell migration assay similar to that described below), that the above antibodies can be readily generated identified, isolated and used.

[0146] In some embodiments, the antibodies to Ten-M4 are selective for various forms of Ten-M and various forms of Ten-M4. For example, in some embodiments, the antibody to Ten-M4 will bind to Ten-M4 more tightly than it will to other forms of Ten-M (*e.g.*, Ten-M2, Ten-M1, and Ten-M3). For example, the antibody can bind 1-5, 5-10, 10-20, 20-30, 30-40, or 40-50 fold more tightly to Ten-M4 than one of or any combination of the other Ten-M proteins. In other embodiments, the antibodies are selective for cell associated and cell dissociated Ten-M proteins and Ten-M4 in particular. For example, in some embodiments, the antibodies can bind more tightly to a Ten-M4 protein that is attached to the cell surface. In other embodiments, the antibodies can bind more tightly to a Ten-M4 protein that has been shed or that is secreted or cleaved from a cell. In some embodiments, the antibody can bind to both forms equally as strongly. In other embodiments, the antibody can effectively bind to only one form of the Ten-M4 protein. The selectivity can be any amount, for example, from 2-10, 10-20, 20-30, 30-40, 40-50, fold more selective, or more, for one form compared to the other form. An example of how to generate such selective antibodies and determine such selectivity is presented below in the examples.

[0147] In other embodiments, the antibodies that bind to Ten-M4 are associated with an agent or compound of some type. The association of the agent with the antibody allows for the delivery of the agent or compound to cells that express Ten-M4. As observed, Ten-M4 is expressed in cancerous cells; therefore, this combination allows the delivery of an agent, such as a cytotoxic agent or therapeutic agent, to a cancer cell. The agent can be associated with the antibody in a variety of ways, for example, it can be directly linked to the antibody, attached via a linker (which can be a cleavable linker), or associated via a secondary antibody. In some embodiments the antibodies comprise epitopes so as to allow binding to the antibodies by other antibodies or agents. As will be appreciated by one of skill in the art, the exact manner by which the agent is associated with the toxin is not critical to the device or method. This, and other issues associated with these compositions and methods of using them are discussed in more detail below, with a particular emphasis in the section entitled "Design and Generation of Other Therapeutics."

Antibody Structure

[0148] The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light"

(about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. *See generally, Fundamental Immunology* Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site.

[0149] Thus, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are the same.

[0150] The chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper variable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk *J. Mol. Biol.* 196:901-917 (1987); Chothia et al. *Nature* 342:878-883 (1989).

[0151] A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. *See, e.g.,* Songsivilai & Lachmann *Clin. Exp. Immunol.* 79: 315-321 (1990), Kostelny et al. *J. Immunol.* 148:1547-1553 (1992). Production of bispecific antibodies can be a relatively labor intensive process compared with production of conventional antibodies and yields and degree of purity are generally lower for bispecific antibodies. Bispecific antibodies do not exist in the form of fragments having a single binding site (*e.g.*, Fab, Fab', and Fv).

Human Antibodies and Humanization of Antibodies

[0152] Human antibodies avoid some of the problems associated with antibodies that possess murine or rat variable and/or constant regions. The presence of such murine or rat derived proteins can lead to the rapid clearance of the antibodies or can lead to the generation of an immune response against the antibody by a patient. In order to avoid the utilization of murine or rat derived antibodies, fully human antibodies can be generated through the introduction of human antibody function into a rodent so that the rodent produces fully human antibodies.

[0153] One method for generating fully human antibodies is through the use of XENOMOUSE® strains of mice which have been engineered to contain 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus. *See* Green et al. *Nature Genetics* 7:13-21 (1994). The XENOMOUSE® strains are available from Abgenix, Inc. (Fremont, CA).

[0154] The production of the XENOMOUSE® is further discussed and delineated in U.S. Patent Application Serial Nos. 07/466,008, filed January 12, 1990, 07/610,515, filed November 8, 1990, 07/919,297, filed July 24, 1992, 07/922,649, filed July 30, 1992, filed 08/031,801, filed March 15,1993, 08/112,848, filed August 27, 1993, 08/234,145, filed April 28, 1994, 08/376,279, filed January 20, 1995, 08/430, 938, April 27, 1995, 08/464,584, filed June 5, 1995, 08/464,582, filed June 5, 1995, 08/463,191, filed June 5, 1995, 08/462,837, filed June 5, 1995, 08/486,853, filed June 5, 1995, 08/486,857, filed June 5, 1995, 08/486,859, filed June 5, 1995, 08/462,513, filed June 5, 1995, 08/724,752, filed October 2, 1996, and 08/759,620, filed December 3, 1996 and U.S. Patent Nos. 6,162,963, 6,150,584, 6,114,598, 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2. *See also* Mendez et al. *Nature Genetics* 15:146-156 (1997) and Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998). *See also* European Patent No., EP 0 463 151 B1, grant published June 12, 1996, International Patent Application No., WO 94/02602, published February 3, 1994, International Patent Application No., WO 96/34096, published October 31, 1996, WO 98/24893, published June 11, 1998, WO 00/76310, published December 21, 2000. The disclosures of each of the above-cited patents, applications, and references are hereby incorporated by reference in their entirety.

[0155] In an alternative approach, others, including GenPharm International, Inc., have utilized a "minilocus" approach. In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of pieces (individual genes) from the Ig locus. Thus, one or more V_H genes, one or more D_H genes, one or more J_H genes, a mu constant region, and a second

constant region (preferably a gamma constant region) are formed into a construct for insertion into an animal. This approach is described in U.S. Patent No. 5,545,807 to Surani et al. and U.S. Patent Nos. 5,545,806, 5,625,825, 5,625,126, 5,633,425, 5,661,016, 5,770,429, 5,789,650, 5,814,318, 5,877,397, 5,874,299, and 6,255,458 each to Lonberg and Kay, U.S. Patent No. 5,591,669 and 6,023.010 to Krimpenfort and Berns, U.S. Patent Nos. 5,612,205, 5,721,367, and 5,789,215 to Berns et al., and U.S. Patent No. 5,643,763 to Choi and Dunn, and GenPharm International U.S. Patent Application Serial Nos. 07/574,748, filed August 29, 1990, 07/575,962, filed August 31, 1990, 07/810,279, filed December 17, 1991, 07/853,408, filed March 18, 1992, 07/904,068, filed June 23, 1992, 07/990,860, filed December 16, 1992, 08/053,131, filed April 26, 1993, 08/096,762, filed July 22, 1993, 08/155,301, filed November 18, 1993, 08/161,739, filed December 3, 1993, 08/165,699, filed December 10, 1993, 08/209,741, filed March 9, 1994, the disclosures of which are hereby incorporated by reference. *See also* European Patent No. 0 546 073 B1, International Patent Application Nos. WO 92/03918, WO 92/22645, WO 92/22647, WO 92/22670, WO 93/12227, WO 94/00569, WO 94/25585, WO 96/14436, WO 97/13852, and WO 98/24884 and U.S. Patent No. 5,981,175, the disclosures of which are hereby incorporated by reference in their entirety. *See further* Taylor et al., 1992, Chen et al., 1993, Tuaillon et al., 1993, Choi et al., 1993, Lonberg et al., (1994), Taylor et al., (1994), and Tuaillon et al., (1995), Fishwild et al., (1996), the disclosures of which are hereby incorporated by reference in their entirety.

[0156] Kirin has also demonstrated the generation of human antibodies from mice in which, through microcell fusion, large pieces of chromosomes, or entire chromosomes, have been introduced. *See* European Patent Application Nos. 773 288 and 843 961, the disclosures of which are hereby incorporated by reference in their entireties.

[0157] Human anti-mouse antibody (HAMA) responses have also led the industry to prepare chimeric or otherwise humanized antibodies. While chimeric antibodies have a human constant region and a murine variable region, it is expected that certain human anti-chimeric antibody (HACA) responses will be observed, particularly in chronic or multi-dose utilizations of the antibody. Thus, it would be desirable to provide fully human antibodies against multimeric enzymes in order to vitiate concerns and/or effects of HAMA or HACA response.

Preparation of Antibodies

[0158] Antibodies, as described herein, were prepared using the XENOMOUSE® technology, as described below. Such mice are capable of producing human immunoglobulin molecules and antibodies and are deficient in the production of murine immunoglobulin molecules and antibodies. Technologies utilized for achieving the same are disclosed in the patents, applications, and references referred to herein. In particular, however, a preferred embodiment of transgenic production of mice and antibodies therefrom is disclosed in U.S. Patent Application Serial No. 08/759,620, filed December 3, 1996 and International Patent Application Nos. WO 98/24893, published June 11, 1998 and WO 00/76310, published December 21, 2000, the disclosures of which are hereby incorporated by reference. *See also* Mendez et al. *Nature Genetics* **15**:146-156 (1997), the disclosure of which is hereby incorporated by reference.

[0159] Through use of such technology, fully human monoclonal antibodies to Ten-M4 have been produced, as described in detail below. Essentially, XENOMOUSE® lines of mice are immunized with an antigen of interest (*e.g.*, human Ten-M4), lymphatic cells (such as B-cells) are recovered from mice that expressed antibodies, and the recovered cell lines are fused with a myeloid-type cell line to prepare immortal hybridoma cell lines. These hybridoma cell lines are screened and selected to identify hybridoma cell lines that produced antibodies specific to the antigen of interest. Provided herein are methods for the production of multiple hybridoma cell lines that produce antibodies specific to the desired multimeric enzyme subunit oligomerization domain. Further, provided herein are characterization of the antibodies produced by such cell lines, including nucleotide and amino acid sequence analyses of the heavy and light chains of such antibodies.

[0160] Alternatively, instead of being fused to myeloma cells to generate hybridomas, the recovered cells, isolated from immunized XENOMOUSE® lines of mice, are screened further for reactivity against the initial antigen, preferably human Ten-M4. Such screening includes ELISA with the desired Ten-M4 protein and functional assays such as TenM4 mediated antibody internalization. (Single B cells secreting antibodies of interest are then isolated using a desired Ten-M4-specific hemolytic plaque assay (Babcook et al., *Proc. Natl. Acad. Sci. USA,* i93:7843-7848 (1996)). Cells targeted for lysis are preferably sheep red blood cells (SRBCs) coated with the desired ten-M4 antigen. In the presence of a B cell culture

secreting the immunoglobulin of interest and complement, the formation of a plaque indicates specific Ten-M4-mediated lysis of the target cells.

[0161] The single antigen-specific plasma cell in the center of the plaque can be isolated and the genetic information that encodes the specificity of the antibody is isolated from the single plasma cell. Using reverse-transcriptase PCR, the DNA encoding the variable region of the antibody secreted can be cloned. Such cloned DNA can then be further inserted into a suitable expression vector, preferably a vector cassette such as a pcDNA, more preferably such a pcDNA vector containing the constant domains of immunoglobulin heavy and light chain. The generated vector can then be transfected into host cells, preferably CHO cells, and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. Herein, is described the isolation of multiple single plasma cells that produce antibodies specific to ten-M4. Further, the genetic material that encodes the specificity of the anti-Ten-M4 antibody is isolated, and introduced into a suitable expression vector that is then transfected into host cells.

[0162] In general, antibodies produced by the above-mentioned cell lines possessed fully human IgG1 or IgG2 heavy chains with human kappa light chains. The antibodies possessed high affinities, typically possessing Kd's of from about 10^{-9} through about 10^{-13} M, when measured by either solid phase and solution phase.

[0163] As mentioned above, anti-Ten-M4 antibodies can be expressed in cell lines other than hybridoma cell lines. Sequences encoding particular antibodies can be used for transformation of a suitable mammalian host cell, such as a CHO cell. Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455 (which patents are hereby incorporated herein by reference). The transformation procedure used depends upon the host to be transformed. Methods for introducing heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

[0164] Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture

Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and a number of other cell lines. Cell lines of particular preference are selected through determining which cell lines have high expression levels and produce antibodies with Ten-M4 binding properties.

[0165] As will be appreciated by one of skill in the art, simply the selection of an antigen does not automatically mean that antibodies generated from the antigen will bind to the full protein in its native environment. Thus, in some embodiments, antibodies are tested for and selected for binding to the native protein, rather than variants of the original protein or antigen. In some embodiments, it is these proteins that are specifically contemplated.

Antibody Sequences

[0166] The heavy chain and light chain variable region nucleotide and amino acid sequences of representative human anti-Ten-M4 antibodies are provided in the sequence listing, the contents of which are summarized in Table 1 below and in FIG. 2 through FIG. 13.

Table 1

mAb ID No.:	**Sequence**	**SEQ ID NO:**
1.16	Nucleotide sequence encoding the variable region of the heavy chain	1
	Amino acid sequence encoding the variable region of the heavy chain	2
	Nucleotide sequence encoding the variable region of the light chain	3
	Amino acid sequence encoding the variable region of the light chain	4
1.20	Nucleotide sequence encoding the variable region of the heavy chain	5
	Amino acid sequence encoding the variable region of the heavy chain	6
	Nucleotide sequence encoding the variable region of the light chain	7
	Amino acid sequence encoding the variable region of the light chain	8
1.44	Nucleotide sequence encoding the variable region of the heavy chain	9
	Amino acid sequence encoding the variable region of the heavy chain	10
	Nucleotide sequence encoding the variable region of the light chain	11
	Amino acid sequence encoding the variable region of the light chain	12

mAb ID No.:	Sequence	SEQ ID NO:
1.47	Nucleotide sequence encoding the variable region of the heavy chain	13
	Amino acid sequence encoding the variable region of the heavy chain	14
	Nucleotide sequence encoding the variable region of the light chain	15
	Amino acid sequence encoding the variable region of the light chain	16
1.48	Nucleotide sequence encoding the variable region of the heavy chain	17
	Amino acid sequence encoding the variable region of the heavy chain	18
	Nucleotide sequence encoding the variable region of the light chain	19
	Amino acid sequence encoding the variable region of the light chain	20
1.58	Nucleotide sequence encoding the variable region of the heavy chain	21
	Amino acid sequence encoding the variable region of the heavy chain	22
	Nucleotide sequence encoding the variable region of the light chain	23
	Amino acid sequence encoding the variable region of the light chain	24
2.13	Nucleotide sequence encoding the variable region of the heavy chain	25
	Amino acid sequence encoding the variable region of the heavy chain	26
	Nucleotide sequence encoding the variable region of the light chain	27
	Amino acid sequence encoding the variable region of the light chain	28
2.15	Nucleotide sequence encoding the variable region of the heavy chain	29
	Amino acid sequence encoding the variable region of the heavy chain	30
	Nucleotide sequence encoding the variable region of the light chain	31
	Amino acid sequence encoding the variable region of the light chain	32
2.36	Nucleotide sequence encoding the variable region of the heavy chain	33
	Amino acid sequence encoding the variable region of the heavy chain	34
	Nucleotide sequence encoding the variable region of the light chain	35
	Amino acid sequence encoding the variable region of the light chain	36
2.59	Nucleotide sequence encoding the variable region of the heavy chain	37
	Amino acid sequence encoding the variable region of the heavy chain	38
	Nucleotide sequence encoding the variable region of the light chain	39
	Amino acid sequence encoding the variable region of the light chain	40

5

Antibody Therapeutics

[0167] Anti-Ten-M4 antibodies can have therapeutic effects in treating symptoms and conditions related to Ten-M4 activity. For example, the antibodies can inhibit the formation of the ten-M4/ten-M4 duplex, thereby inhibiting cancer metastasis, or the antibodies can be associated with an agent and deliver a lethal toxin to a targeted cell. In addition, the anti-Ten-M4 antibodies are useful as diagnostics for the disease states, especially cancer and the metastasis of cancer.

[0168] If desired, the isotype of an anti-Ten-M4 antibody can be switched, for example to take advantage of a biological property of a different isotype. For example, in some circumstances it may be desirable in connection with the generation of antibodies as therapeutic antibodies against Ten-M4 that the antibodies be capable of fixing complement and participating in complement-dependent cytotoxicity (CDC). There are a number of isotypes of antibodies that are capable of the same, including, without limitation, the following: murine IgM, murine IgG2a, murine IgG2b, murine IgG3, human IgM, human IgG1, and human IgG3. It will be appreciated that antibodies that are generated need not initially possess such an isotype but, rather, the antibody as generated can possess any isotype and the antibody can be isotype switched thereafter using conventional techniques that are well known in the art. Such techniques include the use of direct recombinant techniques (*see e.g.*, U.S. Patent No. 4,816,397), cell-cell fusion techniques (*see e.g.*, U.S. Patent Nos. 5,916,771 and 6,207,418), among others.

[0169] By way of example, the anti-ten-M4 antibodies discussed herein are human antibodies. If an antibody possessed desired binding to Ten-M4, it could be readily isotype switched to generate a human IgM, human IgG1, or human IgG3 isotype, while still possessing the same variable region (which defines the antibody's specificity and some of its affinity). Such molecule would then be capable of fixing complement and participating in CDC.

[0170] In the cell-cell fusion technique, a myeloma or other cell line is prepared that possesses a heavy chain with any desired isotype and another myeloma or other cell line is prepared that possesses the light chain. Such cells can, thereafter, be fused and a cell line expressing an intact antibody can be isolated.

[0171] Accordingly, as antibody candidates are generated that meet desired "structural" attributes as discussed above, they can generally be provided with at least certain of the desired "functional" attributes through isotype switching.

[0172] Biologically active antibodies that bind Ten-M4 are preferably used in a sterile pharmaceutical preparation or formulation to reduce the activity of Ten-M4. Anti-Ten-M4 antibodies preferably possess adequate affinity to potently suppress Ten-M4 activity to within the target therapeutic range. The suppression can result from the ability of the antibody to interfere with the binding of Ten-M4 to another Ten-M4 protein. Additionally, the antibodies can alter the conformation or the Ten-M4 proteins so that Ten-M4 signaling events do not generally occur.

[0173] When used for *in vivo* administration, the antibody formulation is preferably sterile. This is readily accomplished by any method know in the art, for example by filtration through sterile filtration membranes. The antibody ordinarily will be stored in lyophilized form or in solution. Sterile filtration may be performed prior to or following lyophilization and reconstitution.

[0174] Therapeutic antibody compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having an adapter that allows retrieval of the formulation, such as a stopper pierceable by a hypodermic injection needle.

[0175] The route of antibody administration is in accord with known methods, *e.g.*, injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intrathecal, inhalation or intralesional routes, or by sustained release systems as noted below. In some situations the antibody is preferably administered by infusion or by bolus injection. In other situations a therapeutic composition comprising the antibody can be administered through the nose or lung, preferably as a liquid or powder aerosol (lyophilized). The composition may also be administered intravenously, parenterally or subcutaneously as desired. When administered systemically, the therapeutic composition should be sterile, pyrogen-free and in a parenterally acceptable solution having due regard for pH, isotonicity, and stability. These conditions are known to those skilled in the art.

[0176] Antibodies for therapeutic use, as described herein, are typically prepared with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. Briefly, dosage formulations of the antibodies described herein are prepared for storage or administration by mixing the antibody having the desired degree of purity with one or more physiologically acceptable carriers, excipients, or stabilizers. These formulations may include, for example, powders, pastes,

ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as Lipofectin™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. The formulation may include buffers such as TRIS HCl, phosphate, citrate, acetate and other organic acid salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidinone; amino acids such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium and/or nonionic surfactants such as TWEEN, PLURONICS or polyethyleneglycol. Other acceptable carriers, excipients and stabilizers are well known to those of skill in the art. Any of the foregoing mixtures may be appropriate in treatments and therapies in accordance with the present invention, provided that the active ingredient in the formulation is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. *See also* Baldrick P. "Pharmaceutical excipient development: the need for preclinical guidance." *Regul. Toxicol. Pharmacol.* 32(2):210-8 (2000), Wang W. "Lyophilization and development of solid protein pharmaceuticals." *Int. J. Pharm.* 203(1-2):1-60 (2000), Charman WN "Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts." *J Pharm Sci* .89(8):967-78 (2000), Powell et al. "Compendium of excipients for parenteral formulations" *PDA J Pharm Sci Technol.* 52:238-311 (1998) and the citations therein for additional information.

[0177] Sterile compositions for injection can be formulated according to conventional pharmaceutical practice as described in *Remington: The Science and Practice of Pharmacy* (20th ed, Lippincott Williams & Wilkens Publishers (2003)). For example, dissolution or suspension of the active compound in a vehicle such as water or naturally occurring vegetable oil like sesame, peanut, or cottonseed oil or a synthetic fatty vehicle like ethyl oleate or the like may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

[0178] The antibodies can also be administered in and released over time from sustained-release preparations. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the polypeptide. The

matrices may be in the form of shaped articles, films or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (*e.g.*, poly(2-hydroxyethyl-methacrylate) as described by Langer *et al.*, *J. Biomed Mater. Res.*, (1981) 15:167-277 and Langer, *Chem. Tech.*, (1982) 12:98-105, or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, *Biopolymers*, (1983) 22:547-556), non-degradable ethylene-vinyl acetate (Langer *et al.*, *supra*), 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 (EP 133,988).

[0179] 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 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 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.

[0180] Sustained-released compositions also include preparations of crystals of the antibody suspended in suitable formulations capable of maintaining crystals in suspension. These preparations when injected subcutaneously or intraperitonealy can produce a sustained release effect. Other compositions also include liposomally entrapped antibodies. Liposomes containing such antibodies are prepared by methods known per se: U.S. Pat. No. DE 3,218,121; Epstein *et al.*, *Proc. Natl. Acad. Sci. USA*, (1985) 82:3688-3692; Hwang *et al.*, *Proc. Natl. Acad. Sci. USA*, (1980) 77:4030-4034; EP 52,322; EP 36,676; EP 88,046; EP 143,949; 142,641; Japanese patent application 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324.

[0181] The dosage of the antibody formulation for a given patient may be determined by the attending physician. In determining the appropriate dosage the physician may take into consideration various factors known to modify the action of therapeutics, including, for example, severity and type of disease, body weight, sex, diet, time and route of administration, other

medications and other relevant clinical factors. Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods.

[0182] An effective amount of the antibodies, described herein, to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it is preferred for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. A typical daily dosage might range from about 0.001 mg/kg to up to 100 mg/kg or more, depending on the factors mentioned above. Typically, the clinician will administer the therapeutic antibody until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays.

[0183] It is expected that the antibodies described herein will have therapeutic effect in treatment of symptoms and conditions resulting from or related to the activity of Ten-M4.

Design and Generation of Other Therapeutics

[0184] In accordance with the present invention and based on the activity of the antibodies that are produced and characterized herein with respect to Ten-M4, the design of other therapeutic modalities is facilitated and disclosed to one of skill in the art. Such modalities include, without limitation, advanced antibody therapeutics, such as bispecific antibodies, immunotoxins, and radiolabeled therapeutics, generation of peptide therapeutics, gene therapies, particularly intrabodies, antisense therapeutics, and small molecules.

[0185] In connection with the generation of advanced antibody therapeutics, where complement fixation is a desirable attribute, it cam be possible to sidestep the dependence on complement for cell killing through the use of bispecifics, immunotoxins, or radiolabels, for example.

[0186] For example, bispecific antibodies can be generated that comprise (i) two antibodies, one with a specificity to Ten-M4 and another to a second molecule, that are conjugated together, (ii) a single antibody that has one chain specific to Ten-M4 and a second chain specific to a second molecule, or (iii) a single chain antibody that has specificity to both Ten-M4 and the other molecule. Such bispecific antibodies can be generated using techniques that are well known; for example, in connection with (i) and (ii) *see e.g.,* Fanger et al. *Immunol Methods* 4:72-81 (1994) and Wright and Harris, *supra.* and in connection with (iii) *see e.g.,* Traunecker et al. *Int. J. Cancer (Suppl.)* 7:51-52 (1992). In each case, the second specificity can

be made as desired. For example, the second specificity can be made to the heavy chain activation receptors, including, without limitation, CD16 or CD64 (*see e.g.,* Deo et al. 18:127 (1997)) or CD89 (*see e.g.,* Valerius et al. *Blood* 90:4485-4492 (1997)). In some embodiments, the antibodies are designed so as to bind to two Ten-M4 proteins. In some embodiments, the antibodies are designed so as to bind to two Ten-M4 proteins, and to further prevent the two Ten-M4 proteins from actually contacting one another in a manner so as to allow signaling to occur. In this embodiment, the result can be beneficial in that the Ten-M4 is being prevented from signaling by the antibody, and each antibody can stop two Ten-M4 molecules.

[0187] Antibodies can also be modified to act as immunotoxins utilizing techniques that are well known in the art. *See e.g.,* Vitetta *Immunol Today* 14:252 (1993). *See also* U.S. Patent No. 5,194,594. In connection with the preparation of radiolabeled antibodies, such modified antibodies can also be readily prepared utilizing techniques that are well known in the art. *See e.g.,* Junghans et al. in *Cancer Chemotherapy and Biotherapy* 655-686 (2d edition, Chafner and Longo, eds., Lippincott Raven (1996)). *See also* U.S. Patent Nos. 4,681,581, 4,735,210, 5,101,827, 5,102,990 (RE 35,500), 5,648,471, and 5,697,902. Each of immunotoxins and radiolabeled molecules would be likely to kill cells expressing the desired multimeric enzyme subunit oligomerization domain. In some embodiments, a pharmaceutical composition comprising an effective amount of the antibody in association with a pharmaceutically acceptable carrier or diluent is provided.

[0188] In some embodiments, an anti-Ten-M4 antibody is linked to an agent (*e.g.,* radioisotope, pharmaceutical composition, or a toxin). Preferably, such antibodies can be used for the treatment of diseases, such diseases can relate to the over or under expression of ten-M proteins and ten-M4 in particular. For example, it is contemplated that the drug possesses the pharmaceutical property selected from the group of antimitotic, alkylating, antimetabolite, antiangiogenic, apoptotic, alkaloid, COX-2, and antibiotic agents and combinations thereof. The drug can be selected from the group of nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, anthracyclines, taxanes, COX-2 inhibitors, pyrimidine analogs, purine analogs, antimetabolites, antibiotics, enzymes, epipodophyllotoxins, platinum coordination complexes, vinca alkaloids, substituted ureas, methyl hydrazine derivatives, adrenocortical suppressants, antagonists, endostatin, taxols, camptothecins, oxaliplatin, doxorubicins and their analogs, and a combination thereof.

[0189] Examples of toxins further include gelonin, Pseudomonas exotoxin (PE), PE40, PE38, diphtheria toxin, ricin, abrin, alpha toxin, saporin, ribonuclease (RNase), DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, Pseudomonas endotoxin, as well as derivatives, combinations and modifications thereof.

[0190] Examples of radioisotopes include gamma-emitters, positron-emitters, and x-ray emitters that may be used for localization and/or therapy, and beta-emitters and alpha-emitters that may be used for therapy. The radioisotopes described previously as useful for diagnostics, prognostics and staging are also useful for therapeutics. Non-limiting examples of anti-cancer or anti-leukemia agents include anthracyclines such as doxorubicin (adriamycin), daunorubicin (daunomycin), idarubicin, detorubicin, carminomycin, epirubicin, esorubicin, and morpholino and substituted derivatives, combinations and modifications thereof. Exemplary pharmaceutical agents include cis-platinum, taxol, calicheamicin, vincristine, cytarabine (Ara-C), cyclophosphamide, prednisone, daunorubicin, idarubicin, fludarabine, chlorambucil, interferon alpha, hydroxyurea, temozolomide, thalidomide, and bleomycin, and derivatives, combinations and modifications thereof. Preferably, the anti-cancer or anti-leukemia is doxorubicin, morpholinodoxorubicin, or morpholinodaunorubicin.

[0191] As will be appreciated by one of skill in the art, in the above embodiments, while affinity values can be important, other factors can be as important or more so, depending upon the particular function of the antibody. For example, for an immunotoxin (toxin associated with an antibody), the act of binding of the antibody to the target can be useful; however, in some embodiments, it is the internalization of the toxin into the cell that is the desired end result. As such, antibodies with a high percent internalization can be desirable in these situations. However, they need not be desirable if the antibody is to prevent duplex formation of the Ten-M4 protein with another Ten-M4 protein. Thus, in one embodiment, antibodies with a high efficiency in internalization are contemplated. A high efficiency of internalization can be measured as a percent internalized antibody, and can be from a low value to 100%. For example, in varying embodiments, 0.1-5, 5-10, 10-20, 20-30, 30-40, 40-45, 45-50, 50-60, 60-70, 70-80, 80-90, 90-99, and 99-100% can be a high efficiency. As will be appreciated by one of skill in the art, the desirable efficiency can be different in different embodiments, depending upon, for example, the associated agent, the amount of antibody that can be administered to an area, the

side effects of the antibody-agent complex, the type (*e.g.*, cancer type) and severity of the problem to be treated.

[0192] In other embodiments, the antibodies disclosed herein provide an assay kit for the detection of Ten-M4 protein in mammalian tissues or cells in order to screen for a disease or disorder associated with changes in levels of Ten-M4. The kit comprises an antibody that binds the antigen protein and means for indicating the reaction of the antibody with the antigen, if present.

[0193] In some embodiments, an article of manufacture is provided comprising a container, comprising a composition containing an anti-Ten-M4 antibody, and a package insert or label indicating that the composition can be used to treat disease mediated by Ten-M4. Preferably a mammal and, more preferably, a human, receives the anti-Ten-M4 antibody.

EXAMPLES

[0194] The following examples, including the experiments conducted and results achieved are provided for illustrative purposes only and are not to be construed as limiting upon the teachings herein.

EXAMPLE 1: Antibody Generation

Immunization of Animals.

[0195] Monoclonal antibodies against ten-M4 were developed by immunizing XenoMouse® mice (IgG2 Kappa XenoMouse Strain), Abgenix, Inc. Fremont, CA) using an antigen with the sequence depicted in FIG. 1C. The antigen also had a V5-6xHis tag added, as shown in FIG. 1D. The antigen that was used to immunize the mice was amino acids 371-830, followed by the V5-HIS tag, as shown in FIG. 1C and FIG. 1D.

[0196] Hybridomas produced from the above immunized mouse were screened for ten-M4 specific monoclonal antibodies. The ELISA plates were coated with soluble ten-M4 (truncated ECD) and incubated at 4°C overnight. After the incubation, the plates were washed with Washing Buffer (0.05% Tween 20 in PBS) 3 times. Blocking Buffer (200μL/well, 0.5% BSA, 0.1% Tween 20, 0.01% Thimerosal in 1x PBS) was added and the plates were incubated at room temperature for 1 hour. After incubation, the plates were washed with Washing Buffer three times. Hybridoma supernatant (50 μL/well), positive and negative controls were added and the plates were incubated at room temperature for 2 hours

[0197] After incubation, the plates were washed three times with Washing Buffer. Goat anti-huIgGfc-HRP detection antibody (100 μL/well) was added and the plates were incubated at room temperature for 1 hour. After the incubation, the plates were washed three times with Washing Buffer. TMB substrate (100 μL/well) was added and the plates allowed to develop for about 10 minutes (until negative control wells barely started to show color), then 50 μL/well of stop solution was added and the plates read on an ELISA plate reader at wavelength 450nm.

[0198] Hybridoma supernatants that were identified as positive for binding in the above ELISA were then assayed for the ability to bind to endogenously expressed TenM4 using the PC3 cell line which naturally expresses the antigen. A FMAT based fluorescence assay was performed for 208 samples identified in the screen above. Briefly, PC3 cells were seeded at 10,000 cells per well in a 96-well microtiter dish. After the cells had adhered, the media was removed and replaced with hybridoma supernatant. After an one hour incubation, the cells were washed and the bound antibody was detected via a Cy5-conjugated anti-Human IgGFc specific polyclonal antibody. Positive wells were imaged using the FMAT reader. Table 2, below, summarizes the number of hybridoma lines that bound to the soluble Ten-M4 (Cur105) truncated ECD and the number of lines which then also bound to the PC3 cell line.

Table 2

Number of Ten-M4-V5HIS Reactive Clones	208
Number of hybridoma lines which bound to PC3 cell line (via FMAT and FACS)	13

[0199] It is clear from this data that relatively few of the antibodies produced by the antigen resulted in antibodies that could actually bind to the targeted protein in conditions where the protein is associated with a cell. This is the result despite the fact that a putatively extracellular portion of the protein was used to generate all of the antibodies.

EXAMPLE 2: STRUCTURAL ANALYSIS OF ANTIBODIES

[0200] The variable heavy chains and the variable light chains for the antibodies shown in Table 1 were sequenced to determine their DNA sequences. The complete sequence information for examples of the anti-Ten-M4 antibodies are shown in the sequence listing submitted herewith, including nucleotide and amino acid sequences. The sequences are also displayed in FIG. 2 through FIG. 13. FIG. 12 displays a sequence comparison of the various hybridoma derived antibody heavy chain regions to a particular germ line heavy chain region. FIG. 13 displays a sequence comparison of the various hybridoma derived antibody light chain regions to a particular germ line light chain region.

EXAMPLE 3: BINDING SPECIFICITY OF VARIOUS TEN-M4 (CURAGEN) ANTIBODIES

[0201] This example demonstrates the specificity of the various antibodies generated. ELISA plates were coated with a truncated form of soluble Ten-M4 corresponding to the extracellular domain (ECD) having amino acids 370-830. The plates also had soluble Ten-M2 and a V5-HIS peptide and incubated 4°C overnight. After incubation, the plates were washed with Washing Buffer (0.05% Tween 20 in PBS) 3 times. Blocking Buffer (1.0% milk, 1x PBS, 200μL/well) was added and the plates were incubated at room temperature for 1 hour. After incubation, the plates were washed with Washing Buffer three times.

[0202] Hybridoma supernatants (50μL/well), and positive and negative controls were added and the plates incubated at room temperature for 2 hours. After incubation, the plates were washed three times with Washing Buffer. Goat anti-huIgGfc-HRP detection antibody (50μL/well) was added and the plates were incubated at room temperature for 1 hour. After the incubation, the plates were washed three times with Washing Buffer. TMB substrate (100 μL/well) was added and the plates allowed to develop for about 30 minutes and then 50 μL/well of stop solution was added and the plates read on an ELISA plate reader at wavelength 450nm.

[0203] The binding profiles of Ten-M4 antibodies to Ten-M4 and to a related homologue Cur026 (TenM2) are presented in Table 3 below. As both the Ten-M4 and Ten-M2 soluble proteins are tagged with V5-HIS a backscreen was performed on a soluble peptide to show specificity to the target antigen.

Table 3

Hybridoma ID	Conc (ug/ml)	Ten-M2 Cur026	Ten-M4 Cur105	biotin-V5-His (OD)
1.16	0.3	4.32	3.75	0.04
1.25	0.1	0.12	1.18	0.04
1.44	0.2	0.12	3.90	0.03
1.47	1.9	0.49	3.23	0.05
1.48	0.1	0.06	1.10	0.04
1.58	0.2	0.19	1.49	0.04
1.97	0.2	0.29	0.32	0.04
2.13	4.1	0.93	3.90	0.04
2.15	7.9	0.92	3.96	0.03
2.36	5.8	0.33	3.83	0.03
2.59	15.2	0.95	3.89	0.04
1.20	0.1	0.08	3.85	0.04
2.40	1.2	0.24	2.09	0.04

[0204] As can be observed from the data above, the described antibodies demonstrated an increase in binding relative to the background level. These results demonstrated that the antibodies can be relatively selective or specific for binding to Ten-M4 over other, closely related antigens and proteins. For example, mAb1.44 demonstrated an increase in selectivity for Ten-M4 compared to Ten-M2 and mAb1.20 demonstrated an increase in activity towards Ten-M4 over Ten-M2.

EXAMPLE 4: INTERNALIZATION ASSAYS OF VARIOUS TEN-M4 ANTIBODIES

[0205] This example demonstrated that many if not all of the above antibodies could be internalized within PC3 cells. As reported below, several of the antibodies were internalized at fairly high levels of efficiency (*e.g.*, a relatively large amount of the antibody can be internalized by the cells).

[0206] The above Ten-M4 antibodies were used to stain PC3 cells. This was done first at 4 degrees Celsius (resulting in no internalization for a background measurement), and was then shifted to 37 degrees Celsius for 30 minutes to induce internalization.

[0207] PC3 cells were removed from culture dishes using Cell Dissociation Media (Sigma), counted, and transferred (100,000 cells) to a 96-well VEE bottom plate. The cells were

spun down, the media removed, and the cells resuspended with 100uL of hybridoma supernatant and incubated for 30 min on ice. The incubation cells were spun down, and bound antibody was detected using a secondary antibody which had been linked to Alex647 dye via a disulphide linkage (anti-Hu IgG Fc-SS-Alexa 647 or anti-Hu IgG Fab-SS-Alexa647 @ 1 μg/ml). The secondary antibody was incubated for 7 min on ice. After the incubation, cells were washed and resuspended with ice cold 10% FCS/PBS. The sample was then split into three samples, the cells were spun down, and the supernatant removed.

[0208] Two of the replicates were resuspended with ice cold 10% FCS/PBS and then incubated on ice for 30 minutes. The other replicate was resuspended with warm 10% FCS/PBS and incubated @ 37°C for 30 minutes. After the 30 minute incubation cells were spun down and resuspended with one of the following buffers. One buffer was 250μL of cold 50mM Glutathione, which was added to the 4 degree sample. This was used as a measure of background fluorescence due to incomplete reduction of the disulphide bond. The second buffer had 250μL of cold 50mM Glutathione, which was added to a 37 degree Celsius replicate. The Glutathione only had access to cell surface secondary antibodies. If the antibody was internalized the disulfide bond would not have been reduced by the Glutathione and the cell would have remained fluorescent. The remaining fluorescent intensity was therefore proportional to the amount of internalization of the antibody. The third buffer was 250μL of cold 10% FCS/PBS, which was added to the other 4 degree sample. This sample was a control to show the maximum fluorescence.

[0209] The samples were then incubated on ice for 30 minutes, spun down, and resuspended with 300μL of ice cold 10% FCS/PBS and analyzed by Flow Cytometry.

[0210] The results are displayed in Table 4.

[0211] Table 4

		Internalization PC3 cells (FACS Geometric Mean Average Binding)			
Antibody ID	**Concentration (ug/ml)**	**Total Bound Fluorescence**	**Internalized Fluorescence**	**Background Fluorescence**	**Calculated % Internalization**
Cells Alone	n/a	3.15	3.09	3.17	n/a
Secondary Alone	n/a	11.42	8.7	3.75	n/a
IgG2 Isotype	1	11.36	8.19	3.93	n/a

Control					
1.47	1.9	27.46	10.62	5.67	23%
1.44	0.2	25.28	11.53	5.03	32%
1.20	0.1	24.49	12.44	5.35	37%
2.13	4.1	23.13	9.5	5.22	24%
2.40	1.2	22.96	10.37	4.94	30%
2.59	15	20.78	9.04	4.61	27%
1.25	0.1	20.38	9.54	4.8	30%
1.58	0.2	19.81	9.7	4.57	34%
1.16	0.3	14.88	9.13	4.41	45%
1.97	0.2	14.45	9.16	4.25	48%
1.48	0.1	13.53	8.77	3.99	50%
2.36	5.8	13.19	7.62	4.06	39%
2.15	7.9	12.41	7.57	3.88	43%

[0212] As can be observed in the above table, all of the antibodies were internalized to some extent. The minimal percent internalization was 23%. Several antibodies were internalized at over 40%, and one antibody, 1.48, was internalized at about 50% internalization.

EXAMPLE 5: ANTIBODY TOXIN CONJUGATES

[0213] This example demonstrates how an antibody conjugated to a toxin was used as an effective composition to prevent cancer cells from proliferating. A clonogenic assay was used to determine whether primary antibodies could induce cancer cell death when the antibody was conjugated with a saporin toxin conjugated secondary antibody reagent. (For example, as described in Kohls and Lappi, "Mab-ZAP: A tool for evaluating antibody efficacy for use in an immunotoxin," *Biotechniques*, 28(1):162-5 (Jan. 2000), hereby incorporated by reference in its entirety).

[0214] Briefly, cells were plated onto flat bottom tissue culture plates at a density of about 3000 cells per well. On day 2 or when cells reached ~25% confluency, 100 ng/well secondary mAb-toxin (goat anti-human IgG-saporin; Advanced Targeting Systems; HUM-ZAP; cat. no. IT-22) was added. An anti-EGFR antibody, specific mAb, or an isotype control mAb was then added to each well at the desired concentration (typically 1 to 500 ng/mL). On day 5, the cells were trypsinized, transferred to a 6 well tissue culture dish, and incubated at 37 °C. Plates were examined daily. On days 10-12, the plates were Giemsa stained and colonies on the plates were counted. Plating efficiency was determined by the number of colonies that eventually formed.

[0215] The cytotoxic chemotherapy reagent 5 Flurouracil (5-FU) was used as the positive control and induced almost complete killing, whereas the saporin conjugated-goat anti-human secondary antibody alone had little effect. A monoclonal antibody (NeoMarkers MS-269-PABX) generated against the EGF-like receptor expressed by both cell lines was used to demonstrate primary antibody and secondary antibody-saporin conjugate specific killing.

[0216] Various concentrations (*e.g.*, between 5 and 1000 pM) of the antibody/toxin conjugates were administered to PC-3 cells under conditions to allow for the internalization of the antibody/toxin conjugates. The cells were then allowed to continue growing for 96 hours. The colonies were then counted to determine the amount of inhibition of PC-3 cell growth. The results are presented in FIG. 14.

[0217] As can be observed in the figure, several antibodies resulted in 50% or more reduction in the concentration of PC-3 cells at concentrations ranging between 100 and 1000 pM. The IC_{50} was also calculated for each of the antibodies and is also presented in FIG. 14. The IC_{50}s were typically in the picomolar range.

EXAMPLE 6: SENSITIVITY OF VARIOUS CANCERS TO ANTIBODY TOXIN CONJUGATES

[0218] This example demonstrates that the growth of various forms of cancer cell lines was inhibited through the use of antibodies 1.20 or 1.44 conjugated to saporin. The results are shown in Table 5 and were obtained by a method similar to that described in Example 5 above.

Table 5

Prostate	**Tumor Type**	**Taqman CT**	**FACS (Fold Shift)**	**Sensitivity to anti-ten-M4 Antibody Drug Conjugate**
PC-3	Prostate	29	30	+
22Rv1	Prostate	ND	4	-
LNCAP	Prostate	40	0	-
DU145	Prostate	40	0	-
NCI-N417	Lung	33	17	+
NCI-H146	Lung	31	10	ND

NCI-H209	Lung	ND	13	ND
NCI-H82	Lung	36	3	+/-
NCI-H520	Lung	ND	10	ND
A549	Lung	40	0	-
SR786	Lymphoma	ND	36	+
Karpass299	Lymphoma	ND	13	ND
SupM2	Lymphoma	ND	20	ND
DEL	Lymphoma	ND	7	ND
Jurkat	Lymphoma	35	0	-
KG-1	Lymphoma	ND	0	ND

[0219] As can be observed in Table 5, several of the various cancer cell lines displayed a noticeable sensitivity to the antibody/toxin conjugates. Thus, the antibody/toxin conjugates can be useful against various types of cancers.

EXAMPLE 7: V GENE USAGE OF VARIOUS ANTIBODIES

[0220] This example demonstrates the various V genes that are associated with the particular antibodies characterized above. The V genes in many of the antibodies were analyzed to determine which genes had been employed in the particular antibodies. The V genes involved in both the heavy and the light chains of the antibodies are presented in Table 6 below.

[0221] Table 6

	Heavy Chain			Light Chain	
Chain Name	**V**	**D**	**J**	**V**	**J**
1.58	VH1-2	D6-19	JH4B	L2	JK4
2.36	VH1-46	D3-22	JH4B	L2	JK2
1.48	VH3-33	D4-23	JH6B	B3	JK3
1.20	VH3-33	D3-3	JH6B	A3	JK4
1.44	"	"	"	A3	JK4
2.13	"	"	"	B3	JK3
2.15	VH3-33	D3-22	JH4B	A30	JK5
1.16	VH1-8	D6-25	JH6B	L1	JK4
1.47	VH6-1	D6-19	JH6B	L5	JK3
2.59	VH3-33	D4-17	JH4B	A20	JK3

[0222] As can be seen in the table above, many of the antibodies involved the VH3-33 gene, as well as the JH6B or JH4B genes.

EXAMPLE: 8 GENERATION AND CHARACTERIZATION OF TEN-M4 NEUTRALIZING ANTIBODIES THAT PREVENT CELL MIGRATION

[0223] This example demonstrates one method for generating an antibody and determining if a given Ten-M4 antibody can effectively prevent the formation of the Ten-M4/Ten-M4 duplex.

[0224] Various sections of the Ten-M4 protein are generated as a selection of antigens. The sections are approximately 10-20 amino acids in length and comprise overlapping sections of SEQ ID NO: 41 or 43. As an initial point, amino acids in the EGF-like repeats, especially those in the EGF-like repeats responsible for duplex formation, can be used to generate antibodies. Antibodies created from such antigens are then incubated with Ten-M4 proteins that are expressed on 786-0 cells. The 786-0 cells have an additional marker on or in them so that they may readily be followed. The 786-0 cells are then placed on an experimental medium similar to that discussed in Example 10. Antibodies that result in cells that are no longer able to migrate in the medium can be effective in preventing duplex formation.

[0225] Duplex formation can also be tested and confirmed *in vivo*. Additionally, binding can be detected in devices such as a BIACORE, in which a Ten-M4 is attached to the chip surface, various antibodies are flowed over the chip, binding of the antibody detected, followed by the flowing the above 786-0 cells, and binding (or absence thereof) of the cells being detected.

EXAMPLE: 9 CHARACTERIZATION OF TEN-M4 NEUTRALIZING ANTIBODIES THAT PREVENT CELL MIGRATION

[0226] A cell migration assay identifies proteins that promote or inhibit cell motility. Cells expressing Ten-M4 proteins are placed in a chamber ($1x10^4 - 3x10^4$ cells/well) suspended above a membrane and a lower chamber. The lower chamber contains purified Ten-M4 protein. The cells are incubated for 6 to 24 h and then assayed quantitatively for migratory activity.

[0227] Collagen I coated inserts (Becton Dickinson) are prepared by rehydration for at least 30 minutes at room temperature with 300 μL of basal media. Approximately 90% confluent T175 cells are treated with 5 mL trypsin, neutralized with 10 mL neutralization

solution (complete media), and centrifuged for 7 minutes at 800 RPM. Cells are resuspended in 10 mL basal media containing 0.1%BSA (diluent) and spun again. Cells are resuspended in diluent, counted, and adjusted to an optimized cell concentration.

[0228] Purified Ten-M4 protein or anti-TenM4 antibodies or control antibodies in 0.5 ml of media is added to the wells alone. Hydrated inserts are placed into each well and 0.5 ml of each cell suspension is added to each insert. Cells are incubated for 24 h. FBS is a positive control for motility factor for cells. After the indicated incubation period, the cells are removed from the upper side of the insert using a cotton swab. The cell adhering to the underside of the filter are stained with 0.2% crystal violet in 70% ethanol, washed with distilled water, and counted under the microscope. Antibodies that prevent migration of the cells in this system can also prevent the migration of cells in more complex systems.

EXAMPLE: 10 PREVENTION OF CANCER METASTASIS IN HUMANS BY ADMINISTERING AN ANTIBODY

[0229] A patient suffering from cancer is identified. A dosage of 5 mg/kg of a Ten-M4 antibody that prevents Ten-M4 duplex formation is administered by intravenous injection to the patient. A booster administration is given three weeks later, and every three weeks thereafter. The Ten-M4 antibody causes a partial or complete inhibition of the metastasis of the cancer.

EXAMPLE 11 TREATMENT OF CANCER BY ADMINISTERING ANTIBODY-TOXIN CONJUGATE

[0230] A patient suffering from prostate cancer is identified. A dosage of 5 mg/kg of the Ten-M4 antibody conjugated to saporin is administered by intravenous injection to the patient. A booster administration is given three weeks later, and every three weeks thereafter. The Ten-M4 antibody conjugated to saporin causes a partial or complete destruction of the cancer cells in the prostate.

INCORPORATION BY REFERENCE

[0231] All references cited herein, including patents, patent applications, papers, text books, and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated herein by reference in their entirety.

EQUIVALENTS

[0232] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The foregoing description and Examples detail certain preferred embodiments of the invention and describes the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

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WHAT WE CLAIM IS:

1. A human monoclonal antibody that binds to TenM4 and comprises a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, and 38.

2. The human monoclonal antibody of Claim 1, further comprising a light chain amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40.

3. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO: 2 and the light chain amino acid comprises the sequence of SEQ ID NO: 4.

4. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO: 6 and the light chain amino acid comprises the sequence of SEQ ID NO: 8.

5. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO: 10 and the light chain amino acid comprises the sequence of SEQ ID NO: 12.

6. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO: 14 and the light chain amino acid comprises the sequence of SEQ ID NO: 16.

7. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO: 18 and the light chain amino acid comprises the sequence of SEQ ID NO: 20.

8. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO: 22 and the light chain amino acid comprises the sequence of SEQ ID NO:24.

9. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO:26 and the light chain amino acid comprises the sequence of SEQ ID NO:28.

10. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO:30 and the light chain amino acid comprises the sequence of SEQ ID NO:32.

11. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO:34 and the light chain amino acid comprises the sequence of SEQ ID NO:36.

12. The human monoclonal antibody of claim 2, wherein the heavy chain amino sequence comprises the sequence of SED ID NO:38 and the light chain amino acid comprises the sequence of SEQ ID NO:40.

FIG. 1A

MDVKERKPYRSLTRRRDAERRYTSSSADSEEGKAPQKSYSSSETLKAYDQDARLAYGSRV
KDIVPQEAEEFCRTGANFTLRELGLEEVTPPHGTLYRTDIGLPQCGYSMGAGSDADMEAD
TVLSPEHPVRLWGRSTRSGRSSCLSSRANSNLTLTDTEHENTETDHPGGLQNHARLRTPP
PPLSHAHTPNQHHAASINSLNRGNFTPRSNPSPAPTDHSLSGEPPAGGAQEPAHAQENWL
LNSNIPLETRNLGKQPFLGTLQDNLIEMDILGASRHDGAYSDGHFLFKPGGTSPLFCTTS
PGYPLTSSTVYSPPPRPLPRSTFARPAFNLKKPSKYCNWKCAALSAIVISATLVILLAYF
VAMHLFGLNW **HLQPMEGQMYEITEDTASSWPVPTDVSLYPSGGTGLETPDRKGKGTTEGK**
PSSFFPEDSFIDSGEIDVGRRASQKIPPGTFWRSQVFIDHPVHLKFNVSLGKAALVGIYG
RKGLPPSHTQFDFVELLDGRRLLTQEARSLEGTPRQSRGTVPPSSHETGFIQYLDSGIWH
LAFYNDGKESEVVSFLTTAIESVDNCPSNCYGNGDCISGTCHCFLGFLGPDCGRASCPVL
CSGNGQYMKGRCLCHSGWKGAECDVPTNQCIDVACSNHGTCITGTCICNPGYKGESCEEV
DCMDPTCSGRGVCVRGECHCFVGWGGTNCETPRATCLDQCSGHGTFLPDTGLCSCDPSWT
GHDCSIEICAADCGGHGVCVGGTCRCEDGWMGAACDQRACHPRCAEHGTCRDGKCECSP
GWNGEHCTIAHYLDRVVKEGCPGLCNGNGRCTLDLNGWHCVCQLGWRGAGC
DTSMETACGDSKDNDGDGLVDCMDPDCCLQPLCHINPLCLGSPNPLDIIQETQVPVSQQNLHSFYD
RIKFLVGRDSTHIIPGENPFDGGHACVIRGQVMTSDGTPLVGVNISFVNNPLFGYTISRQDGSF
DLVTNGGISIILRFERAPFITQEHTLWLPWDRFFVMETIIMRHEENEIPSCDLSNFARPN
PVVSPSPLTSFASSCAEKGPIVPEIQALQEEISISGCKMRLSYLSSRTPGYKSVLRISLT
HPTIPFNLMKVHLMVAVEGRLFRKWFAAAPDLSYYFIWDKTDVYNQKVFGLSEAFVSVGY
EYESCPDLILWEKRTTVLQGYEIDASKLGGWSLDKHHALNIQSGILHKGNGENQFVSQQP
PVIGSIMGNGRRRSISCPSCNGLADGNKLLAPVALTCGSDGSLYVGDFNYIRRIFPSGNV
TNILELRNKDFRHSHSPAHKYYLATDPMSGAVFLSDSNSRRVFKIKSTVVVKDLVKNSEV
VAGTGDQCLPFDDTRCGDGGKATEATLTNPRGITVDKFGLIYFVDGTMIRRIDQNGIIST
LLGSNDLTSARPLSCDSVMDISQVRLEWPTDLAINPMDNSLYVLDNNVVLQISENHQVRI
VAGRPMHCQVPGIDHFLLSKVAIHATLESATALAVSHNGVLYIAETDEKKINRIRQVTTS
GEISLVAGAPSGCDCKNDANCDCFSGDDGYAKDAKLNTPSSLAVCADGELYVADLGNIRI
RFIRKNKPFLNTQNMYELSSPIDQELYLFDTTGKHLYTQSLPTGDYLYNFTYTGDGDITL
ITDNNGNMVNVRRDSTGMPLWLVVPDGQVYWVTMGTNSALKSVTTQGHELAMMTYHGNSG
LLATKSNENGWTTFYEYDSFGRLTNVTFPTGQVSSFRSDTDSSVHVQVETSSKDDVTITT
NLSASGAFYTLLQDQVRNSYYIGADGSLRLLLANGMEVALQTEPHLLAGTVNPTVGKRNV
TLPIDNGLNLVEWRQRKEQARGQVTVFGRRLRVHNRNLLSLDFDRVTRTEKIYDDHRKFT
LRILYDQAGRPSLWSPSSRLNGVNVTYSPGGYIAGIQRGIMSERMEYDQAGRITSRIFAD
GKTWSYTYLEKSMVLLLHSQRQYIFEFDKNDRLSSVTMPNVARQTLETIRSVGYYRNIYQ
PPEGNASVIQDFTEDGHLLHTFYLGTGRRVIYKYGKLSKLAETLYDTTKVSFTYDETAGM
LKTINLQNEGFTCTIRYRQIGPLIDRQIFRFTEEGMVNARFDYNYDNSFRVTSMQAVINE
TPLPIDLYRYDDVSGKTEQFGKFGVIYYDINQIITTAVMTHTKHFDAYGRMKEVQYEIFR
SLMYWMTVQYDNMGRVVKKELKVGPYANTTRYSYEYDADGQLQTVSINDKPLWRYSYDLN
GNLHLLSPGNSARLTPLRYDIRDRITRLGDVQYKMDEDGFLRQRGGDIFEYNSAGLLIKA
YNRAGSWSVRYRYDGLGRRVSSKSSHSHHLQFFYADLTNPTKVTHLYNHSSSEITSLYYD
LQGHLFAMELSSGDEFYIACDNIGTPLAVFSGTGLMIKQILYTAYGEIYMDTNPNFQIII
GYHGGLYDPLTKLVHMGRRDYDVLAGRWTSPDHELWKHLSSSNVMPFNLYMFKNNNPISN
SQDIKCFMTDVNSWLLTFGFQLHNVIPGYPKPDMDAMEPSYELIHTQMKTQEWDNSKSIL
GVQCEVQKQLKAFVTLERFDQLYGSTITSCQQAPKTKKFASSGSVFGKGVKFALKDGRVT
TDIISVANEDGRRVAAILNHAHYLENLHFTIDGVDTHYFVKPGPSEGDLAILGLSGGRRT
LENGVNVTVSQINTVLNGRTRRYTDIQLQYGALCLNTRYGTTLDEEKARVLELARQRAVR
QAWAREQQRLREGEEGLRAWTEGEKQQVLSTGRVQGYDGFFVISVEQYPELSDSANNIHF
MRQSEMGRR

SEQ ID NO: 41

FIG. 1B

GTTTGTGGATGTGGAGGAGCGCGGGCCGGAGGCCATGGACGTGAAGGAGAGGAAGCCTTA
CCGCTCGCTGACCCGGCGCCGCGACGCCGAGCGCCGCTACACCAGCTCGTCCGCGGACA
GCGAGGAGGGCAAAGCCCCGCAGAAATCGTACAGCTCCAGCGAGACCCTGAAGGCCTACG
ACCAGGACGCCCGCCTAGCCTATGGCAGCCGCGTCAAGGACATTGTGCCGCAGGAGGCCG
AGGAATTCTGCCGCACAGGTGCCAACTTCACCCTGCGGGAGCTGGGGCTGGAAGAAGTAA
CGCCCCCTCACGGGACCCTGTACCGGACAGACATTGGCCTGCCCCAATGCGGCTACTCCAT
GGGGGCTGGCTCTGATGCCGACATGGAGGCTGACACGGTGCTGTCCCCTGAGCACCCCGT
GCGTCTGTGGGGCCGGAGCACACGGTCAGGGCGCAGCTCCTGCCTGTCCAGCCGGGCCA
ATTCCAATCTCACACTCACCGACACCGAGCATGAAAACACTGAGACTGATCATCCGGGCGG
CCTGCAGAACCACGCGCGGCTCCGGACGCCGCCGCCGCCGCTCTCGCACGCCCACACCC
CCAACCAGCACCACGCGGCCTCCATTAACTCCCTGAACCGGGGCAACTTCACGCCGAGGA
GCAACCCCAGCCCGGCCCCCACGGACCACTCGCTCTCCGGAGAGCCCCCTGCCGGCGGC
GCCCAGGAGCCTGCCCACGCCCAGGAGAACTGGCTGCTCAACAGCAACATCCCCCTGGAG
ACCAGGAACCTAGGCAAGCAGCCATTCCTAGGGACATTGCAGGACAACCTCATTGAGATGG
ACATTCTCGGCGCCTCCCGCCATGATGGGGCTTACAGTGACGGGCACTTCCTCTTCAAGCC
TGGAGGCACCTCCCCGCTCTTCTGCACCACATCACCAGGGTACCCACTGACGTCCAGCAC
AGTGTACTCTCCTCCGCCCCGACCCCTGCCCCGCAGCACCTTCGCCCGGCCGGCCTTTAA
CCTCAAGAAGCCCTCCAAGTACTGTAACTGGAAGTGCGCAGCCCTGAGCGCCATCGTCAT
CTCAGCCACTCTGGTCATCCTGCTGGCATACTTTGTGGCCATGCACCTGTTTGGCCTAAA
CTGGCACCTGCAGCCGATGGAGGGGCAGATGTATGAGATCACGGAGGACACAGCCAGCAG
TTGGCCTGTGCCAACCGACGTCTCCCTATACCCCTCAGGGGGCACTGGCTTAGAGACCCC
TGACAGGAAAGGCAAAGGAACCACAGAAGGAAAGCCCAGTAGTTTCTTTCCAGAGGACAG
TTTCATAGATTCTGGAGAAATTGATGTGGGAAGGCGAGCCTCCCAGAAGATTCCTCCTGG
CACTTTCTGGAGATCTCAAGTGTTCATAGACCATCCTGTGCATCTGAAATTCAATGTGTC
TCTGGGAAAGGCAGCCCTGGTTGGCATTTATGGCAGAAAAGGCCTCCCTCCTTCACATAC
ACAGTTTGACTTTGTGGAGCTGCTGGATGGCAGGAGGCTCCTAACCCAGGAGGCGCGGAG
CCTAGAGGGGACCCCGCGCCAGTCTCGGGGAACTGTGCCCCCCTCCAGCCATGAGACAGG
CTTCATCCAGTATTTGGATTCAGGAATCTGGCACTTGGCTTTTTACAATGACGGAAAGGA
GTCAGAAGTGGTTTCCTTTCTCACCACTGCCATTGAGTCGGTGGATAACTGCCCCAGCAA
CTGCTATGGCAATGGTGACTGCATCTCTGGGACCTGCCACTGCTTCCTGGGTTTCCTGGG
CCCCGACTGTGGCAGAGCCTCCTGCCCCGTGCTCTGTAGCGGAAATGGCCAATACATGAA
AGGCAGATGCTTGTGCCACAGTGGCTGGAAAGGCGCTGAGTGCGATGTGCCCACCAACCA
GTGTATCGATGTGGCCTGCAGCAACCATGGCACCTGCATCACGGGCACCTGCATCTGCAA
CCCTGGCTACAAGGGCGAGAGCTGTGAGGAAGTGGACTGCATGGACCCCACATGTTCAGG
CCGGGGTGTCTGCGTGAGAGGCGAATGCCATTGCTTTGTGGGATGGGGAGGCACCAACTG
CGAGACCCCCAGGGCCACATGCTTAGACCAGTGTTCAGGCCACGGAACCTTCCTCCCGGA

FIG. 1B Continued

CACCGGGCTTTGCAGCTGTGACCCAAGCTGGACTGGACACGACTGTTCTATCGAGATCTG
TGCTGCCGACTGTGGTGGCCATGGCGTGTGCGTAGGGGGCACCTGCCGCTGCGAGGATGG
CTGGATGGGGGCAGCCTGCGACCAGCGGGCCTGCCACCCGCGCTGTGCCGAGCATGGGA
CCTGCCGCGACGGCAAGTGCGAGTGCAGCCCTGGCTGGAATGGCGAACACTGCACCATCG
CTCACTATCTGGATAGGGTAGTTAAAGAGGGTTGCCCTGGGTTGTGCAATGGCAACGGCAG
ATGTACCTTAGACCTGAATGGTTGGCACTGCGTCTGCCAGCTGGGCTGGAGAGGAGCTGG
CTGTGACACTTCCATGGAGACTGCCTGCGGTGACAGCAAAGACAATGATGGAGATGGCCT
GGTGGACTGCATGGACCCTGACTGCTGCCTCCAGCCCCTGTGCCATATCAACCCGCTGTG
CCTTGGCTCCCCTAACCCTCTGGACATCATCCAGGAGACACAGGTCCCTGTGTCACAGCA
GAACCTACACTCCTTCTATGACCGCATCAAGTTCCTCGTGGGCAGGGACAGCACGCACAT
AATCCCCGGGGAGAACCCCTTTGATGGAGGGCATGCTTGTGTTATTCGTGGCCAAGTGAT
GACATCAGATGGAACCCCCCTGGTTGGTGTGAACATCAGTTTTGTCAATAACCCTCTCTT
TGGATATACAATCAGCAGGCAAGATGGCAGCTTTGACTTGGTGACAAATGGCGGCATCTC
CATCATCCTGCGGTTCGAGCGGGCACCTTTCATCACACAGGAGCACACCCTGTGGCTGCC
ATGGGATCGCTTCTTTGTCATGGAAACCATCATCATGAGACATGAGGAGAATGAGATTCC
CAGCTGTGACCTGAGCAATTTTGCCCGCCCCAACCCAGTCGTCTCTCCATCCCCACTGAC
GTCCTTCGCCAGCTCCTGTGCAGAGAAAGGCCCCATTGTGCCGGAAATTCAGGCTTTGCA
GGAGGAAATCTCTATCTCTGGCTGCAAGATGAGGCTGAGCTACCTGAGCAGCCGGACCCC
TGGCTACAAATCTGTCCTGAGGATCAGCCTCACCCACCCGACCATCCCCTTCAACCTCAT
GAAGGTGCACCTCATGGTAGCGGTGGAGGGCCGCCTCTTCAGGAAGTGGTTCGCTGCAGC
CCCAGACCTGTCCTATTATTTCATTTGGGACAAGACAGACGTCTACAACCAGAAGGTGTT
TGGGCTTTCAGAAGCCTTTGTTTCCGTGGGTTATGAATATGAATCCTGCCCAGATCTAAT
CCTGTGGGAAAAAAGAACAACAGTGCTGCAGGGCTATGAAATTGACGCGTCCAAGCTTGG
AGGATGGAGCCTAGACAAACATCATGCCCTCAACATTCAAAGTGGTATCCTGCACAAAGG
GAATGGGGAGAACCAGTTTGTGTCTCAGCAGCCTCCTGTCATTGGGAGCATCATGGGCAA
TGGGCGCCGGAGAAGCATCTCCTGCCCCAGCTGCAACGGCCTTGCTGACGGCAACAAGCT
CCTGGCCCCAGTGGCCCTCACCTGTGGCTCTGACGGGAGCCTCTATGTGGGTGATTTCAA
CTACATTAGAAGGATCTTCCCCTCTGGAAATGTCACCAACATCCTAGAGCTGAGGAATAA
AGATTTCAGACATAGTCACAGTCCAGCACACAAATACTACCTGGCCACAGACCCCATGAG
TGGGGCCGTCTTCCTTTCTGACAGCAACAGCCGGCGGGTCTTTAAAATCAAGTCCACTGT
GGTGGTGAAGGACCTTGTCAAGAACTCTGAGGTGGTTGCGGGGACAGGTGACCAGTGCCT
CCCCTTTGATGACACTCGCTGCGGGGATGGTGGGAAGGCCACAGAAGCCACACTCACCAA
TCCCAGGGGTATTACAGTGGACAAGTTTGGGCTGATCTACTTCGTGGATGGCACCATGAT
CAGACGCATCGATCAGAATGGGATCATCTCCACCCTGCTCGGCTCTAATGATCTCACATC
AGCCCGGCCACTCAGCTGTGATTCTGTCATGGATATTTCCCAGGTAAGACTGGAGTGGCC
CACAGACTTAGCCATCAACCCAATGGACAACTCACTTTATGTCCTCGACAACAATGTGGT

FIG. 1B Conitued

CCTGCAAATCTCTGAAAACCACCAGGTGCGCATTGTCGCCGGGAGGCCCATGCACTGCCA
GGTCCCTGGCATTGACCACTTCCTGCTAAGCAAGGTGGCCATCCACGCAACCCTGGAGTC
AGCCACCGCTTTGGCTGTTTCACACAATGGGGTCCTGTATATTGCTGAGACTGATGAGAA
AAAGATCAACCGCATCAGGCAGGTCACCACTAGTGGAGAGATCTCACTCGTTGCTGGGGC
CCCCAGTGGCTGTGACTGTAAAAATGATGCCAACTGTGATTGTTTTTCTGGAGACGATGG
TTATGCCAAGGATGCAAAGTTAAATACCCCATCTTCCTTGGCTGTGTGTGCTGATGGGGA
GCTCTACGTGGCCGACCTTGGGAACATCCGAATTCGGTTTATCCGGAAGAACAAGCCTTT
CCTCAACACCCAGAACATGTATGAGCTGTCTTCACCAATTGACCAGGAGCTCTATCTGTT
TGATACCACCGGCAAGCACCTGTACACCCAAAGCCTGCCCACAGGAGACTACCTGTACAA
CTTCACCTACACTGGGGACGGCGACATCACACTCATCACAGACAACAATGGCAACATGGT
AAATGTCCGCCGAGACTCTACTGGGATGCCCCTCTGGCTGGTGGTCCCAGATGGCCAGGT
GTACTGGGTGACCATGGGCACCAACAGTGCACTCAAGAGTGTGACCACACAAGGACACGA
GTTGGCCATGATGACATACCATGGCAATTCCGGCCTTCTGGCAACCAAAAGCAATGAAAA
CGGATGGACAACATTTTATGAGTACGACAGCTTTGGCCGCCTGACAAATGTGACCTTCCC
TACTGGCCAGGTGAGCAGTTTCCGAAGTGATACAGACAGTTCAGTGCATGTCCAGGTAGA
GACCTCCAGCAAGGATGATGTCACCATAACCACCAACCTGTCTGCCTCAGGCGCCTTCTA
CACACTGCTGCAAGACCAAGTCCGGAACAGCTACTACATCGGGGCCGATGGCTCCTTGCG
GCTGCTGCTGGCCAACGGCATGGAGGTGGCGCTGCAGACTGAGCCCCACTTGCTGGCTGG
CACCGTCAACCCCACCGTGGGCAAGAGGAATGTCACGCTGCCCATCGACAACGGCCTCAA
CCTGGTGGAGTGGCGCCAGCGCAAAGAGCAGGCTCGGGGCCAGGTCACTGTCTTTGGGCG
CCGGCTGCGGGTGCACAACCGAAATCTCCTATCTCTGGACTTTGATCGCGTAACACGCAC
AGAGAAGATCTATGATGACCACCGCAAGTTCACCCTTCGGATTCTGTACGACCAGGCGGG
GCGGCCCAGCCTCTGGTCACCCAGCAGCAGGCTGAATGGTGTCAACGTGACATACTCCCC
TGGGGGTTACATTGCTGGCATCCAGAGGGGCATCATGTCTGAAAGAATGGAATACGACCA
GGCGGGCCGCATCACATCCAGGATCTTCGCTGATGGGAAGACATGGAGCTACACATACTT
AGAGAAGTCCATGGTGCTGCTACTACACAGCCAGAGGCAGTATATCTTTGAGTTCGACAA
GAATGACCGCCTCTCTTCTGTGACGATGCCCAACGTGGCGCGGCAGACACTAGAGACCAT
CCGCTCAGTGGGCTACTACAGAAACATCTATCAGCCCCCTGAGGGCAATGCCTCAGTCAT
ACAGGACTTCACTGAGGATGGGCACCTCCTTCACACCTTCTACCTGGGCACTGGCCGCAG
GGTGATATACAAGTATGGCAAACTGTCAAAGCTGGCAGAGACGCTCTATGACACCACCAA
GGTCAGTTTCACCTATGACGAGACGGCAGGCATGCTGAAGACCATCAACCTACAGAATGA
GGGCTTCACCTGCACCATCCGCTACCGTCAGATTGGGCCCCTGATTGACCGACAGATCTT
CCGCTTCACTGAGGAAGGCATGGTCAACGCCCGTTTTGACTACAACTATGACAACAGCTT
CCGGGTGACCAGCATGCAGGCTGTGATCAACGAGACCCCACTGCCCATTGATCTCTATCG
CTATGATGATGTGTCAGGCAAGACAGAGCAGTTTGGGAAGTTTGGTGTCATTTACTATGA
CATTAACCAGATCATCACCACAGCTGTCATGACCCACACCAAGCATTTTGATGCATATGG

FIG. 1B Continued

CAGGATGAAGGAAGTGCAGTATGAGATCTTCCGCTCGCTCATGTACTGGATGACCGTCCA
GTATGATAACATGGGGCGAGTAGTGAAGAAGGAGCTGAAGGTAGGACCCTACGCCAATAC
CACTCGCTACTCCTATGAGTATGATGCTGACGGCCAGCTGCAGACAGTCTCCATCAATGA
CAAGCCACTCTGGCGCTACAGCTACGACCTCAATGGGAACCTGCACTTACTGAGCCCTGG
GAACAGTGCACGGCTCACACCACTACGGTATGACATCCGCGACCGCATCACTCGGCTGGG
TGACGTGCAATACAAGATGGATGAGGATGGCTTCCTGAGGCAGCGGGGCGGTGATATCTT
TGAGTACAACTCAGCTGGCCTGCTCATCAAGGCCTACAACCGGGCTGGCAGCTGGAGTGT
CAGGTACCGCTACGATGGCCTGGGGCGGCGCGTGTCCAGCAAGAGCAGCCACAGCCACCA
CCTGCAGTTCTTCTATGCAGACCTGACCAACCCCACCAAGGTCACCCACCTGTACAACCA
CTCCAGCTCTGAGATCACCTCCCTCTACTACGACTTGCAAGGACACCTCTTTGCCATGGA
GCTGAGCAGTGGTGATGAGTTTTACATAGCTTGTGACAACATCGGGACCCCTCTTGCTGT
CTTTAGTGGAACAGGTTTGATGATCAAGCAAATCCTGTACACAGCCTATGGGGAGATCTA
CATGGATACCAACCCCAACTTTCAGATCATCATAGGCTACCATGGTGGCCTCTATGATCC
ACTCACCAAGCTTGTCCACATGGGCCGGCGAGATTATGATGTGCTGGCCGGACGCTGGAC
TAGCCCAGACCACGAGCTGTGGAAGCACCTTAGTAGCAGCAACGTCATGCCTTTTAATCT
CTATATGTTCAAAAACAACAACCCCATCAGCAACTCCCAGGACATCAAGTGCTTCATGAC
AGATGTTAACAGCTGGCTGCTCACCTTTGGATTCCAGCTACACAACGTGATCCCTGGTTA
TCCCAAACCAGACATGGATGCCATGGAACCCTCCTACGAGCTCATCCACACACAGATGAA
AACGCAGGAGTGGGACAACAGCAAGTCTATCCTCGGGGTACAGTGTGAAGTACAGAAGCA
GCTCAAGGCCTTTGTCACCTTAGAACGGTTTGACCAGCTCTATGGCTCCACAATCACCAG
CTGCCAGCAGGCTCCAAAGACCAAGAAGTTTGCATCCAGCGGCTCAGTCTTTGGCAAGGG
GGTCAAGTTTGCCTTGAAGGATGGCCGAGTGACCACAGACATCATCAGTGTGGCCAATGA
GGATGGGCGAAGGGTTGCTGCCATCTTGAACCATGCCCACTACCTAGAGAACCTGCACTT
CACCATTGATGGGGTGGATACCCATTACTTTGTGAAACCAGGACCTTCAGAAGGTGACCT
GGCCATCCTGGGCCTCAGTGGGGGGCGGCGAACCCTGGAGAATGGGGTCAACGTCACTGT
GTCCCAGATCAACACAGTACTTAATGGCAGGACTAGACGCTACACAGACATCCAGCTCCA
GTACGGGGCACTGTGCTTGAACACACGCTACGGGACAACGTTGGATGAGGAGAAGGCACG
GGTCCTGGAGCTGGCCCGGCAGAGAGCCGTGCGCCAAGCGTGGGCCCGCGAGCAGCAGA
GACTGCGGGAAGGGGAGGAAGGCCTGCGGGCCTGGACAGAGGGGGAGAAGCAGCAGGTG
CTGAGCACAGGGCGGGTGCAAGGCTACGACGGCTTTTTCGTGATCTCTGTCGAGCAGTACC
CAGAACTGTCAGACAGCGCCAACAACATCCACTTCATGAGACAGAGCGAGATGGGCCGGAG
GTGACAGAGAGGAC

SEQ ID NO: 42

FIG. 1C

HLQPMEGQMYEITEDTASSWPVPTDVSLYPSGGTGLETPDRKGKGTTEGK
PSSFFPEDSFIDSGEIDVGRRASQKIPPGTFWRSQVFIDHPVHLKFNVSLGKAALV
GIYGRKGLPPSHTQFDFVELLDGRRLLTQEARSLEGTPRQSRGTVPPSSHETGFIQ
YLDSGIWHLAFYNDGKESEVVSFLTTAIESVDNCPSNCYGNGDCISGTCHCFLGF
LGPDCGRASCPVLCSGNGQYMKGRCLCHSGWKGAECDVPTNQCIDVACSNHGT
CITGTCICNPGYKGESCEEVDCMDPTCSGRGVCVRGECHCFVGWGGTNCETPRA
TCLDQCSGHGTFLPDTGLCSCDPSWTGHDCSIEICAADCGGHGVCVGGTCRCED
GWMGAACDQRACHPRCAEHGTCRDGKCECSPGWNGEHCTIAHYLDRVVKEGC
PGLCNGNGRCTLDLNGWHCVCQLGWRGAGC

SEQ ID NO: 43

FIG. 1D

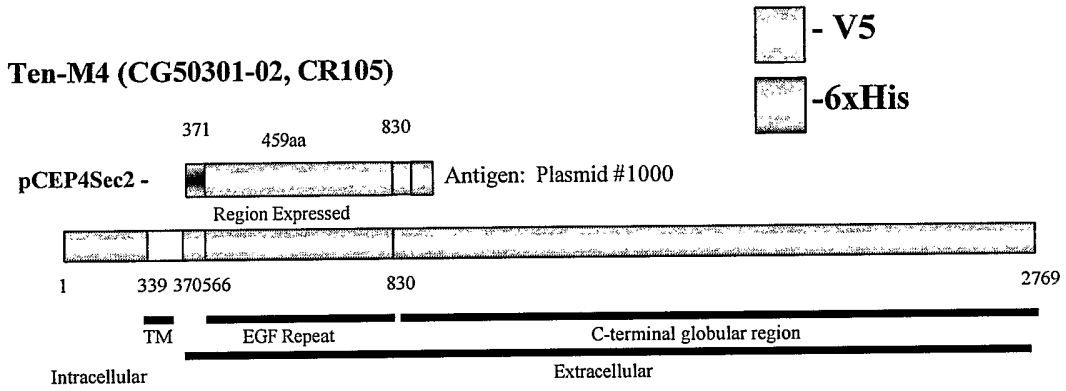

- V5
-6xHis
Ten-M4 (CG50301-02, CR105)
371
459aa
830
pCEP4Sec2 -
Antigen: Plasmid #1000
Region Expressed
1
339 370566
830
2769
TM
EGF Repeat
C-terminal globular region
Intracellular
Extracellular

FIG. 2

A -- 1.16 Nucleotide sequence of heavy chain variable region: SEQ ID NO: 1

5'CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCAGTTATGATATCA
ACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATGGATGA
ACCCTAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCAC
CATGACCTGGAACACCTCCATAAGCACAGCCTACATGGAGCTGAGCAGCCTG
AGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGGCCGCACTACTACT
ACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA**3'**

B -- 1.16 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 2

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWMGWM
NPNSGNTGYAQKFQGRVTMTWNTSISTAYMELSSLRSEDTAVYYCARGPHYYY
GMDVWGQGTTVTVSS

C -- 1.16 Nucleotide sequence of light chain variable region: SEQ ID NO: 3

5'GACATCCAGATGACCCAGTCTCCATCCTCACTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGTCGGGCGAGTCAGGGCATTAGCAATTATTTAGCCT
GGTTTCAGCAGAAACCAGGGAAAGCCCCTAAGTCCCTGATCTATTCTGCATC
CAGTTTGCAAAGTGGGGTCCCATCAAAGTTCAGCGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTA
CTGCCAACAGTATAATAGGTACCCGCTCACTTTCGGCGGAGGGACCAGGGTG
GAGATCAAA**3'**

D -- 1.16 Amino Acid sequence of light chain variable region: SEQ ID NO: 4

DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWFQQKPGKAPKSLIYSASSLQS
GVPSKFSGSGSGTDFTLTISSLQPEDFATYYCQQYNRYPLTFGGGTRVEIK

FIG. 3

A-- 1.20 Nucleotide sequence of heavy chain variable region: SEQ ID NO: 5

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGACGATTTTTGGAGA
GTACTATTATTACGGTCTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTC
TCCTCA**3'**

B-- 1.20 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 6

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIYD
GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARETIFGEYYYY
GLDVWGQGTTVTVSS

C-- 1.20 Nucleotide sequence of light chain variable region: SEQ ID NO: 7

5'GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGC
CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCAAAGTAATGGATA
CAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGTTCCTG
ATCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAG
TGGATCAGGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGAT
GTTGGAATTTATTACTGCGTACAAGCTCTACAAACTCCGCTCACTTTCGGCGG
AGGGACCAAGGTGGAGATCAAG**3'**

D-- 1.20 Amino Acid sequence of light chain variable region: SEQ ID NO: 8

DIVMTQSPLSLPVTPGEPASISCRSSQSLLQSNGYNYLDWYLQKPGQSPQFLIYLG
SNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCVQALQTPLTFGGGTKVEI
K

FIG. 4

A-- 1.44 Nucleotide sequence of heavy chain variable region SEQ ID NO: 9

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGACGATTTTTGGAGA
ATACTACTACTACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCAGCGTC
TCCTCA**3'**

B-- 1.44 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 10

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIW
YDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARETIFGEYY
YYGLDVWGQGTTVSVSS

C-- 1.44 Nucleotide sequence of light chain variable region: SEQ ID NO: 11

5'GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGC
CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCCTAGTAATGGATAC
AACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCAAAGTTCCTGA
TCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGT
GGATCAGGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATG
TTGGGATTTATTACTGCATGCAAACTCTACAAACTCCGCTCACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAA**3'**

D-- 1.44 Amino Acid sequence of light chain variable region: SEQ ID NO: 12

DIVMTQSPLSLPVTPGEPASISCRSSQSLLPSNGYNYLDWYLQKPGQSPKFLIYLG
SNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQTLQTPLTFGGGTKVEI
K

FIG. 5

A-- 1.47 Nucleotide sequence of heavy chain variable region SEQ ID NO: 13

5'CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGAC
CCTCTCACTCACCTGTGCCATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTG
CTTGGAACTGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAG
GACATACTACAGGTCCAAGTGGAAAAAAGATTATGTAGCATCTGTGAAAAGT
CGAATAACCATCAACCCAGACACATCCAAGAACCAGTTCTCCCTGCAGCTGA
ACTCTGTGACTCCCGAGGACACGGCTGTGTATTACTGTGCAAGAGAGCGGTG
GCTGGCCGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACG
GTCACCGTCTCCTCA**3'**

B-- 1.47 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 14

QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTY
YRSKWKKDYVASVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARERWLADY
YYYGMDVWGQGTTVTVSS

C-- 1.47 Nucleotide sequence of light chain variable region: SEQ ID NO: 15

5'GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGCTGGTTAGCCT
GGTATCAGCAGAAACCAGGGAAAGCCCCTAAGGTCCTGATCTATGCTGCATC
CAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTA
TTGTCAACAGGCTAACAGTTTCCCATTCACTTTCGGCCCTGGGACCAAAGTGG
ATATCAAA**3'**

D-- 1.47 Amino Acid sequence of light chain variable region: SEQ ID NO: 16

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKVLIYAASSLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPFTFGPGTKVDIK

FIG. 6

A-- 1.48 Nucleotide sequence of heavy chain variable region SEQ ID NO: 17

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAAGTAATAAACACTATGCAGACTCCGTGAAGGGCCGATTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCATGACTACGGTGG
TAACTCCGAGAGGGGGTATTACTACTACTACGGTATGGACGTCTGGGGC
CAAGGGACCACGGTCACCGTCTCCTCA**3'**

B-- 1.48 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 18

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIW
YDGSNKHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDHDYGG
NSERGYYYYYYGMDVWGQGTTVTVSS

C-- 1.48 Nucleotide sequence of light chain variable region: SEQ ID NO: 19

5'GACATCGTGTTGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG
AGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATTCAGCTCCATCA
ATAAGAACTACTTAGCTTGGTACCAGCAGAAACCAGGCCAGCCTCCTAAGTT
GCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAGTG
GCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGA
AGATGTGGCAGTTTATTACTGTCAGCAATATTACAGTATTCCATTCACTTTCG
GCCCTGGGACCAAAGTGGATATCAAA**3'**

D-- 1.48 Amino Acid sequence of light chain variable region: SEQ ID NO: 20

DIVLTQSPDSLAVSLGERATINCKSSQSVLFSSINKNYLAWYQQKPGQPPKLLIYW
ASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSIPFTFGPGTKVDI
K

FIG. 7

A-- 1.58 Nucleotide sequence of heavy chain variable region SEQ ID NO: 21

5'CAGGTGCAGTTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCA
GTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATATGTA
CTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAAC
CCTAACAGTGGTGGCACAAACTATGTACAGAAGTTTCAGGGCAGGGTCACCA
TGACCAGGGACACGTCCATCAGCACAGCCTACATGGAGCTGAGCAGGCTGAG
ATCTGACGACACGGCCGTGTATTACTGTGCGAGAGACGGGTATAGCACTGGC
TGGTACGAAGGACTTTATTTTGACTACTGGGGCCAGGGAACCCTGGTCACCG
TCTCCTCA**3'**

B-- 1.58 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 22

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMYWVRQAPGQGLEWMGWI
NPNSGGTNYVQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARDGYSTG
WYEGLYFDYWGQGTLVTVSS

C-- 1.58 Nucleotide sequence of light chain variable region: SEQ ID NO: 23

5'GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAA
AGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAACTTAGCCT
GGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATC
CACCAGGGCCACTGGTATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACA
GAGTTCACTCTCACCATCAGCAGCCTGCAGTCTGAAGATTTTGCAGTTTATTA
CTGTCAGCAGTATAATAACTGGCCGCTCACTTTCGGCGGAGGGACCAAGGTG
GAGATCAAA**3'**

D-- 1.58 Amino Acid sequence of light chain variable region: SEQ ID NO: 24

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRA
TGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPLTFGGGTKVEIK

FIG. 8

A-- 2.13 Nucleotide sequence of heavy chain variable region SEQ ID NO: 25

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAGTTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAATGGGTGGCAGTTATATG
GTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCAGATTTTTGGATT
GTTTATTAAGGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACC
ACGGTCACCGTCTCCTCA**3'**

B-- 2.13 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 26

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIW
YDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDQIFGLFI
KDYYYYGMDVWGQGTTVTVSS

C-- 2.13 Nucleotide sequence of light chain variable region: SEQ ID NO: 27

5'GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG
AGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCATCA
ATAGGAACTACTTAACTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAGCT
GCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAGTG
GCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGGTGA
AGATGTGGCAATTTATTACTGTCAGCAATATTATACTACTCCATTCACTTTCG
GCCCTGGGACCAAAGTGGATATCAAA**3'**

D-- 2.13 Amino Acid sequence of light chain variable region: SEQ ID NO: 28

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSINRNYLTWYQQKPGQPPKLLIY
WASTRESGVPDRFSGSGSGTDFTLTISSLQGEDVAIYYCQQYYTTPFTFGPGTKV
DIK

FIG. 9

A-- 2.15 Nucleotide sequence of heavy chain variable region SEQ ID NO: 29

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGTCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGGTCGTCGGTGATTACTTC
CTTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA**3'**

B-- 2.15 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 30

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIW
YDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSSVITSFF
DYWGQGTLVTVSS

C-- 2.15 Nucleotide sequence of light chain variable region: SEQ ID NO: 31

5'GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCT
GGTTTCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATC
CAGTTTGCAAGGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACA
GAATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTA
CTGTCTACAGCATATTACTTACCCTCTCACCTTCGGCCAAGGGACACGACTGG
AGATTAAA**3'**

D-- 2.15 Amino Acid sequence of light chain variable region: SEQ ID NO: 32

DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWFQQKPGKAPKRLIYAASSLQ
GGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHITYPLTFGQGTRLEIK

FIG. 10

A-- 2.36 Nucleotide sequence of heavy chain variable region: SEQ ID NO: 33

5'CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTTTCCTGCAAGGCATCTGGATACACCTTCACCAGCTACTATATGC
ACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAATAATCAA
CTCTAGTGGTGGTAGCACAAGCTACGCACAGAAGTTCCAGGGCAGAGTCACC
ATGACCAGGGACACGTCCACGAGCACAGTCTACATGGAGCTGAGCAGCCTGA
GATCTGAGGACACGGCCGTGTATTACTGTGCGGTTTATTACTATGATAGTAGT
GGTTACCATCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA**3'**

B-- 2.36 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 34

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIIN
SSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAVYYYDSSGY
HLDYWGQGTLVTVSS

C-- 2.36 Nucleotide sequence of light chain variable region: SEQ ID NO: 35

5'GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAA
AGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAACTTAGCCT
GGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATC
CACCAGGGCCTCTGGTATCCCAGCCAGGTTCAGTGGCAGTGGCTCTGGGACA
GAGTTCACTCTCACCATCAGCAGCCTGCAGTCTGAAGATTTTGCAGTTTATTA
CTGTCAGCAGTATAATACCTGGCCTATGTGCAGTTTTGGCCAGGGGACCAAG
CTGGAGATCAAA**3'**

D-- 2.36 Amino Acid sequence of light chain variable region: SEQ ID NO: 36

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRA
SGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNTWPMCSFGQGTKLEIK

FIG. 11

A-- 2.59 Nucleotide sequence of heavy chain variable region: SEQ ID NO: 37

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGTCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCTGGGCTACGGTGA
CTACCTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA**3'**

B-- 2.59 Amino Acid sequence of heavy chain variable region: SEQ ID NO: 38

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIW
YDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLGYGDY
LFDYWGQGTLVTVSS

C-- 2.59 Nucleotide sequence of light chain variable region: SEQ ID NO: 39

5'GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGCCGGGCGAGTCAGGGCATTAGAAATTTTTTAGCCT
GGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATGCTGCATC
CACTTTGCAATCAGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAAGTTATTA
CTGTCAAAAGTATAACAGTGTCCCATTCACTTTCGGCCCTGGGACCAAAGTG
GATATCAAA**3'**

D-- 2.59 Amino Acid sequence of light chain variable region: SEQ ID NO: 40

DIQMTQSPSSLSASVGDRVTITCRASQGIRNFLAWYQQKPGKVPKLLIYAASTLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDVASYYCQKYNSVPFTFGPGTKVDIK

FIG. 12

Chain Name	SEQ ID NO:	V	D	J	FR1	CDR1	FR2
	44	Germline (GL)			QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTGYYMH	WVRQAPGQGLEWMG
1.58	22	VH1-2	D6-19	JH4B	----------	--------Y	----------
	45	GL			QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTSYYMH	WVRQAPGQGLEWMG
2.36	34	VH1-46	D3-22	JH4B	----------	---------	----------
	46	GL			QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
1.48	18	VH3-33	D4-23	JH6B	----------	---------	----------
	47	GL			QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
1.20	6	VH3-33	D3-3	JH6B	----------	---------	----------
1.44	10	"	"	"	----------	---------	----------
2.13	26	"	"	"	----------	---------	----------
	48	GL			QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
2.15	30	VH3-33	D3-22	JH4B	----------	---------	----------
	49	GL			QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTSYDIN	WVRQATGQGLEWMG
1.16	2	VH1-8	D6-25	JH6B	----------	---------	----------
	50	GL			QVQLQQSGPGLVKPSQTLSLTCAIS	GDSVSSNSAAWN	WIRQSPSRGLEWLG
1.47	14	VH6-1	D6-19	JH6B	----------	----------	----------
	51	GL			QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
2.59	38	VH3-33	D4-17	JH4B	----------	---------	----------

Chain Name	SEQ ID NO:	V	D	J	CDR2	FR3
	44	GL			WINPNSGGTNYAQKFQG	RVTMTRDTSISTAYMELSRLRSDDTAVYYCAR
1.58	22	VH1-2	D6-19	JH4B	----------V-----	----------
	45	GL			IINPSGGSTSYAQKFQG	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
2.36	34	VH1-46	D3-22	JH4B	---S----------	----------V
	46	GL			VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
1.48	18	VH3-33	D4-23	JH6B	--------H------	----------
	47	GL			VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
1.20	6	VH3-33	D3-3	JH6B	----------	----------
1.44	10	"	"	"	----------	----------
2.13	26	"	"	"	----------	----------
	48	GL			VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
2.15	30	VH3-33	D3-22	JH4B	----------	----------
	49	GL			WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR
1.16	2	VH1-8	D6-25	JH6B	----------	----W----------
	50	GL			RTYYRSKWYNDYAVSVKS	RITINPDTSKNQFSLQLNSVTPEDTAVYYCAR
1.47	14	VH6-1	D6-19	JH6B	-------KK--VA----	----------
	51	GL			VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
2.59	38	VH3-33	D4-17	JH4B	----------	----------

FIG. 12 Continued

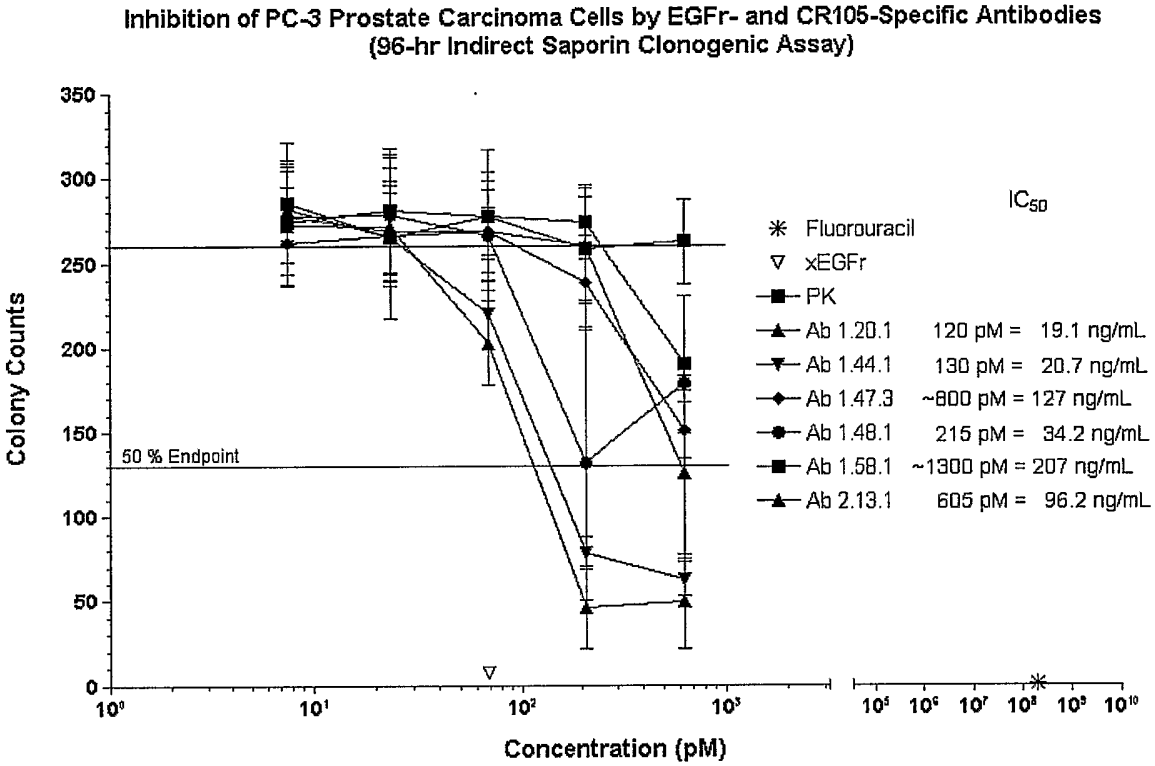
Chain Name	SEQ ID NO:	V	D	J	CDR3	FR4
	44	GL				WGQGTLVTVSS
1.58	22	VH1-2	D6-19	JH4B	DGYSTGWYEGLYFDY	----------
	45	GL				WGQGTLVTVSS
2.36	34	VH1-46	D3-22	JH4B	YYYDSSGYHLDY	----------
	46	GL				WGQGTTVTVSS
1.48	18	VH3-33	D4-23	JH6B	DHDYGGNSERGYYYYYYGMDV	----------
	47	GL				WGQGTTVTVSS
1.20	6	VH3-33	D3-3	JH6B	ETIFGEYYYYGLDV	----------
1.44	10	"	"	"	ETIFGEYYYYGLDV	------S---
2.13	26	"	"	"	DQIFGLFIKDYYYYGMDV	----------
	48	GL				WGQGTLVTVSS
2.15	30	VH3-33	D3-22	JH4B	SSVITSFFDY	----------
	49	GL				WGQGTTVTVSS
1.16	2	VH1-8	D6-25	JH6B	GPHYYYGMDV	----------
	50	GL				WGQGTTVTVSS
1.47	14	VH6-1	D6-19	JH6B	ERWLADYYYYGMDV	----------
	51	GL				WGQGTLVTVSS
2.59	38	VH3-33	D4-17	JH4B	DLGYGDYLFDY	----------

FIG. 13

Chain Name	SEQ ID #	V	J	FR1	CDR1	FR2	CDR2
	52	GL		DIVMTQSPDSLAVSLGERATINC	KSSQSVLYSSNNKNYLA	WYQQKPGQPPKLLIY	WASTRES
2.13	28	B3	JK3	----------	---------I-R---T	----------	-------
1.48	20	"	"	---L----------	------F--I------	----------	-------
	53	GL		DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS
1.20	8	A3	JK4	----------	-------Q--------	----------F---	-------
1.44	12	"	"	----------	-------P--------	----------KF---	-------
	54	GL		EIVMTQSPATLSVSPGERATLSC	RASQSVSSNLA	WYQQKPGQAPRLLIY	GASTRAT
2.36	36	L2	JK2	----------	----------	----------	------S
	55	GL		EIVMTQSPATLSVSPGERATLSC	RASQSVSSNLA	WYQQKPGQAPRLLIY	GASTRAT
1.58	24	L2	JK4	----------	----------	----------	-------
	56	GL		DIQMTQSPSSLSASVGDRVTITC	RASQGISNYLA	WYQQKPGKVPKLLIY	AASTLQS
2.59	40	A20	JK3	----------	------R-F--	----------	-------
	57	GL		DIQMTQSPSSVSASVGDRVTITC	RASQGISSWLA	WYQQKPGKAPKLLIY	AASSLQS
1.47	16	L5	JK3	----------	----------	----------V---	-------
	58	GL		DIQMTQSPSSLSASVGDRVTITC	RASQGISNYLA	WFQQKPGKAPKSLIY	AASSLQS
1.16	4	L1	JK4	----------	----------	----------	S------
	59	GL		DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS
2.15	32	A30	JK5	----------	----------	-F----------	------G

Chain Name	SEQ ID #	V	J	FR3	CDR3	FR4
	52	GL		GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC		FGPGTKVDIK
2.13	28	B3	JK3	----------G----I---	QQYYTTPFT	---------
1.48	20	"	"	----------	QQYYSIPFT	---------
	53	GL		GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC		FGGGTKVEIK
1.20	8	A3	JK4	----------I---	VQALQTPLT	---------
1.44	12	"	"	----------I---	MQTLQTPLT	---------
	54	GL		GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC		FGQGTKLEIK
2.36	36	L2	JK2	----------	QQYNTWPMCS	---------
	55	GL		GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC		FGGGTKVEIK
1.58	24	L2	JK4	----------	QQYNNWPLT	---------
	56	GL		GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC		FGPGTKVDIK
2.59	40	A20	JK3	----------S---	QKYNSVPFT	---------
	57	GL		GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC		FGPGTKVDIK
1.47	16	L5	JK3	----------	QQANSFPFT	---------
	58	GL		GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC		FGGGTKVEIK
1.16	4	L1	JK4	---K----------	QQYNRYPLT	-----R----
	59	GL		GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC		FGQGTRLEIK
2.15	32	A30	JK5	----------	LQHITYPLT	---------

FIG. 14


Inhibition of PC-3 Prostate Carcinoma Cells by EGFr- and CR105-Specific Antibodies
(96-hr Indirect Saporin Clonogenic Assay)
Colony Counts
Concentration (pM)
50 % Endpoint
IC50
Fluorouracil
xEGFr
PK
Ab 1.20.1 120 pM = 19.1 ng/mL
Ab 1.44.1 130 pM = 20.7 ng/mL
Ab 1.47.3 ~800 pM = 127 ng/mL
Ab 1.48.1 215 pM = 34.2 ng/mL
Ab 1.58.1 ~1300 pM = 207 ng/mL
Ab 2.13.1 605 pM = 96.2 ng/mL

21402-679-061 Sequence Listing
SEQUENCE LISTING

<110> Abgenix, Inc.
CuraGen Corporation
Kang, Jaspal
Ettenberg, Seth
Herrmann, John
Rastelli, Luca
Jeffers, Michael
LaRochelle, William

<120> ANTIBODIES DIRECTED TO TEN-M PROTEINS
AND USES THEREOF

<130> 21402-679-061

<140>
<141> 2005-11-17

<150> 60/629,132
<151> 2004-11-17

<160> 59

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 357
<212> DNA
<213> Homo sapiens

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actggacaag ggcttgagtg gatgggatgg atgaacccta acagtggtaa cacaggctat 180
gcacagaagt tccagggcag agtcaccatg acctggaaca cctccataag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagggccg 300
cactactact acggtatgga cgtctggggc caagggacca cggtcaccgt ctcctca 357

<210> 2
<211> 119
<212> PRT
<213> Homo sapiens

<400> 2
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Trp Asn Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Pro His Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly
100 105 110
Thr Thr Val Thr Val Ser Ser
115

<210> 3
<211> 321
<212> DNA
<213> Homo sapiens

21402-679-061 Sequence Listing

<400> 3
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atcacttgtc gggcgagtca gggcattagc aattatttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctattct gcatccagtt tgcaaagtgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tataataggt acccgctcac tttcggcgga 300
gggaccaggg tggagatcaa a 321

<210> 4
<211> 107
<212> PRT
<213> Homo sapiens

<400> 4
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45
Tyr Ser Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Arg Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Arg Val Glu Ile Lys
100 105

<210> 5
<211> 369
<212> DNA
<213> Homo sapiens

<400> 5
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagacg 300
atttttggag agtactatta ttacggtctg gacgtctggg gccaagggac cacggtcacc 360
gtctcctca 369

<210> 6
<211> 122
<212> PRT
<213> Homo sapiens

<400> 6
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Glu Thr Ile Phe Gly Glu Tyr Tyr Tyr Tyr Gly Leu Asp Val Trp
100 105 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

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<210> 7
<211> 336
<212> DNA
<213> Homo sapiens

<400> 7
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atctcctgca ggtctagtca gagcctcctg caaagtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ttcctgatct atttgggttc taatcgggcc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttggaatt tattactgcg tacaagctct acaaactccg 300
ctcactttcg gcggagggac caaggtggag atcaag 336

<210> 8
<211> 112
<212> PRT
<213> Homo sapiens

<400> 8
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Gln Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Phe Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Val Gln Ala
85 90 95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 9
<211> 369
<212> DNA
<213> Homo sapiens

<400> 9
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagacg 300
atttttggag aatactacta ctacggtttg gacgtctggg gccaagggac cacggtcagc 360
gtctcctca 369

<210> 10
<211> 123
<212> PRT
<213> Homo sapiens

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Thr Ile Phe Gly Glu Tyr Tyr Tyr Tyr Gly Leu Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Ser Val Ser Ser
115 120

<210> 11
<211> 336
<212> DNA
<213> Homo sapiens

<400> 11
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg cctagtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccaaag ttcctgatct atttgggttc taatcgggcc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggatt tattactgca tgcaaactct acaaactccg 300
ctcactttcg gcggagggac caaggtggag atcaaa 336

<210> 12
<211> 112
<212> PRT
<213> Homo sapiens

<400> 12
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Pro Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Lys Phe Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Thr
85 90 95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 13
<211> 378
<212> DNA
<213> Homo sapiens

<400> 13
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acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg 120
cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggaaa 180
aaagattatg tagcatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240
cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
agagagcggt ggctggccga ctactactac tacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca 378

<210> 14
<211> 126
<212> PRT
<213> Homo sapiens

<400> 14
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

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

<210> 15
<211> 321
<212> DNA
<213> Homo sapiens

<400> 15
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atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaaggtcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacag gctaacagtt tcccattcac tttcggccct 300
gggaccaaag tggatatcaa a 321

<210> 16
<211> 107
<212> PRT
<213> Homo sapiens

<400> 16
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 17
<211> 390
<212> DNA
<213> Homo sapiens

<400> 17
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaacactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatcat 300
gactacggtg gtaactccga gaggggtat tactactact actacggtat ggacgtctgg 360
ggccaaggga ccacggtcac cgtctcctca 390

<210> 18
<211> 130
<212> PRT
<213> Homo sapiens

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<400> 18
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp His Asp Tyr Gly Gly Asn Ser Glu Arg Gly Tyr Tyr Tyr
100 105 110
Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
115 120 125
Ser Ser
130

<210> 19
<211> 339
<212> DNA
<213> Homo sapiens

<400> 19
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atcaactgca agtccagcca gagtgtttta ttcagctcca tcaataagaa ctacttagct 120
tggtaccagc agaaaccagg ccagcctcct aagttgctca tttactgggc atctacccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttacagtatt 300
ccattcactt tcggccctgg gaccaaagtg gatatcaaa 339

<210> 20
<211> 113
<212> PRT
<213> Homo sapiens

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

<210> 21
<211> 372
<212> DNA
<213> Homo sapiens

<400> 21
caggtgcagt tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc ggctactata tgtactgggt gcgacaggcc 120

21402-679-061 Sequence Listing

cctggacaag ggcttgagtg gatgggatgg atcaacccta acagtggtgg cacaaactat 180
gtacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagacggg 300
tatagcactg gctggtacga aggactttat tttgactact ggggccaggg aaccctggtc 360
accgtctcct ca 372

<210> 22
<211> 124
<212> PRT
<213> Homo sapiens

<400> 22
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30
Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Val Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Tyr Ser Thr Gly Trp Tyr Glu Gly Leu Tyr Phe Asp
100 105 110
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 23
<211> 321
<212> DNA
<213> Homo sapiens

<400> 23
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataact ggccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 24
<211> 107
<212> PRT
<213> Homo sapiens

<400> 24
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 25
<211> 381

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<212> DNA
<213> Homo sapiens

<400> 25
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tcctgtgcag cgtctggatt caccttcagt agttatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggaatg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatcag 300
atttttggat tgtttattaa ggactactac tactacggta tggacgtctg gggccaaggg 360
accacggtca ccgtctcctc a 381

<210> 26
<211> 127
<212> PRT
<213> Homo sapiens

<400> 26
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gln Ile Phe Gly Leu Phe Ile Lys Asp Tyr Tyr Tyr Tyr
100 105 110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 27
<211> 339
<212> DNA
<213> Homo sapiens

<400> 27
gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtgtttta tacagctcca tcaataggaa ctacttaact 120
tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctacccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcagggtga agatgtggca atttattact gtcagcaata ttatactact 300
ccattcactt tcggccctgg gaccaaagtg gatatcaaa 339

<210> 28
<211> 113
<212> PRT
<213> Homo sapiens

<400> 28
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30
Ser Ile Asn Arg Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Leu Gln Gly Glu Asp Val Ala Ile Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Thr Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
100 105 110
Lys

<210> 29
<211> 357
<212> DNA
<213> Homo sapiens

<400> 29
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgtcaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gaggtcgtcg 300
gtgattactt ccttctttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 30
<211> 119
<212> PRT
<213> Homo sapiens

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

<210> 31
<211> 321
<212> DNA
<213> Homo sapiens

<400> 31
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtttca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaggtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag catattactt accctctcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 32
<211> 107
<212> PRT
<213> Homo sapiens

<400> 32
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile

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        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Ile Thr Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105
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<210> 33
<211> 363
<212> DNA
<213> Homo sapiens

<400> 33
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tcctgcaagg catctggata caccttcacc agctactata tgcactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaata atcaactcta gtggtggtag cacaagctac 180
gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc ggtttattac 300
tatgatagta gtggttacca tcttgactac tggggccagg gaaccctggt caccgtctcc 360
tca 363

<210> 34
<211> 121
<212> PRT
<213> Homo sapiens

<400> 34
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 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Ser Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Val Tyr Tyr Tyr Asp Ser Ser Gly Tyr His Leu Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> 35
<211> 324
<212> DNA
<213> Homo sapiens

<400> 35
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ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggcctctgg tatcccagcc 180
aggttcagtg gcagtggctc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataatacct ggcctatgtg cagttttggc 300
caggggacca agctggagat caaa 324

<210> 36
<211> 108
<212> PRT
<213> Homo sapiens

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<400> 36
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Thr Trp Pro Met
85 90 95
Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 37
<211> 360
<212> DNA
<213> Homo sapiens

<400> 37
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg gtctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatctg 300
ggctacggtg actacctctt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 38
<211> 120
<212> PRT
<213> Homo sapiens

<400> 38
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Leu Gly Tyr Gly Asp Tyr Leu Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 39
<211> 321
<212> DNA
<213> Homo sapiens

<400> 39
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atcacttgcc gggcgagtca gggcattaga aatttttag cctggtatca gcagaaacca 120
gggaaagttc ctaagctcct gatctatgct gcatccactt tgcaatcagg ggtcccatct 180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagatgttg caagttatta ctgtcaaaag tataacagtg tcccattcac tttcggccct 300
gggaccaaag tggatatcaa a 321

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<210> 40
<211> 107
<212> PRT
<213> Homo sapiens

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

<210> 41
<211> 2769
<212> PRT
<213> Homo sapiens

<400> 41
Met Asp Val Lys Glu Arg Lys Pro Tyr Arg Ser Leu Thr Arg Arg Arg
1 5 10 15
Asp Ala Glu Arg Arg Tyr Thr Ser Ser Ser Ala Asp Ser Glu Glu Gly
20 25 30
Lys Ala Pro Gln Lys Ser Tyr Ser Ser Ser Glu Thr Leu Lys Ala Tyr
35 40 45
Asp Gln Asp Ala Arg Leu Ala Tyr Gly Ser Arg Val Lys Asp Ile Val
50 55 60
Pro Gln Glu Ala Glu Glu Phe Cys Arg Thr Gly Ala Asn Phe Thr Leu
65 70 75 80
Arg Glu Leu Gly Leu Glu Glu Val Thr Pro Pro His Gly Thr Leu Tyr
85 90 95
Arg Thr Asp Ile Gly Leu Pro Gln Cys Gly Tyr Ser Met Gly Ala Gly
100 105 110
Ser Asp Ala Asp Met Glu Ala Asp Thr Val Leu Ser Pro Glu His Pro
115 120 125
Val Arg Leu Trp Gly Arg Ser Thr Arg Ser Gly Arg Ser Ser Cys Leu
130 135 140
Ser Ser Arg Ala Asn Ser Asn Leu Thr Leu Thr Asp Thr Glu His Glu
145 150 155 160
Asn Thr Glu Thr Asp His Pro Gly Gly Leu Gln Asn His Ala Arg Leu
165 170 175
Arg Thr Pro Pro Pro Pro Leu Ser His Ala His Thr Pro Asn Gln His
180 185 190
His Ala Ala Ser Ile Asn Ser Leu Asn Arg Gly Asn Phe Thr Pro Arg
195 200 205
Ser Asn Pro Ser Pro Ala Pro Thr Asp His Ser Leu Ser Gly Glu Pro
210 215 220
Pro Ala Gly Gly Ala Gln Glu Pro Ala His Ala Gln Glu Asn Trp Leu
225 230 235 240
Leu Asn Ser Asn Ile Pro Leu Glu Thr Arg Asn Leu Gly Lys Gln Pro
245 250 255
Phe Leu Gly Thr Leu Gln Asp Asn Leu Ile Glu Met Asp Ile Leu Gly
260 265 270
Ala Ser Arg His Asp Gly Ala Tyr Ser Asp Gly His Phe Leu Phe Lys
275 280 285
Pro Gly Gly Thr Ser Pro Leu Phe Cys Thr Thr Ser Pro Gly Tyr Pro
290 295 300

Leu Thr Ser Ser Thr Val Tyr Ser Pro Pro Pro Arg Pro Leu Pro Arg
305 310 315 320
Ser Thr Phe Ala Arg Pro Ala Phe Asn Leu Lys Lys Pro Ser Lys Tyr
325 330 335
Cys Asn Trp Lys Cys Ala Ala Leu Ser Ala Ile Val Ile Ser Ala Thr
340 345 350
Leu Val Ile Leu Leu Ala Tyr Phe Val Ala Met His Leu Phe Gly Leu
355 360 365
Asn Trp His Leu Gln Pro Met Glu Gly Gln Met Tyr Glu Ile Thr Glu
370 375 380
Asp Thr Ala Ser Ser Trp Pro Val Pro Thr Asp Val Ser Leu Tyr Pro
385 390 395 400
Ser Gly Gly Thr Gly Leu Glu Thr Pro Asp Arg Lys Gly Lys Gly Thr
405 410 415
Thr Glu Gly Lys Pro Ser Ser Phe Phe Pro Glu Asp Ser Phe Ile Asp
420 425 430
Ser Gly Glu Ile Asp Val Gly Arg Arg Ala Ser Gln Lys Ile Pro Pro
435 440 445
Gly Thr Phe Trp Arg Ser Gln Val Phe Ile Asp His Pro Val His Leu
450 455 460
Lys Phe Asn Val Ser Leu Gly Lys Ala Ala Leu Val Gly Ile Tyr Gly
465 470 475 480
Arg Lys Gly Leu Pro Pro Ser His Thr Gln Phe Asp Phe Val Glu Leu
485 490 495
Leu Asp Gly Arg Arg Leu Leu Thr Gln Glu Ala Arg Ser Leu Glu Gly
500 505 510
Thr Pro Arg Gln Ser Arg Gly Thr Val Pro Pro Ser Ser His Glu Thr
515 520 525
Gly Phe Ile Gln Tyr Leu Asp Ser Gly Ile Trp His Leu Ala Phe Tyr
530 535 540
Asn Asp Gly Lys Glu Ser Glu Val Val Ser Phe Leu Thr Thr Ala Ile
545 550 555 560
Glu Ser Val Asp Asn Cys Pro Ser Asn Cys Tyr Gly Asn Gly Asp Cys
565 570 575
Ile Ser Gly Thr Cys His Cys Phe Leu Gly Phe Leu Gly Pro Asp Cys
580 585 590
Gly Arg Ala Ser Cys Pro Val Leu Cys Ser Gly Asn Gly Gln Tyr Met
595 600 605
Lys Gly Arg Cys Leu Cys His Ser Gly Trp Lys Gly Ala Glu Cys Asp
610 615 620
Val Pro Thr Asn Gln Cys Ile Asp Val Ala Cys Ser Asn His Gly Thr
625 630 635 640
Cys Ile Thr Gly Thr Cys Ile Cys Asn Pro Gly Tyr Lys Gly Glu Ser
645 650 655
Cys Glu Glu Val Asp Cys Met Asp Pro Thr Cys Ser Gly Arg Gly Val
660 665 670
Cys Val Arg Gly Glu Cys His Cys Phe Val Gly Trp Gly Gly Thr Asn
675 680 685
Cys Glu Thr Pro Arg Ala Thr Cys Leu Asp Gln Cys Ser Gly His Gly
690 695 700
Thr Phe Leu Pro Asp Thr Gly Leu Cys Ser Cys Asp Pro Ser Trp Thr
705 710 715 720
Gly His Asp Cys Ser Ile Glu Ile Cys Ala Ala Asp Cys Gly Gly His
725 730 735
Gly Val Cys Val Gly Gly Thr Cys Arg Cys Glu Asp Gly Trp Met Gly
740 745 750
Ala Ala Cys Asp Gln Arg Ala Cys His Pro Arg Cys Ala Glu His Gly
755 760 765
Thr Cys Arg Asp Gly Lys Cys Glu Cys Ser Pro Gly Trp Asn Gly Glu
770 775 780
His Cys Thr Ile Ala His Tyr Leu Asp Arg Val Val Lys Glu Gly Cys
785 790 795 800
Pro Gly Leu Cys Asn Gly Asn Gly Arg Cys Thr Leu Asp Leu Asn Gly
805 810 815
Trp His Cys Val Cys Gln Leu Gly Trp Arg Gly Ala Gly Cys Asp Thr
820 825 830
Ser Met Glu Thr Ala Cys Gly Asp Ser Lys Asp Asn Asp Gly Asp Gly

835 840 845
Leu Val Asp Cys Met Asp Pro Asp Cys Cys Leu Gln Pro Leu Cys His
850 855 860
Ile Asn Pro Leu Cys Leu Gly Ser Pro Asn Pro Leu Asp Ile Ile Gln
865 870 875 880
Glu Thr Gln Val Pro Val Ser Gln Gln Asn Leu His Ser Phe Tyr Asp
885 890 895
Arg Ile Lys Phe Leu Val Gly Arg Asp Ser Thr His Ile Ile Pro Gly
900 905 910
Glu Asn Pro Phe Asp Gly Gly His Ala Cys Val Ile Arg Gly Gln Val
915 920 925
Met Thr Ser Asp Gly Thr Pro Leu Val Gly Val Asn Ile Ser Phe Val
930 935 940
Asn Asn Pro Leu Phe Gly Tyr Thr Ile Ser Arg Gln Asp Gly Ser Phe
945 950 955 960
Asp Leu Val Thr Asn Gly Gly Ile Ser Ile Ile Leu Arg Phe Glu Arg
965 970 975
Ala Pro Phe Ile Thr Gln Glu His Thr Leu Trp Leu Pro Trp Asp Arg
980 985 990
Phe Phe Val Met Glu Thr Ile Ile Met Arg His Glu Glu Asn Glu Ile
995 1000 1005
Pro Ser Cys Asp Leu Ser Asn Phe Ala Arg Pro Asn Pro Val Val Ser
1010 1015 1020
Pro Ser Pro Leu Thr Ser Phe Ala Ser Ser Cys Ala Glu Lys Gly Pro
1025 1030 1035 1040
Ile Val Pro Glu Ile Gln Ala Leu Gln Glu Glu Ile Ser Ile Ser Gly
1045 1050 1055
Cys Lys Met Arg Leu Ser Tyr Leu Ser Ser Arg Thr Pro Gly Tyr Lys
1060 1065 1070
Ser Val Leu Arg Ile Ser Leu Thr His Pro Thr Ile Pro Phe Asn Leu
1075 1080 1085
Met Lys Val His Leu Met Val Ala Val Glu Gly Arg Leu Phe Arg Lys
1090 1095 1100
Trp Phe Ala Ala Ala Pro Asp Leu Ser Tyr Tyr Phe Ile Trp Asp Lys
1105 1110 1115 1120
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1125 1130 1135
Ser Val Gly Tyr Glu Tyr Glu Ser Cys Pro Asp Leu Ile Leu Trp Glu
1140 1145 1150
Lys Arg Thr Thr Val Leu Gln Gly Tyr Glu Ile Asp Ala Ser Lys Leu
1155 1160 1165
Gly Gly Trp Ser Leu Asp Lys His His Ala Leu Asn Ile Gln Ser Gly
1170 1175 1180
Ile Leu His Lys Gly Asn Gly Glu Asn Gln Phe Val Ser Gln Gln Pro
1185 1190 1195 1200
Pro Val Ile Gly Ser Ile Met Gly Asn Gly Arg Arg Arg Ser Ile Ser
1205 1210 1215
Cys Pro Ser Cys Asn Gly Leu Ala Asp Gly Asn Lys Leu Leu Ala Pro
1220 1225 1230
Val Ala Leu Thr Cys Gly Ser Asp Gly Ser Leu Tyr Val Gly Asp Phe
1235 1240 1245
Asn Tyr Ile Arg Arg Ile Phe Pro Ser Gly Asn Val Thr Asn Ile Leu
1250 1255 1260
Glu Leu Arg Asn Lys Asp Phe Arg His Ser His Ser Pro Ala His Lys
1265 1270 1275 1280
Tyr Tyr Leu Ala Thr Asp Pro Met Ser Gly Ala Val Phe Leu Ser Asp
1285 1290 1295
Ser Asn Ser Arg Arg Val Phe Lys Ile Lys Ser Thr Val Val Val Lys
1300 1305 1310
Asp Leu Val Lys Asn Ser Glu Val Val Ala Gly Thr Gly Asp Gln Cys
1315 1320 1325
Leu Pro Phe Asp Asp Thr Arg Cys Gly Asp Gly Gly Lys Ala Thr Glu
1330 1335 1340
Ala Thr Leu Thr Asn Pro Arg Gly Ile Thr Val Asp Lys Phe Gly Leu
1345 1350 1355 1360
Ile Tyr Phe Val Asp Gly Thr Met Ile Arg Arg Ile Asp Gln Asn Gly
1365 1370 1375

Ile Ile Ser Thr Leu Leu Gly Ser Asn Asp Leu Thr Ser Ala Arg Pro
1380 1385 1390
Leu Ser Cys Asp Ser Val Met Asp Ile Ser Gln Val Arg Leu Glu Trp
1395 1400 1405
Pro Thr Asp Leu Ala Ile Asn Pro Met Asp Asn Ser Leu Tyr Val Leu
1410 1415 1420
Asp Asn Asn Val Val Leu Gln Ile Ser Glu Asn His Gln Val Arg Ile
1425 1430 1435 1440
Val Ala Gly Arg Pro Met His Cys Gln Val Pro Gly Ile Asp His Phe
1445 1450 1455
Leu Leu Ser Lys Val Ala Ile His Ala Thr Leu Glu Ser Ala Thr Ala
1460 1465 1470
Leu Ala Val Ser His Asn Gly Val Leu Tyr Ile Ala Glu Thr Asp Glu
1475 1480 1485
Lys Lys Ile Asn Arg Ile Arg Gln Val Thr Thr Ser Gly Glu Ile Ser
1490 1495 1500
Leu Val Ala Gly Ala Pro Ser Gly Cys Asp Cys Lys Asn Asp Ala Asn
1505 1510 1515 1520
Cys Asp Cys Phe Ser Gly Asp Asp Gly Tyr Ala Lys Asp Ala Lys Leu
1525 1530 1535
Asn Thr Pro Ser Ser Leu Ala Val Cys Ala Asp Gly Glu Leu Tyr Val
1540 1545 1550
Ala Asp Leu Gly Asn Ile Arg Ile Arg Phe Ile Arg Lys Asn Lys Pro
1555 1560 1565
Phe Leu Asn Thr Gln Asn Met Tyr Glu Leu Ser Ser Pro Ile Asp Gln
1570 1575 1580
Glu Leu Tyr Leu Phe Asp Thr Thr Gly Lys His Leu Tyr Thr Gln Ser
1585 1590 1595 1600
Leu Pro Thr Gly Asp Tyr Leu Tyr Asn Phe Thr Tyr Thr Gly Asp Gly
1605 1610 1615
Asp Ile Thr Leu Ile Thr Asp Asn Asn Gly Asn Met Val Asn Val Arg
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Arg Asp Ser Thr Gly Met Pro Leu Trp Leu Val Val Pro Asp Gly Gln
1635 1640 1645
Val Tyr Trp Val Thr Met Gly Thr Asn Ser Ala Leu Lys Ser Val Thr
1650 1655 1660
Thr Gln Gly His Glu Leu Ala Met Met Thr Tyr His Gly Asn Ser Gly
1665 1670 1675 1680
Leu Leu Ala Thr Lys Ser Asn Glu Asn Gly Trp Thr Thr Phe Tyr Glu
1685 1690 1695
Tyr Asp Ser Phe Gly Arg Leu Thr Asn Val Thr Phe Pro Thr Gly Gln
1700 1705 1710
Val Ser Ser Phe Arg Ser Asp Thr Asp Ser Ser Val His Val Gln Val
1715 1720 1725
Glu Thr Ser Ser Lys Asp Asp Val Thr Ile Thr Thr Asn Leu Ser Ala
1730 1735 1740
Ser Gly Ala Phe Tyr Thr Leu Leu Gln Asp Gln Val Arg Asn Ser Tyr
1745 1750 1755 1760
Tyr Ile Gly Ala Asp Gly Ser Leu Arg Leu Leu Leu Ala Asn Gly Met
1765 1770 1775
Glu Val Ala Leu Gln Thr Glu Pro His Leu Leu Ala Gly Thr Val Asn
1780 1785 1790
Pro Thr Val Gly Lys Arg Asn Val Thr Leu Pro Ile Asp Asn Gly Leu
1795 1800 1805
Asn Leu Val Glu Trp Arg Gln Arg Lys Glu Gln Ala Arg Gly Gln Val
1810 1815 1820
Thr Val Phe Gly Arg Arg Leu Arg Val His Asn Arg Asn Leu Leu Ser
1825 1830 1835 1840
Leu Asp Phe Asp Arg Val Thr Arg Thr Glu Lys Ile Tyr Asp Asp His
1845 1850 1855
Arg Lys Phe Thr Leu Arg Ile Leu Tyr Asp Gln Ala Gly Arg Pro Ser
1860 1865 1870
Leu Trp Ser Pro Ser Ser Arg Leu Asn Gly Val Asn Val Thr Tyr Ser
1875 1880 1885
Pro Gly Gly Tyr Ile Ala Gly Ile Gln Arg Gly Ile Met Ser Glu Arg
1890 1895 1900
Met Glu Tyr Asp Gln Ala Gly Arg Ile Thr Ser Arg Ile Phe Ala Asp

1905 1910 1915 1920
Gly Lys Thr Trp Ser Tyr Thr Tyr Leu Glu Lys Ser Met Val Leu Leu
1925 1930 1935
Leu His Ser Gln Arg Gln Tyr Ile Phe Glu Phe Asp Lys Asn Asp Arg
1940 1945 1950
Leu Ser Ser Val Thr Met Pro Asn Val Ala Arg Gln Thr Leu Glu Thr
1955 1960 1965
Ile Arg Ser Val Gly Tyr Tyr Arg Asn Ile Tyr Gln Pro Pro Glu Gly
1970 1975 1980
Asn Ala Ser Val Ile Gln Asp Phe Thr Glu Asp Gly His Leu Leu His
1985 1990 1995 2000
Thr Phe Tyr Leu Gly Thr Gly Arg Arg Val Ile Tyr Lys Tyr Gly Lys
2005 2010 2015
Leu Ser Lys Leu Ala Glu Thr Leu Tyr Asp Thr Thr Lys Val Ser Phe
2020 2025 2030
Thr Tyr Asp Glu Thr Ala Gly Met Leu Lys Thr Ile Asn Leu Gln Asn
2035 2040 2045
Glu Gly Phe Thr Cys Thr Ile Arg Tyr Arg Gln Ile Gly Pro Leu Ile
2050 2055 2060
Asp Arg Gln Ile Phe Arg Phe Thr Glu Glu Gly Met Val Asn Ala Arg
2065 2070 2075 2080
Phe Asp Tyr Asn Tyr Asp Asn Ser Phe Arg Val Thr Ser Met Gln Ala
2085 2090 2095
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2100 2105 2110
Val Ser Gly Lys Thr Glu Gln Phe Gly Lys Phe Gly Val Ile Tyr Tyr
2115 2120 2125
Asp Ile Asn Gln Ile Ile Thr Thr Ala Val Met Thr His Thr Lys His
2130 2135 2140
Phe Asp Ala Tyr Gly Arg Met Lys Glu Val Gln Tyr Glu Ile Phe Arg
2145 2150 2155 2160
Ser Leu Met Tyr Trp Met Thr Val Gln Tyr Asp Asn Met Gly Arg Val
2165 2170 2175
Val Lys Lys Glu Leu Lys Val Gly Pro Tyr Ala Asn Thr Thr Arg Tyr
2180 2185 2190
Ser Tyr Glu Tyr Asp Ala Asp Gly Gln Leu Gln Thr Val Ser Ile Asn
2195 2200 2205
Asp Lys Pro Leu Trp Arg Tyr Ser Tyr Asp Leu Asn Gly Asn Leu His
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2225 2230 2235 2240
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2245 2250 2255
Glu Asp Gly Phe Leu Arg Gln Arg Gly Gly Asp Ile Phe Glu Tyr Asn
2260 2265 2270
Ser Ala Gly Leu Leu Ile Lys Ala Tyr Asn Arg Ala Gly Ser Trp Ser
2275 2280 2285
Val Arg Tyr Arg Tyr Asp Gly Leu Gly Arg Arg Val Ser Ser Lys Ser
2290 2295 2300
Ser His Ser His His Leu Gln Phe Phe Tyr Ala Asp Leu Thr Asn Pro
2305 2310 2315 2320
Thr Lys Val Thr His Leu Tyr Asn His Ser Ser Ser Glu Ile Thr Ser
2325 2330 2335
Leu Tyr Tyr Asp Leu Gln Gly His Leu Phe Ala Met Glu Leu Ser Ser
2340 2345 2350
Gly Asp Glu Phe Tyr Ile Ala Cys Asp Asn Ile Gly Thr Pro Leu Ala
2355 2360 2365
Val Phe Ser Gly Thr Gly Leu Met Ile Lys Gln Ile Leu Tyr Thr Ala
2370 2375 2380
Tyr Gly Glu Ile Tyr Met Asp Thr Asn Pro Asn Phe Gln Ile Ile Ile
2385 2390 2395 2400
Gly Tyr His Gly Gly Leu Tyr Asp Pro Leu Thr Lys Leu Val His Met
2405 2410 2415
Gly Arg Arg Asp Tyr Asp Val Leu Ala Gly Arg Trp Thr Ser Pro Asp
2420 2425 2430
His Glu Leu Trp Lys His Leu Ser Ser Ser Asn Val Met Pro Phe Asn
2435 2440 2445

Leu Tyr Met Phe Lys Asn Asn Asn Pro Ile Ser Asn Ser Gln Asp Ile
2450 2455 2460
Lys Cys Phe Met Thr Asp Val Asn Ser Trp Leu Leu Thr Phe Gly Phe
2465 2470 2475 2480
Gln Leu His Asn Val Ile Pro Gly Tyr Pro Lys Pro Asp Met Asp Ala
2485 2490 2495
Met Glu Pro Ser Tyr Glu Leu Ile His Thr Gln Met Lys Thr Gln Glu
2500 2505 2510
Trp Asp Asn Ser Lys Ser Ile Leu Gly Val Gln Cys Glu Val Gln Lys
2515 2520 2525
Gln Leu Lys Ala Phe Val Thr Leu Glu Arg Phe Asp Gln Leu Tyr Gly
2530 2535 2540
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2545 2550 2555 2560
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2565 2570 2575
Gly Arg Val Thr Thr Asp Ile Ile Ser Val Ala Asn Glu Asp Gly Arg
2580 2585 2590
Arg Val Ala Ala Ile Leu Asn His Ala His Tyr Leu Glu Asn Leu His
2595 2600 2605
Phe Thr Ile Asp Gly Val Asp Thr His Tyr Phe Val Lys Pro Gly Pro
2610 2615 2620
Ser Glu Gly Asp Leu Ala Ile Leu Gly Leu Ser Gly Gly Arg Arg Thr
2625 2630 2635 2640
Leu Glu Asn Gly Val Asn Val Thr Val Ser Gln Ile Asn Thr Val Leu
2645 2650 2655
Asn Gly Arg Thr Arg Arg Tyr Thr Asp Ile Gln Leu Gln Tyr Gly Ala
2660 2665 2670
Leu Cys Leu Asn Thr Arg Tyr Gly Thr Thr Leu Asp Glu Glu Lys Ala
2675 2680 2685
Arg Val Leu Glu Leu Ala Arg Gln Arg Ala Val Arg Gln Ala Trp Ala
2690 2695 2700
Arg Glu Gln Gln Arg Leu Arg Glu Gly Glu Glu Gly Leu Arg Ala Trp
2705 2710 2715 2720
Thr Glu Gly Glu Lys Gln Gln Val Leu Ser Thr Gly Arg Val Gln Gly
2725 2730 2735
Tyr Asp Gly Phe Phe Val Ile Ser Val Glu Gln Tyr Pro Glu Leu Ser
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<210> 42
<211> 8354
<212> DNA
<213> Homo sapiens

<400> 42
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<210> 43
<211> 460
<212> PRT
<213> Homo sapiens

<400> 43
His Leu Gln Pro Met Glu Gly Gln Met Tyr Glu Ile Thr Glu Asp Thr
1 5 10 15

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Ala Ser Ser Trp Pro Val Pro Thr Asp Val Ser Leu Tyr Pro Ser Gly
            20                  25                  30
Gly Thr Gly Leu Glu Thr Pro Asp Arg Lys Gly Lys Gly Thr Thr Glu
        35                  40                  45
Gly Lys Pro Ser Ser Phe Phe Pro Glu Asp Ser Phe Ile Asp Ser Gly
    50                  55                  60
Glu Ile Asp Val Gly Arg Arg Ala Ser Gln Lys Ile Pro Pro Gly Thr
65                  70                  75                  80
Phe Trp Arg Ser Gln Val Phe Ile Asp His Pro Val His Leu Lys Phe
                85                  90                  95
Asn Val Ser Leu Gly Lys Ala Ala Leu Val Gly Ile Tyr Gly Arg Lys
            100                 105                 110
Gly Leu Pro Pro Ser His Thr Gln Phe Asp Phe Val Glu Leu Leu Asp
        115                 120                 125
Gly Arg Arg Leu Leu Thr Gln Glu Ala Arg Ser Leu Glu Gly Thr Pro
    130                 135                 140
Arg Gln Ser Arg Gly Thr Val Pro Pro Ser Ser His Glu Thr Gly Phe
145                 150                 155                 160
Ile Gln Tyr Leu Asp Ser Gly Ile Trp His Leu Ala Phe Tyr Asn Asp
                165                 170                 175
Gly Lys Glu Ser Glu Val Val Ser Phe Leu Thr Thr Ala Ile Glu Ser
            180                 185                 190
Val Asp Asn Cys Pro Ser Asn Cys Tyr Gly Asn Gly Asp Cys Ile Ser
        195                 200                 205
Gly Thr Cys His Cys Phe Leu Gly Phe Leu Gly Pro Asp Cys Gly Arg
    210                 215                 220
Ala Ser Cys Pro Val Leu Cys Ser Gly Asn Gly Gln Tyr Met Lys Gly
225                 230                 235                 240
Arg Cys Leu Cys His Ser Gly Trp Lys Gly Ala Glu Cys Asp Val Pro
                245                 250                 255
Thr Asn Gln Cys Ile Asp Val Ala Cys Ser Asn His Gly Thr Cys Ile
            260                 265                 270
Thr Gly Thr Cys Ile Cys Asn Pro Gly Tyr Lys Gly Glu Ser Cys Glu
        275                 280                 285
Glu Val Asp Cys Met Asp Pro Thr Cys Ser Gly Arg Gly Val Cys Val
    290                 295                 300
Arg Gly Glu Cys His Cys Phe Val Gly Trp Gly Gly Thr Asn Cys Glu
305                 310                 315                 320
Thr Pro Arg Ala Thr Cys Leu Asp Gln Cys Ser Gly His Gly Thr Phe
                325                 330                 335
Leu Pro Asp Thr Gly Leu Cys Ser Cys Asp Pro Ser Trp Thr Gly His
            340                 345                 350
Asp Cys Ser Ile Glu Ile Cys Ala Ala Asp Cys Gly Gly His Gly Val
        355                 360                 365
Cys Val Gly Gly Thr Cys Arg Cys Glu Asp Gly Trp Met Gly Ala Ala
    370                 375                 380
Cys Asp Gln Arg Ala Cys His Pro Arg Cys Ala Glu His Gly Thr Cys
385                 390                 395                 400
Arg Asp Gly Lys Cys Glu Cys Ser Pro Gly Trp Asn Gly Glu His Cys
                405                 410                 415
Thr Ile Ala His Tyr Leu Asp Arg Val Val Lys Glu Gly Cys Pro Gly
            420                 425                 430
Leu Cys Asn Gly Asn Gly Arg Cys Thr Leu Asp Leu Asn Gly Trp His
        435                 440                 445
Cys Val Cys Gln Leu Gly Trp Arg Gly Ala Gly Cys
    450                 455                 460


<210> 44
<211> 109
<212> PRT
<213> Homo sapiens

<400> 44
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
```

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

<210> 45
<211> 109
<212> PRT
<213> Homo sapiens

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

<210> 46
<211> 109
<212> PRT
<213> Homo sapiens

<400> 46
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 47
<211> 109
<212> PRT
<213> Homo sapiens

<400> 47
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105
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<210> 48
<211> 109
<212> PRT
<213> Homo sapiens

<400> 48

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105
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<210> 49
<211> 109
<212> PRT
<213> Homo sapiens

<400> 49

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105
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<210> 50
<211> 112
<212> PRT
<213> Homo sapiens

<400> 50

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Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1               5                  10                  15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
```

```
        35                  40                  45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95
Tyr Tyr Cys Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105                 110


<210> 51
<211> 109
<212> PRT
<213> Homo sapiens

<400> 51
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105


<210> 52
<211> 104
<212> PRT
<213> Homo sapiens

<400> 52
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1               5                  10                  15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
            20                  25                  30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Phe Gly
                85                  90                  95
Pro Gly Thr Lys Val Asp Ile Lys
            100


<210> 53
<211> 103
<212> PRT
<213> Homo sapiens

<400> 53
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1               5                  10                  15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45
```

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gly Gly
85 90 95
Gly Thr Lys Val Glu Ile Lys
100

<210> 54
<211> 98
<212> PRT
<213> Homo sapiens

<400> 54
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gly Gln Gly Thr Lys Leu Glu
85 90 95
Ile Lys

<210> 55
<211> 98
<212> PRT
<213> Homo sapiens

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

<210> 56
<211> 98
<212> PRT
<213> Homo sapiens

<400> 56
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Val Ala Thr Tyr Tyr Cys Phe Gly Pro Gly Thr Lys Val Asp
85 90 95
Ile Lys

<210> 57
<211> 98
<212> PRT
<213> Homo sapiens

<400> 57
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Phe Gly Pro Gly Thr Lys Val Asp
85 90 95
Ile Lys

<210> 58
<211> 98
<212> PRT
<213> Homo sapiens

<400> 58
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Phe Gly Gly Gly Thr Lys Val Glu
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Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Glu Asp Phe Ala Thr Tyr Tyr Cys Phe Gly Gln Gly Thr Arg Leu Glu
85 90 95
Ile Lys