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EP 2 251 351 B1

Description

TECHNICAL FIELD

- 5 **[0001]** The present invention relates generally to epitopes of sclerostin protein, including human sclerostin protein, and antibodies capable of binding to sclerostin or fragments thereof.

BACKGROUND OF THE INVENTION

- 10 **[0002]** Two or three distinct phases of changes to bone mass occur over the life of an individual (*see* Riggs, West J. Med. 154:63-77 (1991)). The first phase occurs in both men and women and proceeds to attainment of a peak bone mass. This first phase is achieved through linear growth of the endochondral growth plates and radial growth due to a rate of periosteal apposition. The second phase begins around age 30 for trabecular bone (flat bones such as the vertebrae and pelvis) and about age 40 for cortical bone (*e.g.*, long bones found in the limbs) and continues to old age.
- 15 This phase is characterized by slow bone loss and occurs in both men and women. In women, a third phase of bone loss also occurs, most likely due to postmenopausal estrogen deficiencies. During this phase alone, women may lose an additional bone mass from the cortical bone and from the trabecular compartment (*see* Riggs, *supra*).

- [0003]** Loss of bone mineral content can be caused by a wide variety of conditions and may result in significant medical problems. For example, osteoporosis is a debilitating disease in humans and is characterized by marked decreases in skeletal bone mass and mineral density, structural deterioration of bone, including degradation of bone microarchitecture and corresponding increases in bone fragility (*i.e.*, decreases in bone strength), and susceptibility to fracture in afflicted individuals. Osteoporosis in humans is generally preceded by clinical osteopenia (bone mineral density that is greater than one standard deviation but less than 2.5 standard deviations below the mean value for young adult bone), a condition found in approximately 25 million people in the United States. Another 7-8 million patients in the United States have been diagnosed with clinical osteoporosis (defined as bone mineral content greater than 2.5 standard deviations below that of mature young adult bone). The frequency of osteoporosis in the human population increases with age. Among Caucasians, osteoporosis is predominant in women who, in the United States, comprise 80% of the osteoporosis patient pool. The increased fragility and susceptibility to fracture of skeletal bone in the aged is aggravated by the greater risk of accidental falls in this population. Fractured hips, wrists, and vertebrae are among the most common injuries associated with osteoporosis. Hip fractures in particular are extremely uncomfortable and expensive for the patient, and for women, correlate with high rates of mortality and morbidity.
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- [0004]** Although osteoporosis has been regarded as an increase in the risk of fracture due to decreased bone mass, few of the presently available treatments for skeletal disorders can increase the bone density of adults, and most of the presently available treatments work primarily by inhibiting further bone resorption rather than stimulating new bone formation. Estrogen is now being prescribed to retard bone loss. However, some controversy exists over whether patients gain any long-term benefit and whether estrogen has any effect on patients over 75 years old. Moreover, use of estrogen is believed to increase the risk of breast and endometrial cancer. Calcitonin, osteocalcin with vitamin K, or high doses of dietary calcium, with or without vitamin D, have also been suggested for postmenopausal women. High doses of calcium, however, often have undesired gastrointestinal side effects, and serum and urinary calcium levels must be continuously monitored (*e.g.*, Khosla and Riggs, Mayo Clin. Proc. 70:978982, 1995).
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- [0005]** Other current therapeutic approaches to osteoporosis include bisphosphonates (*e.g.*, Fosamax™, Actonel™, Bonviva™, Zometa™, olpadronate, neridronate, skelid, bonefos), parathyroid hormone, calcilytics, calcimimetics (*e.g.*, cinacalcet), statins, anabolic steroids, lanthanum and strontium salts, and sodium fluoride. Such therapeutics, however, are often associated with undesirable side effects (*see* Khosla and Riggs, *supra*).
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- [0006]** Sclerostin, the product of the SOST gene, is absent in sclerosteosis, a skeletal disease characterized by bone overgrowth and strong dense bones (Brunkow *et al.*, Am. J. Hum. Genet., 68:577-589, 2001; Balemans *et al.*, Hum. Mol. Genet., 10:537-543, 2001). The amino acid sequence of human sclerostin is reported by Brunkow *et al. ibid* and is disclosed herein as SEQ ID NO:1.

- [0007]** WO 2005/014650 and WO 2005/003158 describe antibodies to sclerostin. Avsian-Kretchmer and Hsueh (2004) Molecular Endocrinology 18(1), 1-12 describes comparative genome analysis of eight-membered ring cysteine knot-containing bone morphogenetic protein antagonists.
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BRIEF SUMMARY OF THE INVENTION

- 55 **[0008]** Disclosed herein are compositions that can be used to increase at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength, and that therefore may be used to treat a wide variety of conditions in which an increase in at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength is desirable. The present invention also offers other related advan-

tages described herein.

[0009] The invention relates to regions (epitopes) of human sclerostin recognized by the antibodies disclosed herein, methods of using these epitopes, and methods of making such epitopes.

[0010] The invention also relates to epitopes specific to the cystine-knot region of sclerostin, and antibodies specifically binding to that region.

[0011] The antibodies may specifically bind to sclerostin. The antibodies may cross-block the binding of at least one antibody disclosed herein to sclerostin and/or be cross-blocked from binding sclerostin by at least one antibody disclosed herein. The antibodies can also be characterized by their binding pattern to human sclerostin peptides in a "human sclerostin peptide epitope competition binding assay" as disclosed herein.

[0012] The antibodies can increase at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength in a mammal.

[0013] The antibodies can block the inhibitory effect of sclerostin in a cell based mineralization assay.

[0014] The invention relates to methods of obtaining epitopes suitable for use as immunogens for generating, in mammals, such as antibodies capable of binding specifically to sclerostin; in certain embodiments the antibodies generated are capable of neutralizing sclerostin activity *in vivo*.

[0015] The invention further relates to a composition for eliciting an antibody specific for sclerostin when the composition is administered to an animal, the composition comprising a polypeptide consisting of the amino acid sequences of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5, wherein SEQ ID NO:2 and 4 are joined by a disulfide bond at amino acid positions 57 and 111 with reference to SEQ ID NO:1, and SEQ ID NO:3 and 5 are joined by (a) a disulfide bond at amino acid positions 82 and 142 with reference to SEQ ID NO:1, and (b) a disulfide bond at amino acid positions 86 and 144 with reference to SEQ ID NO:1.

[0016] The invention also relates to polypeptide T20.6 consisting of a multiply truncated human sclerostin protein of SEQ ID NO:1, wherein amino acids 1-50, 65-72, 91-100, 118-137, and 150-190 of SEQ ID NO:1 are absent from the polypeptide; this polypeptide may be obtained by tryptic digestion of human sclerostin, and the protein may be isolated by HPLC fractionation.

[0017] The disclosure further relates to immunogenic portion T20.6 of human sclerostin comprising amino acids 51-64, 73-90, 101-117, and 138-149 of SEQ ID NO:1, wherein the immunogenic portion comprises:

- (a) a disulfide bond between amino acids 57 and 111;
- (b) a disulfide bond between amino acids 82 and 142; and
- (c) a disulfide bond between amino acids 86 and 144.

[0018] The disclosure further relates to an immunogenic portion T20.6 derivative of human sclerostin comprising amino acids 57-64, 73-86, 111-117, and 138-144 of SEQ ID NO:1, wherein the immunogenic portion comprises:

- (a) a disulfide bond between amino acids 57 and 111;
- (b) a disulfide bond between amino acids 82 and 142; and
- (c) a disulfide bond between amino acids 86 and 144.

[0019] The disclosure yet further relates to a polypeptide consisting essentially of a human sclerostin protein of SEQ ID NO:1 truncated at the C-terminal and N-terminal ends, wherein amino acids 1-85 and 112-190 of SEQ ID NO:1 are absent from the polypeptide.

[0020] The disclosure also relates to an immunogenic portion of human sclerostin, comprising amino acids 86-111 of SEQ ID NO: 1; the immunogenic portion may consist essentially of contiguous amino acids CGPARLLPNAIGRGKWWRPSPGPDFRC (SEQ ID NO:6).

[0021] The disclosure further relates to an immunogenic portion of rat sclerostin, comprising amino acids 92-109 of SEQ ID NO:98; the immunogenic portion may consist essentially of contiguous amino acids PNAIGRVKWWRPNGPDFRC (SEQ ID NO:96).

[0022] The disclosure still further relates to an immunogenic portion of rat sclerostin, comprising amino acids 99-120 of SEQ ID NO:98; the immunogenic portion may consist essentially of contiguous amino acids KWWRPNGPDFRCIP-DRYRAQRV (SEQ ID NO:97).

[0023] The invention relates to a method of producing an immunogenic portion of human sclerostin, comprising the steps of:

- (a) treating human sclerostin to achieve complete tryptic digestion;
- (b) collecting the tryptic digest sample having average molecular weight of 7,122.0 Daltons (theoretical mass 7121.5 Daltons) or retention time of about 20.6 minutes as determined by elution from a reverse-phase HPLC column with linear gradient from 0.05% trifluoroacetic acid to 90% acetonitrile in 0.05% TFA at a flow rate of 0.2ml/min; and

(c) purifying the immunogenic portion.

[0024] The disclosure also relates to a method of generating an antibody capable of specifically binding to sclerostin, the method comprising:

- (a) immunizing an animal with a composition comprising polypeptide T20.6 or a derivative of T20.6;
- (b) collecting sera from the animal; and
- (c) isolating from the sera an antibody capable of specifically binding to sclerostin.

[0025] The disclosure also relates to a method of detecting an anti-sclerostin antibody in a biological sample, comprising the steps of

- (a) contacting the biological sample with polypeptide T20.6 or a derivative of T20.6 under conditions allowing a complex to form between the antibody and the polypeptide; and
- (b) detecting the presence or absence of the complex,

wherein the presence of the complex indicates that the biological sample contains an anti-sclerostin antibody.

[0026] The disclosure further relates to a sclerostin antibody that cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, or Ab-D to a sclerostin protein. The antibody may also be cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, or Ab-D. The isolated antibody, or an antigen-binding fragment thereof, may be a polyclonal antibody, a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody or the like.

[0027] The disclosure further relates to a sclerostin antibody that is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, or Ab-D. The isolated antibody, or an antigen-binding fragment thereof, may be a polyclonal antibody, a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody or the like.

[0028] The disclosure further relates to an isolated antibody that cross-blocks the binding of at least one of antibodies 1-24 (Ab-1 to Ab-24) to a sclerostin protein. The antibody may also be cross-blocked from binding to sclerostin by at least one of antibodies 1-24 (Ab-1 to Ab-24). The isolated antibody, or an antigen-binding fragment thereof, may be a polyclonal antibody, a monoclonal antibody, a humanized antibody, a human antibody, or a chimeric antibody.

[0029] The disclosure further relates to an isolated antibody that is cross-blocked from binding to sclerostin by at least one of antibodies 1-24 (Ab-1 to Ab-24); the isolated antibody, or an antigen-binding fragment thereof, may be a polyclonal antibody, a monoclonal antibody, a humanized antibody, a human antibody, or a chimeric antibody.

[0030] The disclosure further relates to an isolated antibody that exhibits a similar binding pattern to human sclerostin peptides in a "human sclerostin peptide epitope competition binding assay" as that exhibited by at least one of the antibodies Ab-A, Ab-B, Ab-C or Ab-D; the isolated antibody, or an antigen-binding fragment thereof, may be a polyclonal antibody, a monoclonal antibody, a humanized antibody, a human antibody, or a chimeric antibody.

[0031] The disclosure still further relates to treating a bone disorder associated with at least one of low bone formation, low bone mineral density, low bone mineral content, low bone mass, low bone quality and low bone strength in a mammalian subject. A subject in need of such treatment is provided with an amount of an anti-sclerostin antibody or sclerostin-binding fragment thereof sufficient to increase at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength.

[0032] The disclosure also relates to an isolated sclerostin polypeptide or fragments thereof, wherein the polypeptide contains 6 conserved cysteine residues and the fragments thereof comprise from 7 to 14 amino acids of SEQ ID NO:2; 8 to 17 amino acids of SEQ ID NO:3; 8 to 18 residues of SEQ ID NO:4; and 6 to 12 residues of SEQ ID NO:5, and the polypeptide or fragments thereof are stabilized by disulfide bonds between SEQ ID NO:2 and 4, and between SEQ ID NO:3 and 5; the polypeptide or fragments may comprise 10-14 amino acids of SEQ ID NO:2; 14 to 17 amino acids of SEQ ID NO:3; 13 to 18 amino acids of SEQ ID NO:4; and 8 to 12 residues of SEQ ID NO:5; and the polypeptide or fragments may comprise SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5.

[0033] Provided herein are antibodies that specifically bind to human sclerostin. The antibodies may cross-block the binding of at least one antibody disclosed herein to human sclerostin and/or be cross-blocked from binding human sclerostin by at least one antibody disclosed herein.

[0034] Also disclosed is an isolated antibody, or an antigen-binding fragment thereof, that can increase at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength in a mammal.

[0035] Also disclosed is an isolated antibody, or an antigen-binding fragment thereof, that can block the inhibitory effect of sclerostin in a cell based mineralization assay.

[0036] Also disclosed is an antibody that specifically binds to human sclerostin and has at least one CDR sequence selected from SEQ ID NOs: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 78, 79, 80, 81, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 237, 238, 239,

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[0037] Also disclosed is an antibody that specifically binds to human sclerostin and has at least one CDR sequence selected from SEQ ID NOs:39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 78, 79, 80, 81, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 351, 352, 353, 358, 359, and 360, and variants thereof.

[0038] Also disclosed are regions of human sclerostin which are important for the *in vivo* activity of the protein.

[0039] These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040]

Figure 1 depicts the amino acid sequences of the mature form (signal peptides cleaved off) of the light chain (Figure 1A) (SEQ ID NO:23) and heavy chain (Figure 1B) (SEQ ID NO:27) for the anti-human sclerostin and anti-mouse sclerostin antibody Ab-A.

Figure 2 depicts the amino acid sequences of the mature form (signal peptides cleaved off) of the light chain (Figure 2A) (SEQ ID NO:31) and heavy chain (Figure 2B) (SEQ ID NO:35) for the anti-human sclerostin and anti-mouse sclerostin antibody Ab-B.

Figure 3 depicts the amino acid sequences of the mature form (signal peptides cleaved off) of the light chain (Figure 3A) (SEQ ID NO:15) and heavy chain (Figure 3B) (SEQ ID NO: 19) for the anti-human sclerostin and anti-mouse sclerostin antibody Ab-C.

Figure 4 depicts the amino acid sequences of the mature form (signal peptides cleaved off) of the light chain (Figure 4A) (SEQ ID NO:7) and heavy chain (Figure 4B) (SEQ ID NO: 11) for the anti-human sclerostin and anti-mouse sclerostin antibody Ab-D.

Figure 5 depicts bone mineral density in mice measured at two skeletal sites (lumbar vertebrae and tibial metaphysis) after 3 weeks of treatment with vehicle, PTH (1-34), Ab-A or Ab-B.

Figure 6 shows bone mineral density in mice measured at two skeletal sites (lumbar vertebrae and tibial metaphysis) after 2 weeks of treatment with vehicle, PTH (1-34) or Ab-C.

Figure 7 depicts bone mineral density in mice measured at two skeletal sites (lumbar vertebrae and tibial metaphysis) after 3 weeks of treatment with vehicle or Ab-D.

Figure 8 depicts the amino acid sequence of the mature form (signal peptide cleaved off) of human sclerostin (SEQ ID NO:1). Also depicted is the nucleotide sequence of the human sclerostin coding region that encodes the mature form of human sclerostin. The eight cysteines are numbered C1 through C8. The cystine-knot is formed by three disulfide bonds (C1-C5; C3-C7; C4-C8). C2 and C6 also form a disulfide bond, however this disulfide is not part of the cystine-knot.

Figure 9 depicts a schematic of the basic structure of human sclerostin. There is an N-terminal arm (from the first Q to C1) and a C-terminal arm (from C8 to the terminal Y). In between these arms there is the cystine-knot structure (formed by three disulfides: C1-C5; C3-C7; C4-C8) and three loops which are designated Loop1, Loop 2 and Loop 3. The distal regions of Loop 1 and Loop 3 are linked by the C2-C6 disulfide. Potential trypsin cleavage sites are indicated (arginine=R and lysine=K). Some of the potential AspN cleavage sites are indicated (only aspartic acid (D) residues are shown).

Figure 10 depicts the HPLC peptide maps of human sclerostin after digestion with either trypsin or AspN. The human sclerostin peptides generated by trypsin digestion are indicated (T19.2, T20, T20.6 and T21-22) as are the human sclerostin peptides generated by AspN digestion (AspN14.6, AspN18.6 and AspN22.7-23.5).

Figure 11 depicts sequence and mass information for the isolated human sclerostin disulfide linked peptides generated by trypsin digestion. Seq. pos. = sequence position. Obs. = observed. Observed mass was determined by ESI-LC-MS analysis.

Figure 12 depicts sequence and mass information for the isolated human sclerostin peptides generated by AspN digestion. The AspN22.7-23.5 peptide contains the 4 disulfide bonds. Seq. pos. = sequence position. Obs. = observed. Observed mass was determined by ESI-LC-MS analysis.

Figure 13 shows a linear schematic of four human sclerostin peptides (T19.2, T20, T20.6 and T21-22) generated by trypsin digestion.

Figure 14 shows a linear schematic of five human sclerostin peptides (AspN14.6, AspN18.6 and AspN22.7-23.5) generated by AspN digestion. The AspN14.6 HPLC peak is composed of three peptides not linked by any disulfide bonds.

Figure 15 shows the resonance unit (Ru) signal from the Biacore-based "human sclerostin peptide epitope competition binding assay." Relative Mab binding to various human sclerostin-peptides (in solution) versus Mab binding to intact mature form human sclerostin (immobilized on Biacore chip) was assessed. Data shown is for Ab-A. Human sclerostin, peptides used were T19.2, T20, T20.6, T21-22, AspN14.6, AspN18.6 and AspN22.7-23.5.

Figure 16 shows the resonance unit (Ru) signal from the Biacore-based "human sclerostin peptide epitope competition binding assay." Relative Mab binding to various human sclerostin-peptides (in solution) versus Mab binding to intact mature form human sclerostin (immobilized on Biacore chip) was assessed. Data shown is for Ab-B. Human sclerostin peptides used were T19.2, T20, T20.6, T21-22, AspN14.6, AspN18.6 and AspN22.7-23.5.

Figure 17 shows the resonance unit (Ru) signal from the Biacore-based "human sclerostin peptide epitope competition binding assay." Relative Mab binding to various human sclerostin-peptides (in solution) versus Mab binding to intact mature form human sclerostin (immobilized on Biacore chip) was assessed. Data shown is for Ab-C. Human sclerostin peptides used were T19.2, T20, T20.6, T21-22, AspN14.6, AspN18.6 and AspN22.7-23.5.

Figure 18 shows the resonance unit (Ru) signal from Biacore-based "human sclerostin peptide epitope competition binding assay." Relative Mab binding to various human sclerostin-peptides (in solution) versus Mab binding to intact mature form human sclerostin (immobilized on Biacore chip) was assessed. Data shown is for Ab-D. Human sclerostin peptides used were T19.2, T20, T20.6, T21-22, AspN14.6, AspN18.6 and AspN22.7-23.5.

Figure 19 shows two Mab binding epitopes of human sclerostin. Figure 19A shows sequence of the Loop 2 epitope for binding of Ab-A and Ab-B to human sclerostin (SEQ ID NO:6). Figure 19B shows sequence, disulfide bonding and schematic of the T20.6 epitope for binding of Ab-C and Ab-D to human sclerostin (SEQ ID NO:2-5).

Figure 20 depicts the HPLC peptide maps of human sclerostin after digestion with trypsin. Figure 20A shows digestion of the human sclerostin Ab-D complex. Figure 20B shows digestion of human sclerostin alone. The T19.2, T20, T20.6 and T21-22 peptide peaks are indicated.

Figure 21 shows the sequence, disulfide bonding and schematic of the "T20.6 derivative 1 (cystine-knot + 4 arms)" epitope for binding of Ab-D to human sclerostin. (SEQ ID NO:70-73).

Figure 22 shows results from the MC3T3-E1-BF osteoblast cell line mineralization assay used for identifying anti-sclerostin neutralizing Mabs. Mouse sclerostin (Scl) was used at 1 μ g/ml. Monoclonal antibodies were used at 10 and 5 μ g/ml. Extent of mineralization (various types of insoluble calcium phosphate) was quantitated by measuring calcium.

Figure 23 depicts results from the MC3T3-E1-BF osteoblast cell line mineralization assay used for identifying anti-sclerostin neutralizing Mabs. Human sclerostin (Scl) was used at 1 μ g/ml. Monoclonal antibodies were used at 8 and 4 μ g/ml. Extent of mineralization (various types of insoluble calcium phosphate) was quantitated by measuring calcium.

Figure 24 shows results from the MC3T3-E1-BF osteoblast cell line mineralization assay used for identifying anti-sclerostin neutralizing Mabs. Human sclerostin (Scl) was used at 1 μ g/ml. Monoclonal antibodies were used at 10 μ g/ml. Extent of mineralization (various types of insoluble calcium phosphate) was quantitated by measuring calcium.

Figure 25 depicts results from an inflammation-induced bone loss SCID mouse model. Ab-A treatment protected mice from inflammation-related bone loss associated with colitis when measured as total bone mineral density (Figure 25A), vertebral bone density (Figure 25B), and femur bone density (Figure 25C).

DETAILED DESCRIPTION

[0041] The present invention relates to regions of the human sclerostin protein that contain epitopes recognized by antibodies that also bind to full-length sclerostin, and methods of making and using these epitopes. The invention also provides antibodies that specifically bind to sclerostin or portions of sclerostin. The antibodies are useful to block or impair binding of human sclerostin to one or more ligand.

[0042] Recombinant human sclerostin/SOST is commercially available from R&D Systems (Minneapolis, MN, USA; 2006 cat# 1406-ST-025). Additionally, recombinant mouse sclerostin/SOST is commercially available from R&D Systems (Minneapolis, MN, USA; 2006 cat# 1589-ST-025). Research grade sclerostin binding monoclonal antibodies are commercially available from R&D Systems (Minneapolis, MN, USA; mouse monoclonal: 2006 cat# MAB1406; rat monoclonal: 2006 cat# MAB1589). U.S. Patent Nos. 6,395,511 and 6,803,453, and U.S. Patent Publications 20040009535 and 20050106683 refer to anti-sclerostin antibodies generally.

[0043] As used herein, the term human sclerostin is intended to include the protein of SEQ ID NO:1 and allelic variants thereof. Sclerostin can be purified from 293T host cells that have been transfected by a gene encoding sclerostin by elution of filtered supernatant of host cell culture fluid using a Heparin HP column, using a salt gradient. The preparation and further purification using cation exchange chromatography are described in Examples 1 and 2.

[0044] The "binding agents" of the invention as described hereinafter are antibodies, as defined herein. The term "antibody" refers to an intact antibody, or a binding fragment thereof. An antibody may comprise a complete antibody molecule (including polyclonal, monoclonal, chimeric, humanized, or human versions having full length heavy and/or light chains), or comprise an antigen binding fragment thereof. Antibody fragments include F(ab')₂, Fab, Fab', Fv, Fc, and Fd fragments, and can be incorporated into single domain antibodies, single-chain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (See e.g., Hollinger and Hudson, 2005, Nature Biotechnology, 23, 9, 1126-1136). Antibody polypeptides are also disclosed in U. S. Patent No. 6,703,199, including fibronectin polypeptide monobodies. Other antibody polypeptides are disclosed in U.S. Patent Publication 2005/0238646, which are single-chain polypeptides.

[0045] Antigen binding fragments derived from an antibody can be obtained, for example, by proteolytic hydrolysis of the antibody, for example, pepsin or papain digestion of whole antibodies according to conventional methods. By way of example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S fragment termed F(ab')₂. This fragment can be further cleaved using a thiol reducing agent to produce 3.5S Fab' monovalent fragments. Optionally, the cleavage reaction can be performed using a blocking group for the sulfhydryl groups that result from cleavage of disulfide linkages. As an alternative, an enzymatic cleavage using papain produces two monovalent Fab fragments and an Fc fragment directly. These methods are described, for example, by Goldenberg, U.S. Patent No. 4,331,647, Nisonoff et al., Arch. Biochem. Biophys. 89:230, 1960; Porter, Biochem. J. 73:119, 1959; Edelman et al., in Methods in Enzymology 1:422 (Academic Press 1967); and by Andrews, S.M. and Titus, J.A. in Current Protocols in Immunology (Coligan J.E., et al., eds), John Wiley & Sons, New York (2003). pages 2.8.1-2.8.10 and 2.10A.1-2.10A.5. Other methods for cleaving antibodies, such as separating heavy chains to form monovalent light-heavy chain fragments (Fd), further cleaving of fragments, or other enzymatic, chemical, or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody.

[0046] An antibody fragment may also be any synthetic or genetically engineered protein. For example, antibody fragments include isolated fragments consisting of the light chain variable region, "Fv" fragments consisting of the variable regions of the heavy and light chains, recombinant single chain polypeptide molecules in which light and heavy variable regions are connected by a peptide linker (scFv proteins).

[0047] Another form of an antibody fragment is a peptide comprising one or more complementarity determining regions (CDRs) of an antibody. CDRs (also termed "minimal recognition units", or "hypervariable region") can be obtained by constructing polynucleotides that encode the CDR of interest. Such polynucleotides are prepared, for example, by using the polymerase chain reaction to synthesize the variable region using mRNA of antibody-producing cells as a template (see, for example, Larrick et al., Methods: A Companion to Methods in Enzymology 2:106, 1991; Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in Monoclonal Antibodies: Production, Engineering and Clinical Application, Ritter et al. (eds.), page 166 (Cambridge University Press 1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in Monoclonal Antibodies: Principles and Applications, Birch et al., (eds.), page 137 (Wiley-Liss, Inc. 1995)).

[0048] Thus, in one embodiment, the binding agent comprises at least one CDR as described herein. The binding agent may comprise at least two, three, four, five or six CDR's as described herein. The binding agent further may comprise at least one variable region domain of an antibody described herein. The variable region domain may be of any size or amino acid composition and will generally comprise at least one CDR sequence responsible for binding to human sclerostin, for example CDR-H1, CDR-H2, CDR-H3 and/or the light chain CDRs specifically described herein and which is adjacent to or in frame with one or more framework sequences. In general terms, the variable (V) region domain may be any suitable arrangement of immunoglobulin heavy (V_H) and/or light (V_L) chain variable domains. Thus, for example, the V region domain may be monomeric and be a V_H or V_L domain, which is capable of independently binding human sclerostin with an affinity at least equal to 1×10^{-7} M or less as described below. Alternatively, the V region domain may be dimeric and contain V_H-V_H, V_H-V_L, or V_L-V_L dimers. The V region dimer comprises at least one V_H and at least one V_L chain that may be non-covalently associated (hereinafter referred to as F_V). If desired, the chains may be covalently coupled either directly, for example via a disulfide bond between the two variable domains, or through a linker, for example a peptide linker, to form a single chain Fv (scF_V).

[0049] The variable region domain may be any naturally occurring variable domain or an engineered version thereof. By engineered version is meant a variable region domain that has been created using recombinant DNA engineering techniques. Such engineered versions include those created, for example, from a specific antibody variable region by insertions, deletions, or changes in or to the amino acid sequences of the specific antibody. Particular examples include engineered variable region domains containing at least one CDR and optionally one or more framework amino acids from a first antibody and the remainder of the variable region domain from a second antibody.

[0050] The variable region domain may be covalently attached at a C-terminal amino acid to at least one other antibody domain or a fragment thereof. Thus, for example, a V_H domain that is present in the variable region domain may be linked to an immunoglobulin CH1 domain, or a fragment thereof. Similarly a V_L domain may be linked to a C_K domain or a fragment thereof. In this way, for example, the antibody may be a Fab fragment wherein the antigen binding domain contains associated V_H and V_L domains covalently linked at their C-termini to a CH1 and C_K domain, respectively. The

CH1 domain may be extended with further amino acids, for example to provide a hinge region or a portion of a hinge region domain as found in a Fab' fragment, or to provide further domains, such as antibody CH2 and CH3 domains.

[0051] As described herein, binding agents comprise at least one of these CDRs. For example, one or more CDR may be incorporated into known antibody framework regions (IgG1, IgG2, etc.), or conjugated to a suitable vehicle to enhance the half-life thereof. Suitable vehicles include, but are not limited to Fc, polyethylene glycol (PEG), albumin, transferrin, and the like. These and other suitable vehicles are known in the art. Such conjugated CDR peptides may be in monomeric, dimeric, tetrameric, or other form. In one embodiment, one or more water-soluble polymer is bonded at one or more specific position, for example at the amino terminus, of a binding agent.

[0052] In certain preferred embodiments, a binding agent comprises one or more water soluble polymer attachments, including, but not limited to, polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. See, e.g., U.S. Pat. Nos. 4,640,835, 4,496,689, 4,301,144, 4,670,417, 4,791,192 and 4,179,337. In certain embodiments, a derivative binding agent comprises one or more of monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol, as well as mixtures of such polymers. In certain embodiments, one or more water-soluble polymer is randomly attached to one or more side chains. In certain embodiments, PEG can act to improve the therapeutic capacity for a binding agent, such as an antibody. Certain such methods are discussed, for example, in U.S. Pat. No. 6,133,426.

[0053] It will be appreciated that a binding agent of the present invention may have at least one amino acid substitution, providing that the binding agent retains binding specificity. Therefore, modifications to the binding agent structures are encompassed within the scope of the invention. These may include amino acid substitutions, which may be conservative or non-conservative, that do not destroy the sclerostin binding capability of a binding agent. Conservative amino acid substitutions may encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties. A conservative amino acid substitution may also involve a substitution of a native amino acid residue with a normative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position.

[0054] Non-conservative substitutions may involve the exchange of a member of one class of amino acids or amino acid mimetics for a member from another class with different physical properties (e.g. size, polarity, hydrophobicity, charge). Such substituted residues may be introduced into regions of the human antibody that are homologous with non-human antibodies, or into the non-homologous regions of the molecule.

[0055] Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such variants could be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change may be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or in combination with other mutations.

[0056] A skilled artisan will be able to determine suitable variants of the polypeptide as set forth herein using well-known techniques. In certain embodiments, one skilled in the art may identify suitable areas of the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity. In certain embodiments, one can identify residues and portions of the molecules that are conserved among similar polypeptides. In certain embodiments, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

[0057] Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues which are important for activity or structure in similar proteins. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

[0058] One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of such information, one skilled in the art may predict the alignment of amino acid residues of an antibody with respect to its three dimensional structure. In certain embodiments, one skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules.

[0059] A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., Curr. Op. in Biotech., 7(4):422-427 (1996); Chou et al., Biochemistry, 13(2):222-245 (1974); Chou et al, Biochemistry, 113(2):211-222 (1974); Chou et al., Adv. Enzymol. Relat. Areas Mol. Biol., 47:45-148 (1978); Chou et al., Ann. Rev. Biochem., 47:251-276 and Chou et al., Biophys. J., 26:367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon

homology modeling. For example, two polypeptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., *Nucl. Acid. Res.*, 27(1):244-247 (1999). It has been suggested (Brenner et al., *Curr. Op. Struct. Biol.*, 7(3):369-376 (1997)) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate.

[0060] Additional methods of predicting secondary structure include "threading" (Jones, D., *Curr. Opin. Struct. Biol.*, 7(3):377-87 (1997); Sippl et al., *Structure*, 4(1):15-19 (1996)), "profile analysis" (Bowie et al., *Science*, 253:164-170 (1991); Gribskov et al., *Meth. Enzym.*, 183:146-159 (1990); Gribskov et al., *Proc. Nat. Acad. Sci.*, 84(13):4355-4358 (1987)), and "evolutionary linkage" (See Holm, *supra* (1999), and Brenner, *supra* (1997)).

[0061] In certain embodiments, variants of binding agents include glycosylation variants wherein the number and/or type of glycosylation site has been altered compared to the amino acid sequences of a parent polypeptide. In certain embodiments, variants comprise a greater or a lesser number of N-linked glycosylation sites than the native protein. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. Additional preferred antibody variants include cysteine variants wherein one or more cysteine residues are deleted from or substituted for another amino acid (e.g., serine) as compared to the parent amino acid sequence. Cysteine variants may be useful when antibodies must be refolded into a biologically active conformation such as after the isolation of insoluble inclusion bodies. Cysteine variants generally have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

[0062] Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. In certain embodiments, amino acid substitutions can be used to identify important residues of antibodies to sclerostin, or to increase or decrease the affinity of the antibodies to sclerostin described herein.

[0063] According to certain embodiments, 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/or (4) confer or modify other physiochemical or functional properties on such polypeptides. According to certain embodiments, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) may be made in the naturally-occurring sequence (in certain embodiments, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts). In certain embodiments, a conservative amino acid substitution typically may 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 al. *Nature* 354:105 (1991).

[0064] In certain embodiments, binding agents of the invention may be chemically bonded with polymers, lipids, or other moieties.

[0065] The binding agents may comprise at least one of the CDRs described herein incorporated into a biocompatible framework structure. In one example, the biocompatible framework structure comprises a polypeptide or portion thereof that is sufficient to form a conformationally stable structural support, or framework, or scaffold, which is able to display one or more sequences of amino acids that bind to an antigen (e.g., CDRs, a variable region, etc.) in a localized surface region. Such structures can be a naturally occurring polypeptide or polypeptide "fold" (a structural motif), or can have one or more modifications, such as additions, deletions or substitutions of amino acids, relative to a naturally occurring polypeptide or fold. These scaffolds can be derived from a polypeptide of any species (or of more than one species), such as a human, other mammal, other vertebrate, invertebrate, plant, bacteria or virus.

[0066] Typically the biocompatible framework structures are based on protein scaffolds or skeletons other than immunoglobulin domains. For example, those based on fibronectin, ankyrin, lipocalin, neocarzinostatin, cytochrome b, CP1 zinc finger, PST1, coiled coil, LACI-D1, Z domain and tendramisat domains may be used (See e.g., , Nygren and Uhlen, 1997, *Current Opinion in Structural Biology*, 7, 463-469).

[0067] In preferred embodiments, it will be appreciated that the binding agents of the invention include the humanized antibodies described herein. Humanized antibodies such as those described herein can be produced using techniques known to those skilled in the art (Zhang, W., et al., *Molecular Immunology*. 42(12):1445-1451, 2005; Hwang W. et al.,

Methods. 36(1):35-42, 2005; Dall'Acqua WF, et al., Methods 36(1):43-60, 2005; and Clark, M., Immunology Today. 21(8):397-402, 2000).

[0068] Additionally, one skilled in the art will recognize that suitable binding agents include portions of these antibodies, such as one or more of CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and CDR-L3 as specifically disclosed herein. At least one of the regions of CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and CDR-L3 may have at least one amino acid substitution, provided that the binding agent retains the binding specificity of the non-substituted CDR. The non-CDR portion of the binding agent may be a non-protein molecule, wherein the binding agent cross-blocks the binding of an antibody disclosed herein to sclerostin and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be a non-protein molecule in which the binding agent exhibits a similar binding pattern to human sclerostin peptides in a "human sclerostin peptide epitope competition binding assay" as that exhibited by at least one of antibodies Ab-C, Ab-D, Ab-2, Ab-3, Ab-11, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-21 and Ab-22, and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be composed of amino acids, wherein the binding agent is a recombinant binding protein or a synthetic peptide, and the recombinant binding protein cross-blocks the binding of an antibody disclosed herein to sclerostin and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be composed of amino acids, wherein the binding agent is a recombinant binding protein, and the recombinant binding protein exhibits a similar binding pattern to human sclerostin peptides in the human sclerostin peptide epitope competition binding assay (described hereinbelow) as that exhibited by at least one of the antibodies Ab-C, Ab-D, Ab-2, Ab-3, Ab-11, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-21 and Ab-22, and/or neutralizes sclerostin. Where an antibody comprises one or more of CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and CDR-L3 as described above, it may be obtained by expression from a host cell containing DNA coding for these sequences. A DNA coding for each CDR sequence may be determined on the basis of the amino acid sequence of the CDR and synthesized together with any desired antibody variable region framework and constant region DNA sequences using oligonucleotide synthesis techniques, site-directed mutagenesis and polymerase chain reaction (PCR) techniques as appropriate. DNA coding for variable region frameworks and constant regions is widely available to those skilled in the art from genetic sequences databases such as GenBank®. Each of the above-mentioned CDRs will be typically located in a variable region framework at positions 31-35 (CDR-H1), 50-65 (CDR-H2) and 95-102 (CDR-H3) of the heavy chain and positions 24-34 (CDR-L1), 50-56 (CDR-L2) and 89-97 (CDR-L3) of the light chain according to the Kabat numbering system (Kabat et al., 1987 in Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, NIH, USA).

[0069] Once synthesized, the DNA encoding an antibody of the invention or fragment thereof may be propagated and expressed according to any of a variety of well-known procedures for nucleic acid excision, ligation, transformation, and transfection using any number of known expression vectors. Thus, in certain embodiments expression of an antibody fragment may be preferred in a prokaryotic host, such as *Escherichia coli* (see, e.g., Pluckthun et al., 1989 Methods Enzymol. 178:497-515). In certain other embodiments, expression of the antibody or a fragment thereof may be preferred in a eukaryotic host cell, including yeast (e.g., *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and *Pichia pastoris*), animal cells (including mammalian cells) or plant cells. Examples of suitable animal cells include, but are not limited to, myeloma (such as a mouse NSO line), COS, CHO, or hybridoma cells. Examples of plant cells include tobacco, corn, soybean, and rice cells.

[0070] One or more replicable expression vectors containing DNA encoding an antibody variable and/or constant region may be prepared and used to transform an appropriate cell line, for example, a non-producing myeloma cell line, such as a mouse NSO line or a bacteria, such as *E. coli*, in which production of the antibody will occur. In order to obtain efficient transcription and translation, the DNA sequence in each vector should include appropriate regulatory sequences, particularly a promoter and leader sequence operatively linked to the variable domain sequence. Particular methods for producing antibodies in this way are generally well-known and routinely used. For example, basic molecular biology procedures are described by Maniatis et al. (Molecular Cloning, A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory, New York, 1989; see also Maniatis et al, 3rd ed., Cold Spring Harbor Laboratory, New York, (2001)). DNA sequencing can be performed as described in Sanger et al. (PNAS 74:5463, (1977)) and the Amersham International plc sequencing handbook, and site directed mutagenesis can be carried out according to methods known in the art (Kramer et al., Nucleic Acids Res. 12:9441, (1984); Kunkel Proc. Natl. Acad. Sci. USA 82:488-92 (1985); Kunkel et al., Methods in Enzymol. 154:367-82 (1987); the Anglian Biotechnology Ltd handbook). Additionally, numerous publications describe techniques suitable for the preparation of antibodies by manipulation of DNA, creation of expression vectors, and transformation and culture of appropriate cells (Mountain A and Adair, J R in Biotechnology and Genetic Engineering Reviews (ed. Tombs, M P, 10, Chapter 1, 1992, Intercept, Andover, UK); "Current Protocols in Molecular Biology", 1999, F.M. Ausubel (ed.), Wiley Interscience, New York).

[0071] Where it is desired to improve the affinity of antibodies according to the invention containing one or more of the above-mentioned CDRs can be obtained by a number of affinity maturation protocols including maintaining the CDRs (Yang et al., J. Mol. Biol., 254, 392-403, 1995), chain shuffling (Marks et al., Biotechnology, 10, 779-783, 1992), use of mutation strains of *E. coli*. (Low et al., J. Mol. Biol., 250, 350-368, 1996), DNA shuffling (Patten et al., Curr. Opin. Biotechnol., 8, 724-733, 1997), phage display (Thompson et al., J. Mol. Biol., 256, 7-88, 1996) and sexual PCR (Cramer,

et al., Nature, 391, 288-291, 1998). All of these methods of affinity maturation are discussed by Vaughan et al. (Nature Biotechnology, 16, 535-539, 1998).

[0072] Other antibodies according to the invention may be obtained by conventional immunization and cell fusion procedures as described herein and known in the art. Monoclonal antibodies of the invention may be generated using a variety of known techniques. In general, monoclonal antibodies that bind to specific antigens may be obtained by methods known to those skilled in the art (see, for example, Kohler et al., Nature 256:495, 1975; Coligan et al. (eds.), Current Protocols in Immunology, 1:2.5.12.6.7 (John Wiley & Sons 1991); U.S. Patent Nos. RE 32,011, 4,902,614, 4,543,439, and 4,411,993; Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Plenum Press, Kennett, McKearn, and Bechtol (eds.) (1980); and Antibodies: A Laboratory Manual, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press (1988); Picklesley et al., "Production of monoclonal antibodies against proteins expressed in *E. coli*," in DNA Cloning 2: Expression Systems, 2nd Edition, Glover et al. (eds.), page 93 (Oxford University Press 1995)). Antibody fragments may be derived therefrom using any suitable standard technique such as proteolytic digestion, or optionally, by proteolytic digestion (for example, using papain or pepsin) followed by mild reduction of disulfide bonds and alkylation. Alternatively, such fragments may also be generated by recombinant genetic engineering techniques as described herein.

[0073] Monoclonal antibodies can be obtained by injecting an animal, for example, a rat, hamster, a rabbit, or preferably a mouse, including for example a transgenic or a knock-out, as known in the art, with an immunogen comprising human sclerostin of SEQ ID NO: 1, or a fragment thereof, according to methods known in the art and described herein. The presence of specific antibody production may be monitored after the initial injection and/or after a booster injection by obtaining a serum sample and detecting the presence of an antibody that binds to human sclerostin or peptide using any one of several immunodetection methods known in the art and described herein. From animals producing the desired antibodies, lymphoid cells, most commonly cells from the spleen or lymph node, are removed to obtain B-lymphocytes. The B lymphocytes are then fused with a drug-sensitized myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal and that optionally has other desirable properties (e.g., inability to express endogenous Ig gene products, e.g., P3X63 - Ag 8.653 (ATCC No. CRL 1580); NSO, SP20) to produce hybridomas, which are immortal eukaryotic cell lines. The lymphoid (e.g., spleen) cells and the myeloma cells may be combined for a few minutes with a membrane fusion-promoting agent, such as polyethylene glycol or a nonionic detergent, and then plated at low density on a selective medium that supports the growth of hybridoma cells but not unfused myeloma cells. A preferred selection media is HAT (hypoxanthine, aminopterin, thymidine). After a sufficient time, usually about one to two weeks, colonies of cells are observed. Single colonies are isolated, and antibodies produced by the cells may be tested for binding activity to human sclerostin, using any one of a variety of immunoassays known in the art and described herein. The hybridomas are cloned (e.g., by limited dilution cloning or by soft agar plaque isolation) and positive clones that produce an antibody specific to sclerostin are selected and cultured. The monoclonal antibodies from the hybridoma cultures may be isolated from the supernatants of hybridoma cultures. An alternative method for production of a murine monoclonal antibody is to inject the hybridoma cells into the peritoneal cavity of a syngeneic mouse, for example, a mouse that has been treated (e.g., pristane-primed) to promote formation of ascites fluid containing the monoclonal antibody. Monoclonal antibodies can be isolated and purified by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography (see, for example, Coligan at pages 2.7.1-2.7.12 and pages 2.9.1-2.9.3; Baines et al., "Purification of Immunoglobulin G (IgG)," in Methods in Molecular Biology, Vol. 10, pages 79-104 (The Humana Press, Inc. 1992)). Monoclonal antibodies may be purified by affinity chromatography using an appropriate ligand selected based on particular properties of the antibody (e.g., heavy or light chain isotype, binding specificity, etc.). Examples of a suitable ligand, immobilized on a solid support, include Protein A, Protein G, an anticonstant region (light chain or heavy chain) antibody, an anti-idiotypic antibody, and a TGF-beta binding protein, or fragment or variant thereof.

[0074] An antibody of the present invention may also be a human monoclonal antibody. Human monoclonal antibodies may be generated by any number of techniques with which those having ordinary skill in the art will be familiar. Such methods include, but are not limited to, Epstein Barr Virus (EBV) transformation of human peripheral blood cells (e.g., containing B lymphocytes), *in vitro* immunization of human B cells, fusion of spleen cells from immunized transgenic mice carrying inserted human immunoglobulin genes, isolation from human immunoglobulin V region phage libraries, or other procedures as known in the art and based on the disclosure herein. For example, human monoclonal antibodies may be obtained from transgenic mice that have been engineered to produce specific human antibodies in response to antigenic challenge. Methods for obtaining human antibodies from transgenic mice are described, for example, by Green et al., Nature Genet. 7:13, 1994; Lonberg et al., Nature 368:856, 1994; Taylor et al., Int. Immun. 6:579, 1994; U.S. Patent No. 5,877,397; Bruggemann et al., 1997 Curr. Opin. Biotechnol. 8:455-58; Jakobovits et al., 1995 Ann. N. Y. Acad. Sci. 764:525-35. In this technique, elements of the human heavy and light chain locus are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy chain and light chain loci (see also Bruggemann et al., Curr. Opin. Biotechnol. 8:455-58 (1997)). For example, human immunoglobulin transgenes may be mini-gene constructs, or transloci on yeast artificial chromosomes, which undergo B cell-specific DNA

rearrangement and hypermutation in the mouse lymphoid tissue. Human monoclonal antibodies may be obtained by immunizing the transgenic mice, which may then produce human antibodies specific for sclerostin. Lymphoid cells of the immunized transgenic mice can be used to produce human antibody-secreting hybridomas according to the methods described herein. Polyclonal sera containing human antibodies may also be obtained from the blood of the immunized animals.

[0075] Another method for generating human antibodies of the invention includes immortalizing human peripheral blood cells by EBV transformation. See, e.g., U.S. Patent No. 4,464,456. Such an immortalized B cell line (or lymphoblastoid cell line) producing a monoclonal antibody that specifically binds to sclerostin can be identified by immunodetection methods as provided herein, for example, an ELISA, and then isolated by standard cloning techniques. The stability of the lymphoblastoid cell line producing an anti-sclerostin antibody may be improved by fusing the transformed cell line with a murine myeloma to produce a mouse-human hybrid cell line according to methods known in the art (see, e.g., Glasky et al., Hybridoma 8:377-89 (1989)). Still another method to generate human monoclonal antibodies is *in vitro* immunization, which includes priming human splenic B cells with human sclerostin, followed by fusion of primed B cells with a heterohybrid fusion partner. See, e.g., Boerner et al., 1991 J. Immunol. 147:86-95.

[0076] In certain embodiments, a B cell that is producing an anti-human sclerostin antibody is selected and the light chain and heavy chain variable regions are cloned from the B cell according to molecular biology techniques known in the art (WO 92/02551; US patent 5,627,052; Babcook et al., Proc. Natl. Acad. Sci. USA 93:7843-48 (1996)) and described herein. B cells from an immunized animal may be isolated from the spleen, lymph node, or peripheral blood sample by selecting a cell that is producing an antibody that specifically binds to sclerostin. B cells may also be isolated from humans, for example, from a peripheral blood sample. Methods for detecting single B cells that are producing an antibody with the desired specificity are well known in the art, for example, by plaque formation, fluorescence-activated cell sorting, *in vitro* stimulation followed by detection of specific antibody, and the like. Methods for selection of specific antibody-producing B cells include, for example, preparing a single cell suspension of B cells in soft agar that contains human sclerostin. Binding of the specific antibody produced by the B cell to the antigen results in the formation of a complex, which may be visible as an immunoprecipitate. After the B cells producing the desired antibody are selected, the specific antibody genes may be cloned by isolating and amplifying DNA or mRNA according to methods known in the art and described herein.

[0077] An additional method for obtaining antibodies of the invention is by phage display. See, e.g., Winter et al., 1994 Annu. Rev. Immunol. 12:433-55; Burton et al., 1994 Adv. Immunol. 57:191-280. Human or murine immunoglobulin variable region gene combinatorial libraries may be created in phage vectors that can be screened to select Ig fragments (Fab, Fv, sFv, or multimers thereof) that bind specifically to TGF-beta binding protein or variant or fragment thereof. See, e.g., U.S. Patent No. 5,223,409; Huse et al., 1989 Science 246:1275-81; Sastry et al., Proc. Natl. Acad. Sci. USA 86:5728-32 (1989); Alting-Mees et al., Strategies in Molecular Biology 3:1-9 (1990); Kang et al., 1991 Proc. Natl. Acad. Sci. USA 88:4363-66; Hoogenboom et al., 1992 J. Molec. Biol. 227:381-388; Schlebusch et al., 1997 Hybridoma 16:47-52 and references cited therein. For example, a library containing a plurality of polynucleotide sequences encoding Ig variable region fragments may be inserted into the genome of a filamentous bacteriophage, such as M13 or a variant thereof, in frame with the sequence encoding a phage coat protein. A fusion protein may be a fusion of the coat protein with the light chain variable region domain and/or with the heavy chain variable region domain. According to certain embodiments, immunoglobulin Fab fragments may also be displayed on a phage particle (see, e.g., U.S. Patent No. 5,698,426).

[0078] Heavy and light chain immunoglobulin cDNA expression libraries may also be prepared in lambda phage, for example, using λ ImmunoZapTM(H) and λ ImmunoZapTM(L) vectors (Stratagene, La Jolla, California). Briefly, mRNA is isolated from a B cell population, and used to create heavy and light chain immunoglobulin cDNA expression libraries in the λ ImmunoZap(H) and λ ImmunoZap(L) vectors. These vectors may be screened individually or co-expressed to form Fab fragments or antibodies (see Huse et al., *supra*; see also Sastry et al., *supra*). Positive plaques may subsequently be converted to a non-lytic plasmid that allows high level expression of monoclonal antibody fragments from *E. coli*.

[0079] In one embodiment, in a hybridoma the variable regions of a gene expressing a monoclonal antibody of interest are amplified using nucleotide primers. These primers may be synthesized by one of ordinary skill in the art, or may be purchased from commercially available sources. (See, e.g., Stratagene (La Jolla, California), which sells primers for mouse and human variable regions including, among others, primers for V_{Ha}, V_{Hb}, V_{Hc}, V_{Hd}, C_{H1}, V_L and C_L regions.) These primers may be used to amplify heavy or light chain variable regions, which may then be inserted into vectors such as ImmunoZAPTMH or ImmunoZAPTML (Stratagene), respectively. These vectors may then be introduced into *E. coli*, yeast, or mammalian-based systems for expression. Large amounts of a single-chain protein containing a fusion of the V_H and V_L domains may be produced using these methods (see Bird et al., Science 242:423-426, 1988).

[0080] Once cells producing antibodies according to the invention have been obtained using any of the above-described immunization and other techniques, the specific antibody genes may be cloned by isolating and amplifying DNA or mRNA therefrom according to standard procedures as described herein. The antibodies produced therefrom may be sequenced and the CDRs identified and the DNA coding for the CDRs may be manipulated as described previously to

generate other antibodies according to the invention.

[0081] Preferably the binding agents specifically bind to sclerostin. As with all binding agents and binding assays, one of skill in this art recognizes that the various moieties to which a binding agent should not detectably bind in order to be therapeutically effective and suitable would be exhaustive and impractical to list. Therefore, for a binding agent disclosed herein, the term "specifically binds" refers to the ability of a binding agent to bind to sclerostin, preferably human sclerostin, with greater affinity than it binds to an unrelated control protein. Preferably the control protein is hen egg white lysozyme. Preferably the binding agents bind to sclerostin with an affinity that is at least, 50, 100, 250, 500, 1000, or 10,000 times greater than the affinity for a control protein. A binding agent may have a binding affinity for human sclerostin of less than or equal to 1×10^{-10} M, less than or equal to 1×10^{-11} M, or less than or equal to 1×10^{-12} M.

[0082] Affinity may be determined by an affinity ELISA assay. In certain embodiments, affinity may be determined by a BIAcore assay. In certain embodiments, affinity may be determined by a kinetic method. In certain embodiments, affinity may be determined by an equilibrium/solution method. Such methods are described in further detail herein or known in the art.

[0083] Sclerostin binding agents of the present invention preferably modulate sclerostin function in the cell-based assay described herein and/or the *in vivo* assay described herein and/or bind to one or more of the epitopes described herein and/or cross-block the binding of one of the antibodies described in this application and/or are cross-blocked from binding sclerostin by one of the antibodies described in this application. Accordingly such binding agents can be identified using the assays described herein.

[0084] In certain embodiments, binding agents are generated by first identifying antibodies that bind to one more of the epitopes provided herein and/or neutralize in the cell-based and/or *in vivo* assays described herein and/or cross-block the antibodies described in this application and/or are cross-blocked from binding sclerostin by one of the antibodies described in this application. The CDR regions from these antibodies are then used to insert into appropriate biocompatible frameworks to generate sclerostin binding agents. The non-CDR portion of the binding agent may be composed of amino acids, or may be a non-protein molecule. The assays described herein allow the characterization of binding agents. Preferably the binding agents of the present invention are antibodies as defined herein.

[0085] It will be understood by one skilled in the art that some proteins, such as antibodies, may undergo a variety of posttranslational modifications. The type and extent of these modifications often depends on the host cell line used to express the protein as well as the culture conditions. Such modifications may include variations in glycosylation, methionine oxidation, diketopiperazine formation, aspartate isomerization and asparagine deamidation. A frequent modification is the loss of a carboxy-terminal basic residue (such as lysine or arginine) due to the action of carboxypeptidases (as described in Harris, R.J. Journal of Chromatography 705:129-134, 1995).

[0086] Antibodies referred to as Ab-A, Ab-B, Ab-C, Ab-D and Ab-1 are described below. "HC" refers to the heavy chain and "LC" refers to the light chain. For some antibodies below, the CDRs are box shaded and the constant (C) regions are shown in bold italics.

Ab-D

[0087] Antibody D (also referred to herein as Ab-D and Mab-D) is a mouse antibody which exhibits high affinity binding to sclerostin. The BIAcore binding pattern of Ab-D is shown in Figure 18.

[0088] The amino acid sequence of the mature form (signal peptide removed) of Ab-D light chain:

1 DVQMIQSPSS LSASLGDIVT MTCQASQGTSLNLNWFQOKP GKAPKLLIYG
 51 SSNLEDGVPS RFGSRYGTD FTLTISSLED EDLATYFCLQ HSYLPYTFGG
 101 GTKLEIKRAD APTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
 151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:7)

[0089] Nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-D LC is as follows:

1 GATGTCCAGA TGATTCAGTC TCCATCCTCC CTGTCTGCAT CTTTGGGAGA
 51 CATAGTCACC ATGACTTGCC AGGCAAGTCA GGGCACTAGC ATTAATTTAA
 101 ACTGGTTTCA GCAAAAACCA GGAAGGCTC CTAAGCTCCT GATCTATGGT
 151 TCAAGCAACT TGGAAGATGG GGTCCCATCA AGGTTCAAGT GCAGTAGATA
 201 TGGGACAGAT TTCACTCTCA CCATCAGCAG CCTGGAGGAT GAAGATCTGG
 251 CAACTTATTT CTGTCTACAA CATAGTTATC TCCCGTACAC GTTCGGAGGG
 301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
 NO:8)

[0090] The amino acid sequence of Ab-D LC including signal peptide is as follows:

1 MNTRAPAEFL GFLLLWFLGA RCDVQMIQSP SLSASLGDI VTMTQASQG
 51 TSINLNWFQQ KPGKAPKLLI YGSSNLEDGV PSRFSGSRYG TDFTLTISL
 101 EDEDLATYFC LQHSYLPYTF GGGTKLEIKR ADAAPTVSIF PPSSEQLTSG
 151 GASVVCFLNN FYPKDINVKW KIDGSRQNG VLNSWTDQDS KDSTYSMSST
 201 LTLTKDEYER HNSYTCEATH KTSTSPIVKS FNRNEC (SEQ ID NO:9)

[0091] Nucleic acid sequence of Ab-D LC including signal peptide encoding sequence:

1 ATGAACACGA GGGCCCCTGC TGAGTTCCTT GGGTTCCTGT TGCTCTGGTT
 51 TTTAGGTGCC AGATGTGATG TCCAGATGAT TCAGTCTCCA TCCTCCCTGT
 101 CTGCATCTTT GGGAGACATA GTCACCATGA CTTGCCAGGC AAGTCAGGGC

151 ACTAGCATTA ATTTAAACTG GTTTCAGCAA AAACCAGGGA AGGCTCCTAA
 201 GCTCCTGATC TATGGTTCAA GCAACTTGGA AGATGGGGTC CCATCAAGGT
 251 TCAGTGGCAG TAGATATGGG ACAGATTTCA CTCTCACCAT CAGCAGCCTG
 301 GAGGATGAAG ATCTGGCAAC TTATTTCTGT CTACAACATA GTTATCTCCC
 351 GTACACGTTT GGAGGGGGGA CCAAGCTGGA AATAAAACGG GCTGATGCTG
 401 CACCAACTGT ATCCATCTTC CCACCATCCA GTGAGCAGTT AACATCTGGA
 451 GGTGCCTCAG TCGTGTGCTT CTTGAACAAC TTCTACCCCA AAGACATCAA
 501 TGTCAAGTGG AAGATTGATG GCAGTGAACG ACAAATGGC GTCCTGAACA
 551 GTTGGACTGA TCAGGACAGC AAAGACAGCA CCTACAGCAT GAGCAGCACC
 601 CTCACGTTGA CCAAGGACGA GTATGAACGA CATAACAGCT ATACCTGTGA
 651 GGCCACTCAC AAGACATCAA CTTACCCCAT TGTCAGAGC TTCAACAGGA
 701 ATGAGTGTTA G (SEQ ID NO:10)

[0092] The amino acid sequence of the mature form (signal peptide removed) of Ab-D HC heavy chain is as follows:

1 EVQLQQSGPE LVTPGASVKI SCKASGYTFT DHYMSWVKQS HGKSLEWIGD
 51 INPYSGEITY NQKFKGTATL TVDKSSSIAY MEIRGLTSED SAVYYCARD
 101 YDASPFAYWG QGTLVTVSAA KTPPSVYPL APGSAAQTNS MVTLGCLVKG
 151 YFPEPVTVTW NSGSLSSGVH TFAVLQSDL YTLSSSVTVP SSTWPSETVT
 201 CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLIT
 251 LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS
 301 ELPIMHQDWL NGKEFKCRVN SPAFPAPIEK TISKTKGRPK APQVYTIPPP
 351 KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY
 401 FIYSKLVNQK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK (SEQ ID NO:11)

[0093] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-D HC is:

1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTGGTGACGC CTGGGGCTTC
 51 AGTGAAGATA TCTTGTAAGG CTTCTGGATA CACATTCAC T GACCACTACA
 101 TGAGCTGGGT GAAGCAGAGT CATGGAAAA GCCTTGAGTG GATTGGAGAT
 151 ATTAATCCCT ATTCTGGTGA AACTACCTAC AACCAGAAAGT TCAAGGGCAC
 201 GGCCACATTG ACTGTAGACA AGTCTTCCAG TATAGCCTAC ATGGAGATCC
 251 GCGGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGAGATGAT
 301 TACGACGCCT CTCCGTTTGC TTAGTGGGGC CAAGGGACTC TGGTCACTGT
 351 CTCTGCAGCC AAAACGACAC CCCCATCTGT CTATCCACTG GCCCCTGGAT
 401 CTGCTGCCCC AACTAACTCC ATGGTGACCC TGGGATGCCT GGTCAAGGGC
 451 TATTTCCCTG AGCCAGTGAC AGTGACCTGG AACTCTGGAT CCCTGTCCAG
 501 CGGTGTGCAC ACCTTCCAG CTGTCCTGCA GTCTGACCTC TACTCTCTGA
 551 GCAGCTCAGT GACTGTCCCC TCCAGCACCT GGCCAGCGA GACCGTCACC
 601 TGCAACGTTG CCCACCCGGC CAGCAGCACC AAGGTGGACA AGAAAATTGT
 651 GCCCAGGGAT TGTGGTTGTA AGCCTTGCAT ATGTACAGTC CCAGAAGTAT
 701 CATCTGTCTT CATCTTCCCC CCAAAGCCCA AGGATGTGCT CACCATTACT
 751 CTGACTCCTA AGGTCACGTG TGTGTGGTA GACATCAGCA AGGATGATCC
 801 CGAGGTCCAG TTCAGCTGGT TTGTAGATGA TGTGGAGGTG CACACAGCTC
 851 AGACGCAACC CCGGGAGGAG CAGTTCAACA GCACTTTCCG CTCAGTCAGT
 901 GAACTTCCCA TCATGCACCA GGACTGGCTC AATGGCAAGG AGTTCAAATG
 951 CAGGGTCAAC AGTCCAGCTT TCCCTGCCCC CATCGAGAAA ACCATCTCCA
 1001 AAACCAAAGG CAGACCGAAG GCTCCACAGG TGTACACCAT TCCACCTCCC
 1051 AAGGAGCAGA TGGCCAAGGA TAAAGTCAGT CTGACCTGCA TGATAACAGA

1101 CTTCTTCCCT GAAGACATTA CTGTGGAGTG GCAGTGGAAT GGGCAGCCAG
 1151 CGGAGAACTA CAAGAACT CAGCCCATCA TGGACACAGA TGGCTCTTAC
 1201 TTCATCTACA GCAAGCTCAA TGTGCAGAAG AGCAACTGGG AGGCAGGAAA
 1251 TACTTTCACC TGCTCTGTGT TACATGAGGG CCTGCACAAC CACCATACTG
 1301 AGAAGAGCCT CTCCCACTCT CCTGGTAAAT GA (SEQ ID NO:12)

[0094] The amino acid sequence of Ab-D HC including signal peptide is:

1 MRCRWIFLFL LSGTAGVLSE VQLQQSGPEL VTPGASVKIS CKASGYTFTD
 51 HYMSWVKQSH GKSLEWIGDI NPYSGETTYN QKFKGTATLT VDKSSSIAYM
 101 EIRGLTSEDS AVYYCARDYD DASPFAYWGQ GTLVTVSAAK TTPPSVYPLA
 151 PGSAAQTNSM VTLGCLVKGY FPEPVTVTWN SGSLSSGVHT FPAVLQSDLY
 201 TLSSSVTVPS STWPSETVTC NVAHPASSTK VDKKIVPRDC GCKPCICTVP
 251 EVSSVFIFPP KPKDVLITL TPKVTCVVVD ISKDDPEVQF SWFVDDVEVH
 301 TAQTQPREEQ FNSTFRSVSE LPIMHQDWLN GKEFKCRVNS PAFPAPIEKT
 351 ISKTKGRPKA PQVYTIPPPK EQMAKDKVSL TCMITDFFPE DITVEWQWNG
 401 QPAENYKNTQ PIMDTDGSYF IYSKLNVQKS NWEAGNTFTC SVLHEGLHNH
 451 HTEKSLSHSP GK (SEQ ID NO:13)

[0095] The nucleic acid sequence of Ab-D HC including signal peptide encoding sequence is:

1 ATGAGATGCA GGTGGATCTT TCTCTTTCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGAACTG GTGACGCCTG
 101 GGGCTTCAGT GAAGATATCT TGTAAGGCTT CTGGATACAC ATTCAGTGAC
 151 CACTACATGA GCTGGGTGAA GCAGAGTCAT GGAAAAAGCC TTGAGTGGAT
 201 TGGAGATATT AATCCCTATT CTGGTGAAAC TACCTACAAC CAGAAGTTCA
 251 AGGGCACGGC CACATTGACT GTAGACAAGT CTTCCAGTAT AGCCTACATG
 301 GAGATCCGCG GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 351 AGATGATTAC GACGCCTCTC CGTTTGCTTA CTGGGGCCAA GGGACTCTGG
 401 TCACTGTCTC TGCAGCCAAA ACGACACCCC CATCTGTCTA TCCACTGGCC
 451 CCTGGATCTG CTGCCCAAAC TAACTCCATG GTGACCCTGG GATGCCTGGT
 501 CAAGGGCTAT TTCCCTGAGC CAGTGACAGT GACCTGGAAC TCTGGATCCC
 551 TGTCCAGCGG TGTGCACACC TTCCAGCTG TCCTGCAGTC TGACCTCTAC
 601 ACTCTGAGCA GCTCAGTGAC TGTCCCCTCC AGCACCTGGC CCAGCGAGAC
 651 CGTCACCTGC AACGTTGCCC ACCCGGCCAG CAGCACCAAG GTGGACAAGA
 701 AAATTGTGCC CAGGGATTGT GGTGTGAAGC CTTGCATATG TACAGTCCCA
 751 GAAGTATCAT CTGTCTTCAT CTTCCCCCA AAGCCCAAGG ATGTGCTCAC
 801 CATTACTCTG ACTCCTAAGG TCACGTGTGT TGTGGTAGAC ATCAGCAAGG
 851 ATGATCCCGA GGTCCAGTTC AGCTGGTTTG TAGATGATGT GGAGGTGCAC
 901 ACAGCTCAGA CGCAACCCCG GGAGGAGCAG TTCAACAGCA CTTTCCGCTC
 951 AGTCAGTGAA CTTCCCATCA TGCACCAGGA CTGGCTCAAT GGCAAGGAGT
 1001 TCAAATGCAG GGTCAACAGT CCAGCTTTCC CTGCCCCCAT CGAGAAAACC
 1051 ATCTCCAAAA CCAAAGGCAG ACCGAAGGCT CCACAGGTGT ACACCATTC
 1101 ACCTCCCAAG GAGCAGATGG CCAAGGATAA AGTCAGTCTG ACCTGCATGA
 1151 TAACAGACTT CTTCCCTGAA GACATTACTG TGGAGTGGCA GTGGAATGGG
 1201 CAGCCAGCGG AGAACTACAA GAACACTCAG CCCATCATGG ACACAGATGG
 1251 CTCTTACTTC ATCTACAGCA AGCTCAATGT GCAGAAGAGC AACTGGGAGG
 1301 CAGGAAATAC TTTACCTGC TCTGTGTTAC ATGAGGGCCT GCACAACCAC
 1351 CATACTGAGA AGAGCCTCTC CCACTCTCCT GTTAAATGA (SEQ ID NO:14)

[0096] The CDR (complementarity determining region) sequences in the variable region of the heavy chain of Ab-D are as follows:

CDR-H1: DHYMS (SEQ ID NO:39)
 CDR-H2: DINPYSGETTYNQKFKG (SEQ ID NO:40)
 CDR-H3: DDYDASPFAY (SEQ ID NO:41)

[0097] The light chain variable region CDR sequences of Ab-D are:

CDR-L1: QASQGTSINLN (SEQ ID NO:42)
 CDR-L2: GSSNLED (SEQ ID NO:43)
 CDR-L3: LQHSYLPYT (SEQ ID NO:44)

Ab-C

[0098] Antibody C (also referred to herein as Ab-C and Mab-C) is a mouse antibody which exhibits high affinity binding to sclerostin. The BIAcore binding pattern of Ab-C is shown in Figure 17. The amino acid sequence of the mature form (signal peptide removed) of Ab-C Light Chain is as follows:

1 DIVLTQSPAS LTVSLGLRAT ISCKASQSVD YDGDSYMNWY QOKPGQPPKL
 51 LIYAASNLES GIPARFSGNG SGTDFTLNIH PVEEEDAVTY YCQQSNEDPW
 101 TFGGGTKLEI KRADAAPTVS IFPPSSEQLT SGGASVVCFL NNFYPKDINV
 151 KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS STLTLTKDEY ERHNSYTCEA
 201 THKTSTSPIV KSFNRNEC (SEQ ID NO:15)

[0099] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-C LC is:

1 GACATTGTGC TGACCCAATC TCCAGCTTCT TTGACTGTGT CTCTAGGCCT
 51 GAGGGCCACC ATCTCCTGCA AGGCCAGCCA AAGTGTTGAT TATGATGGTG
 101 ATAGTTATAT GAACTGGTAC CAGCAGAAAC CAGGACAGCC ACCCAAATC
 151 CTCATCTATG CTGCATCCAA TCTAGAATCT GGGATCCCAG CCAGGTTTAG
 201 TGGCAATGGG TCTGGGACAG ACTTCACCCT CAACATCCAT CCTGTGGAGG
 251 AGGAGGATGC TGTAACCTAT TACTGTCAAC AAAGTAATGA GGATCCGTGG
 301 ACGTTCGGTG GAGGCACCAA GCTGGAAATC AAACGGGCTG ATGCTGCACC
 351 AACTGTATCC ATCTTCCCAC CATCCAGTGA GCAGTTAACA TCTGGAGGTG
 401 CCTCAGTCGT GTGCTTCTTG AACAACCTCT ACCCCAAAGA CATCAATGTC
 451 AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC TGAACAGTTG
 501 GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC AGCACCCTCA
 551 CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC CTGTGAGGCC
 601 ACTCACAAGA CATCAACTTC ACCCATGTC AAGAGCTTCA ACAGGAATGA
 651 GTGTTAG (SEQ ID NO:16)

[0100] The amino acid sequence of Ab-C LC including signal peptide is:

1 METDTILLWV LLLWVPGSTG DIVLTQSPAS LTVSLGLRAT ISCKASQSVD
 51 YDGDSYMNWY QOKPGQPPKL LIYAASNLES GIPARFSGNG SGTDFTLNIH
 101 PVEEEDAVTY YCQQSNEDPW TFGGGTKLEI KRADAAPTVS IFPPSSEQLT

151 SGGASVVCFL NNFYPKDINV KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS
 201 STLTLTKDEY ERHNSYTCEA THKTSTSPIV KSFNRNEC (SEQ ID NO:17)

[0101] The nucleic acid sequence of Ab-C LC including signal peptide encoding sequence is:

1 ATGGAGACAG ACACAATCCT GCTATGGGTG CTGCTGCTCT GGGTTCCAGG
 51 CTCCACTGGT GACATTGTGC TGACCCAATC TCCAGCTTCT TTGACTGTGT
 101 CTCTAGGCCT GAGGGCCACC ATCTCCTGCA AGGCCAGCCA AAGTGTTGAT
 5 151 TATGATGGTG ATAGTTATAT GAACTGGTAC CAGCAGAAAC CAGGACAGCC
 201 ACCCAAATC CTCATCTATG CTGCATCCAA TCTAGAATCT GGGATCCCAG
 251 CCAGGTTTAG TGGCAATGGG TCTGGGACAG ACTTCACCCT CAACATCCAT
 301 CCTGTGGAGG AGGAGGATGC TGTAACCTAT TACTGTCAAC AAAGTAATGA
 10 351 GGATCCGTGG ACGTTCGGTG GAGGCACCAA GCTGGAAATC AAACGGGCTG
 401 ATGCTGCACC AACTGTATCC ATCTTCCCAC CATCCAGTGA GCAGTTAACA
 451 TCTGGAGGTG CCTCAGTCGT GTGCTTCTTG AACAACTTCT ACCCCAAAGA
 501 CATCAATGTC AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC
 15 551 TGAACAGTTG GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC
 601 AGCACCTCA CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC
 651 CTGTGAGGCC ACTCACAAGA CATCAACTTC ACCCATTGTC AAGAGCTTCA
 701 ACAGGAATGA GTGTTAG (SEQ ID NO:18)

Ab-C Heavy Chain

[0102] The amino acid sequence of the mature form (signal peptide removed) of Ab-C HCis:

1 EVQLQQSGPE LVKPGTSVKM SCKASGYTFT DCYMNWVKQS HGKSLEWIGD
 51 INPFNGGTTY NQKFKGKATL TVDKSSSTAY MQLNSLTSDS SAVYYCARSH
 101 YYFDGRVPWD AMDYWGQGS VTVSSAKTTP PSVYPLAPGS AAQTNSMVTL
 151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
 30 201 PSETVTCNVA HPASSTKYDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
 251 DVLITITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
 301 TFRSVSELP MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
 351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPI
 401 DTDGSYFIYS KLVNQKSNWE AGNTFTCSVL HEGLHNHHT E KSLSHSPGK (SEQ
 35 ID NO:19)

[0103] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-C HC is as follows:

1 GAGGTCCAGC TGCAACAATC TGGACCTGAG CTGGTGAAGC CTGGGACTTC
 51 AGTGAAGATG TCCTGTAAGG CTTCTGGATA CACATTCCT GACTGCTACA
 101 TGAAGTGGGT GAAGCAGAGC CATGGGAAGA GCCTTGAATG GATTGGAGAT
 151 ATTAATCCTT TCAACGGTGG TACTACCTAC AACCAGAAGT TCAAGGGCAA
 45 201 GGCCACATTG ACTGTAGACA AATCCTCCAG CACAGCCTAC ATGCAGCTCA
 251 ACAGCCTGAC ATCTGACGAC TCTGCAGTCT ATTACTGTGC AAGATCCCAT
 301 TATTACTTCG ATGGTAGAGT CCCTTGGGAT GCTATGGACT ACTGGGGTCA
 351 AGGAACCTCA GTCACCGTCT CCTCAGCCAA AACGACACCC CCATCTGTCT
 50 401 ATCCACTGGC CCCTGGATCT GCTGCCCAA CTAACCTCAT GGTGACCCTG
 451 GGATGCCTGG TCAAGGGCTA TTTCCTGAG CCAGTGACAG TGACCTGGAA

501 CTCTGGATCC CTGTCCAGCG GTGTGCACAC CTTCCCAGCT GTCCTGCAGT
 551 CTGACCTCTA CACTCTGAGC AGCTCAGTGA CTGTCCCCTC CAGCACCTGG
 601 CCCAGCGAGA CCGTCACCTG CAACGTTGCC CACCCGGCCA GCAGCACCAA
 5 651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTTGTAAG CCTTGCATAT
 701 GTACAGTCCC AGAAGTATCA TCTGTCTTCA TCTTCCCCC AAAGCCCAAG
 751 GATGTGCTCA CCATTACTCT GACTCCTAAG GTCACGTGTG TTGTGGTAGA
 801 CATCAGCAAG GATGATCCCG AGGTCCAGTT CAGCTGGTTT GTAGATGATG
 10 851 TGGAGGTGCA CACAGCTCAG ACGCAACCCC GGGAGGAGCA GTTCAACAGC
 901 ACTTTCCGCT CAGTCAGTGA ACTTCCCATC ATGCACCAGG ACTGGCTCAA
 951 TGGCAAGGAG TTCAAATGCA GGGTCAACAG TGCAGCTTTC CCTGCCCCCA
 1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGCA GACCGAAGGC TCCACAGGTG
 15 1051 TACACCATTC CACCTCCCAA GGAGCAGATG GCCAAGGATA AAGTCAGTCT
 1101 GACCTGCATG ATAACAGACT TCTTCCCTGA AGACATTACT GTGGAGTGGC
 1151 AGTGAATGG GCAGCCAGCG GAGAACTACA AGAACACTCA GCCCATCATG
 1201 GACACAGATG GCTCTTACTT CATCTACAGC AAGCTCAATG TGCAGAAGAG
 1251 CAACTGGGAG GCAGGAAATA CTTTCACCTG CTCTGTGTGA CATGAGGGCC
 20 1301 TGCACAACCA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA
 (SEQ ID NO:20)

[0104] The amino acid sequence of Ab-C HC including signal peptide is:

1 MGWNWIFLFL LSGTAGVYSE VQLQQSGPEL VKPGTSVKMS CKASGYTFTD
 51 CYMNWVKQSH GKSLEWIGDI NPFNGGTTYN QKFKGKATLT VDKSSSTAYM
 101 QLNSLTSDDS AVYYCARSHY YFDGRVPWDA MDYWGQGTSV TVSSAKTTPP
 30 151 SVYPLAPGSA AQTNSMVTLG CLVKGYFPEP VTVTWNSGSL SSGVHTFPAV
 201 LQSDLYTLSS SVTVPSSTWP SETVTCNVAH PASSTKVDKK IVPRDCGCKP
 251 CICTVPEVSS VFIFPPKPKD VLTITLTPKV TCVVVDISKD DPEVQFSWFV
 301 DDVEVHTAQT QPREEQFNST FRSVSELPIM HQDWLNGKEF KCRVNSAAFP
 35 351 APIEKTISKI KGRPKAPQVY TIPPPKEQMA KDKVSLTCMI TDFFPEDITV
 401 EWQWNGQPAE NYKNTQPIMD TDGSYFIYSK LNVQKSNWEA GNTFTCSVLH
 451 EGLHNHHTTEK SLSHSPGK (SEQ ID NO:21)

[0105] The nucleic acid sequence of Ab-C HC including signal peptide encoding sequence is:

1 ATGGGATGGA ACTGGATCTT TCTCTTCCTC TTGTCAGGAA CTGCAGGTGT
 51 CTACTCTGAG GTCCAGCTGC AACAACTCTGG ACCTGAGCTG GTGAAGCCTG
 101 GGACTTCAGT GAAGATGTCC TGTAAGGCTT CTGGATACAC ATTCAGTGAC
 5 151 TGCTACATGA ACTGGGTGAA GCAGAGCCAT GGAAGAGCC TTGAATGGAT
 201 TGGAGATATT AATCCTTTCA ACGGTGGTAC TACCTACAAC CAGAAGTTCA
 251 AGGGCAAGGC CACATTGACT GTAGACAAAT CCTCCAGCAC AGCCTACATG
 301 CAGCTCAACA GCCTGACATC TGACGACTCT GCAGTCTATT ACTGTGCAAG
 10 351 ATCCCATTAT TACTTCGATG GTAGAGTCCC TTGGGATGCT ATGGACTACT
 401 GGGGTCAAGG AACCTCAGTC ACCGTCTCCT CAGCCAAAAC GACACCCCCA
 451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAATA ACTCCATGGT
 501 GACCCTGGGA TGCCTGGTCA AGGGCTATTT CCCTGAGCCA GTGACAGTGA
 15 551 CCTGGAAGTC TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
 601 CTGCAGTCTG ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCCTCCAG
 651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCAC CCGGCCAGCA
 701 GCACCAAGGT GGACAAGAAA ATTGTGCCCA GGGATTGTGG TTGTAAGCCT
 20 751 TGCATATGTA CAGTCCCAGA AGTATCATCT GTCTTCATCT TCCCCCAAA
 801 GCCCAAGGAT GTGCTCACCA TTAATCTGAC TCCTAAGGTC ACGTGTGTTG

851 TGGTAGACAT CAGCAAGGAT GATCCCGAGG TCCAGTTCAG CTGGTTTGTG
 25 901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
 951 CAACAGCACT TTCCGCTCAG TCAGTGAAGT TCCCATCATG CACCAGGACT
 1001 GGCTCAATGG CAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCCT
 1051 GCCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGCAGAC CGAAGGCTCC
 30 1101 ACAGGTGTAC ACCATTCCAC CTCCCAAGGA GCAGATGGCC AAGGATAAAG
 1151 TCAGTCTGAC CTGCATGATA ACAGACTTCT TCCCTGAAGA CATTACTGTG
 1201 GAGTGGCAGT GGAATGGGCA GCCAGCGGAG AACTACAAGA AACTCAGCC
 1251 CATCATGGAC ACAGATGGCT CTTACTTCAT CTACAGCAAG CTCAATGTGC
 35 1301 AGAAGAGCAA CTGGGAGGCA GGAAATACTT TCACCTGCTC TGTGTTACAT
 1351 GAGGGCCTGC ACAACCACCA TACTGAGAAG AGCCTCTCCC ACTCTCCTGG
 1401 TAAATGA (SEQ ID NO:22)

[0106] The CDR (complementarity determining region) sequences in the variable region of the heavy chain of Ab-C
 40 are as follows:

CDR-H1: DCYMN (SEQ ID NO:45)
 CDR-H2: DINPFNGGTTYNQKFKG (SEQ ID NO:46)
 CDR-H3: SHYYFDGRVPWDAMDY (SEQ ID NO:47)

[0107] The light chain variable region CDR sequences of Ab-C are:

CDR-L1: KASQSVDYDGDSYNIN (SEQ ID NO:48)
 CDR-L2: AASNLES (SEQ ID NO:49)
 CDR-L3: QQSNEDPWT (SEQ ID NO:50)

Ab-A

[0108] Antibody A (also referred to herein as Ab-A and Mab-A) is a rabbit-mouse chimeric antibody which exhibits
 55 high affinity binding to sclerostin. The BIAcore binding pattern of Ab-A is shown in Figure 15.

Ab-A Light Chain

[0109] The amino acid sequence of the mature form (signal peptide removed) of Ab-A LC:

1 AQVLTQTPAS VSAAVGGTVT INCQSSQSVY DNNWLAWFQQ KPGQPPKLLI
 51 YDASDLASGV PSRFSGSGSG TQFTLTISGV QCADAATYYC QGAYNDVIYA
 101 FGGGTEVVVK RTDAAPT~~VS~~I FPPSSEQLTS GGASVVCFLN NFYPKDINVK
 151 WKIDGSE~~RQ~~N GVLNSWTDQD SKDSTYSMSS TLTLTKDEYE RHNSYTCEAT
 201 HKTSTSPIVK SFNRNEC (SEQ ID NO:23)

[0110] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-ALC:

1 GCGCAAGTGC TGACCCAGAC TCCAGCCTCC GTGTCTGCAG CTGTGGGAGG
 51 CACAGTCACC ATCAATTGCC AGTCCAGTCA GAGTGTTTAT GATAACAAC
 101 GGTTAGCCTG GTTTCAGCAG AAACCAGGGC AGCCTCCCAA GCTCCTGATT
 151 TATGATGCAT CCGATCTGGC ATCTGGGGTC CCATCGCGGT TCAGTGGCAG
 201 TGGATCTGGG ACACAGTTCA CTCTACCAT CAGCGGCGTG CAGTGTGCCG
 251 ATGCTGCCAC TTA~~CT~~ACTGT CAAGGCGCTT ATAATGATGT TATTTATGCT
 301 TTCGGCGGAG GGACCGAGGT GGTGGTCAAA CGTACGGATG CTGCACCAAC
 351 TGTATCCATC TTCCCACCAT CCAGTGAGCA GTTAACATCT GGAGGTGCCT
 401 CAGTCGTGTG CTTCTTGAAC AACTTCTACC CCAAAGACAT CAATGTCAAG
 451 TGGAAGATTG ATGGCAGTGA ACGACAAAAT GCGTCCTGA ACAGTTGGAC
 501 TGATCAGGAC AGCAAAGACA GCACCTACAG CATGAGCAGC ACCCTCACGT
 551 TGACCAAGGA CGAGTATGAA CGACATAACA GCTATACCTG TGAGGCCACT
 601 CACAAGACAT CAACTTCACC CATTGTCAAG AGCTTCAACA GGAATGAGTG
 651 TTAG (SEQ ID NO:24)

[0111] The amino acid sequence of Ab-A LC including signal peptide is:

1 MDTRAPTQLL GLLLLWLPGA TFAQVLTQTP ASVSAAVGGT VTINCQSSQS
 51 VYDNNWLAWF QQKPGQPPKL LIYDASDLAS GVPSRFSGSG SGTQFTLTIS
 101 GVQCADAATY YCQGAYNDVI YAFGGGTEVV VKRTDAAPT~~V~~ SIFPPSSEQL
 151 TSGGASVVCFLNNFYPKDIN VKWKIDGSE~~R~~QNGVLNSWTD QDSKDSTYSM
 201 SSTLTLTKDE YERHNSYTCE ATHKTSTSPI VKSFNRNEC (SEQ ID NO:25)

[0112] The nucleic acid sequence of Ab-A LC including signal peptide encoding sequence is:

1 ATGGACACGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC TGCTCTGGCT
 51 CCCAGGTGCC ACATTTGCGC AAGTGCTGAC CCAGACTCCA GCCTCCGTGT
 101 CTGCAGCTGT GGGAGGCACA GTCACCATCA ATTGCCAGTC CAGTCAGAGT
 5 151 GTTTATGATA ACAACTGGTT AGCCTGGTTT CAGCAGAAAC CAGGGCAGCC
 201 TCCCAAGCTC CTGATTTATG ATGCATCCGA TCTGGCATCT GGGGTCCCAT
 251 CGCGGTTT CAG TGGCAGTGA TCTGGGACAC AGTTCACCTCT CACCATCAGC
 301 GCGGTGCAGT GTGCCGATGC TGCCACTTAC TACTGTCAAG GCGCTTATAA
 10 351 TGATGTTATT TATGCTTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAACGTA
 401 CGGATGCTGC ACCAACTGTA TCCATCTTCC CACCATCCAG TGAGCAGTTA
 451 ACATCTGGAG GTGCCTCAGT CGTGTGCTTC TTGAACAACT TCTACCCCAA
 501 AGACATCAAT GTCAAGTGA AGATTGATGG CAGTGAACGA CAAAATGGCG
 551 TCCTGAACAG TTGGACTGAT CAGGACAGCA AAGACAGCAC CTACAGCATG
 15 601 AGCAGCACCC TCACGTTGAC CAAGGACGAG TATGAACGAC ATAACAGCTA
 651 TACCTGTGAG GCCACTCACA AGACATCAAC TTCACCCATT GTCAAGAGCT
 701 TCAACAGGAA TGAGTGTTAG (SEQ ID NO:26)

[0113] The amino acid sequence of the mature form (signal peptide removed) of Ab-A HC is:

1 QSLEESGGRL VTPGTPLTLT CTASGFSLS¹YWMNWVRQAP GEGLEWIGT¹
 51 DSGGR¹TDYAS WAKGRFTISR TSTTMDLKMT SLTTGDTARY FCARNWNLWG
 25 101 QGTLVTVSSA *STKGPSVYPL APGSAAQ¹TNS MVTLGCLVKG YFPEPVTVTW*
 151 *NSGSLSSGVH TFP AVLQSDL YTLSSSVTVP SSTWPSETVT CNVAHPASST*
 201 *KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVL¹TIT LTPKVTCVVV*
 251 *DISKDDPEVQ FSWFVDDVEV HTAQ¹TQPREE QFNSTFRSVS ELPIMHQDWL*
 30 301 *NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPPP KEQMAKDKVS*
 351 *LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMNTNGSY FVYSKLVN¹QK*

401 SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK (SEQ ID NO:27)

[0114] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-A HC:

1 CAGTCGCTGG AGGAGTCCGG GGGTCGCCTG GTCACGCCTG GGACACCCCT
 51 GACACTCACC TGCACAGCCT CTGGATTCTC CCTCAGTAGT TATTGGATGA
 101 ACTGGGTCCG CCAGGCTCCA GGGGAGGGGC TGAATGGAT CGGAACCATT
 5 151 GATTCTGGTG GTAGGACGGA CTACGCGAGC TGGGCAAAG GCCGATTCAC
 201 CATCTCCAGA ACCTCGACTA CGATGGATCT GAAAATGACC AGTCTGACGA
 251 CCGGGGACAC GGCCCGTTAT TTCTGTGCCA GAAATTGGAA CTTGTGGGGC
 301 CAAGGCACCC TCGTCACCGT CTCGAGCGCT TCTACAAAGG GCCCATCTGT
 10 351 CTATCCACTG GCCCCTGGAT CTGCTGCCCA AACTAACTCC ATGGTGACCC
 401 TGGGATGCCT GGTCAAGGGC TATTTCCTG AGCCAGTGAC AGTGACCTGG
 451 AACTCTGGAT CCCTGTCCAG CGGTGTGCAC ACCTTCCCAG CTGTCCTGCA
 501 GTCTGACCTC TACACTCTGA GCAGCTCAGT GACTGTCCCC TCCAGCACCT
 551 GGCCAGCGA GACCGTCACC TGCAACGTTG CCCACCCGGC CAGCAGCACC
 15 601 AAGGTGGACA AGAAAATTGT GCCCAGGGAT TGTGGTTGTA AGCCTTGCA
 651 ATGTACAGTC CCAGAAGTAT CATCTGTCTT CATCTTCCCC CCAAAGCCCA
 701 AGGATGTGCT CACCATTACT CTGACTCCTA AGGTCACGTG TGTGTGGTA
 751 GACATCAGCA AGGATGATCC CGAGGTCCAG TTCAGCTGGT TTGTAGATGA
 20 801 TGTGGAGGTG CACACAGCTC AGACGCAACC CCGGGAGGAG CAGTTCAACA
 851 GCACTTCCG CTCAGTCAGT GAACTTCCCA TCATGCACCA GGAAGTGGTC
 901 AATGGCAAGG AGTTCAAATG CAGGGTCAAC AGTGCAGCTT TCCCTGCCCC
 951 CATCGAGAAA ACCATCTCCA AAACCAAAGG CAGACCGAAG GCTCCACAGG
 25 1001 TGTACACCAT TCCACCTCCC AAGGAGCAGA TGGCCAAGGA TAAAGTCAGT
 1051 CTGACCTGCA TGATAACAGA CTTCTTCCCT GAAGACATTA CTGTGGAGTG
 1101 GCAGTGGAAAT GGGCAGCCAG CGGAGAACTA CAAGAACACT CAGCCCATCA
 1151 TGGACACAGA TGGCTCTTAC TTCGTCTACA GCAAGCTCAA TGTGCAGAAG
 30 1201 AGCAACTGGG AGGCAGGAAA TACTTTCACC TGCTCTGTGT TACATGAGGG
 1251 CCTGCACAAC CACCATACTG AGAAGAGCCT CTCCCACTCT CCTGGTAAAT
 1301 GA (SEQ ID NO:28)

[0115] The amino acid sequence of the Ab-A HC including signal peptide is:

1 METGLRWLLL VAVLKGVHCQ SLEESGGRLV TPGTPLTLTC TASGFSLSY
 51 WMNWVRQAPG EGLEWIGTID SGGRTDYASW AKGRFTISRT STTMDLKMTS
 101 LTTGDTARYF CARNWNLWGQ GTLTVTSSAS TKGPSVYPLA PGSAAQTNSM
 40 151 VTLGCLVKGY FPEPVTVTWN SGSLSSGVHT FPAVLQSDLY TLSSSVTVPS
 201 STWPSETVTC NVAHPASSTK VDKKIVPRDC GCKPCICTVP EVSSVFIFPP
 251 KPKDVLTTIL TPKVTCVVVD ISKDDPEVQF SWFVDDVEVH TAQTQPREEQ
 301 FNSTFRSVSE LPIMHQDWLN GKEFKCRVNS AAFPAPIEKT ISKTKGRPKA
 45 351 PQVYTIPPPK EQMAKDKVSL TCMITDFFPE DITVEWQWNG QPAENYKNTQ
 401 PIMNTNGSYF VYSKLVQKS NWEAGNTFTC SVLHEGLHNH HTEKSLSHSP
 451 GK (SEQ ID NO:29)

[0116] The nucleic acid sequence of Ab-A HC including signal peptide encoding sequence:

1 ATGGAGACTG GGCTGCGCTG GCTTCTCCTG GTCGCTGTGC TCAAAGGTGT
 51 CCACTGTCAG TCGCTGGAGG AGTCCGGGGG TCGCCTGGTC ACGCCTGGGA
 55 101 CACCCCTGAC ACTCACCTGC ACAGCCTCTG GATTCTCCCT CAGTAGTTAT

151 TGGATGAACT GGGTCCGCCA GGCTCCAGGG GAGGGGCTGG AATGGATCGG
 201 AACCATTTGAT TCTGGTGGTA GGACGGACTA CGCGAGCTGG GCAAAAGGCC
 251 GATTCACCAT CTCCAGAACC TCGACTACGA TGGATCTGAA AATGACCAGT
 301 CTGACGACCG GGGACACGGC CCGTTATTTT TGTGCCAGAA ATTGGAACCT
 351 GTGGGGCCAA GGCACCCTCG TCACCGTCTC GAGCGCTTCT ACAAAGGGCC
 401 CATCTGTCTA TCCACTGGCC CCTGGATCTG CTGCCCAAAC TAACTCCATG
 451 GTGACCCTGG GATGCCTGGT CAAGGGCTAT TTCCCTGAGC CAGTGACAGT
 501 GACCTGGAAC TCTGGATCCC TGTCCAGCGG TGTGCACACC TTCCAGCTG
 551 TCCTGCAGTC TGACCTCTAC ACTCTGAGCA GCTCAGTGAC TGTCCCCTCC
 601 AGCACCTGGC CCAGCGAGAC CGTCACCTGC AACGTTGCC ACCCGGCCAG
 651 CAGCACCAAG GTGGACAAGA AAATTGTGCC CAGGGATTGT GGTGTGAAGC
 701 CTTGCATATG TACAGTCCCA GAAGTATCAT CTGTCTTCAT CTTCCCCCA
 751 AAGCCCAAGG ATGTGCTCAC CATTACTCTG ACTCCTAAGG TCACGTGTGT
 801 TGTGGTAGAC ATCAGCAAGG ATGATCCCGA GGTCCAGTTC AGCTGGTTTG
 851 TAGATGATGT GGAGGTGCAC ACAGCTCAGA CGCAACCCCG GGAGGAGCAG
 901 TTCAACAGCA CTTTCCGCTC AGTCAGTGAA CTTCCCATCA TGCACCAGGA
 951 CTGGCTCAAT GGCAAGGAGT TCAAATGCAG GGTCAACAGT GCAGCTTTCC
 1001 CTGCCCCCAT CGAGAAAACC ATCTCCAAAA CCAAAGGCAG ACCGAAGGCT
 1051 CCACAGGTGT ACACCATTC ACCTCCCAAG GAGCAGATGG CCAAGGATAA
 1101 AGTCAGTCTG ACCTGCATGA TAACAGACTT CTTCCCTGAA GACATTACTG
 1151 TGGAGTGGCA GTGGAATGGG CAGCCAGCGG AGAACTACAA GAACACTCAG
 1201 CCCATCATGG ACACAGATGG CTCTTACTTC GTCTACAGCA AGCTCAATGT
 1251 GCAGAAGAGC AACTGGGAGG CAGGAAATAC TTTCACCTGC TCTGTGTTAC
 1301 ATGAGGGCCT GCACAACCAC CATACTGAGA AGAGCCTCTC CCACTCTCCT
 1351 GGTAATGA (SEQ ID NO:30)

[0117] The CDR (complementarity determining region) sequences in the variable region of the heavy chain of Ab-A are as follows:

CDR-H1: SYWMN (SEQ ID NO:51)
 CDR-H2: TIDSGRTDYASWAKG (SEQ ID NO:52)
 CDR-H3: NWNL (SEQ ID NO:53)

[0118] The light chain variable region CDR sequences of Ab-A are:

CDR-L1: QSSQSVYDNNWLA (SEQ ID NO:54)
 CDR-L2: DASDLAS (SEQ ID NO:55)
 CDR-L3: QGAYNDVIYA (SEQ ID NO:56)

[0119] Ab-A was humanized, and is referred to as Antibody 1 (also referred to herein as Ab-1), having the following sequences:

The nucleic acid sequence of the Ab-1 LC variable region including signal peptide encoding sequence is

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGT
 GCCACATTTGCTCAAGTTCTGACCCAGAGTCCAAGCAGTCTCTCCGCCAGCGTAGGC

GATCGTGTGACTATTACCTGTCAATCTAGTCAGAGCGTGTATGATAACAATTGGCTG
 GCGTGGTACCAGCAAAAACCGGGCAAAGCCCCGAAGCTGCTCATCTATGACGCGTC
 CGATCTGGCTAGCGGTGTGCCAAGCCGTTTCAGTGGCAGTGGCAGCGGTAAGTACTGACT
 TTACCCTCACAATTTTCGTCTCTCCAGCCGGAAGATTTGCGCACTTACTATTGTCAAG
 GTGCTTACAACGATGTGATTTATGCCTTCGGTCAGGGCACTAAAGTAGAAATCAAAA
 CGT (SEQ ID NO:74)

[0120] The amino acid sequence of Ab-1 LC variable region including signal peptide is:

MDTRAPTQLLGLLLWLPGATFAQVLTQSPSSLSASVGDRVTTTCQSSQSVYDNNWLA
WYQQKPGKAPKLLIYDASDLASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQGA
YNDVIYAFGQGTKVEIKR (SEQ ID NO:75)

[0121] The nucleic acid sequence of Ab-1 HC variable region including signal peptide encoding sequence is:

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCACTGT
 GAGGTGCAGCTGTTGGAGTCTGGAGGCGGGCTTGTCCAGCCTGGAGGGAGCCTGCG
 TCTCTCTTGTGCAGCAAGCGGCTTCAGCTTATCCTCTTACTGGATGAATTGGGTGCG
 GCAGGCACCTGGGAAGGGCCTGGAGTGGGTGGGCACCATTTGATTCCGGAGGCCGTA
 CAGACTACGCGTCTTGGGCAAAGGGCCGTTTCACCATTTCCCGCGACAACCTCCAAA
 AATACCATGTACCTCCAGATGAACTCTCTCCGCGCAGAGGACACAGCACGTTATTA
 CTGTGCACGCAACTGGAATCTGTGGGGTCAAGGTACTCTTGTAACAGTCTCGAGC
 (SEQ ID NO:76)

[0122] Amino acid sequence of Ab-1 HC variable region including signal peptide

METGLRWLLLVAVLKGVHCEVQLLESGGGLVQPGGSLRLSCAASGFSLSSYWMNWVR
QAPGKGLEWVGTIDSGGRTDYASWAKGRFTISRDN SKNTMYLQMNSLRAEDTARYYC
ARNWNLWGQGTLVTVSS (SEQ ID NO:77)

[0123] The CDR (complementarity determining region) sequences in the variable region of the heavy chain of Ab-1 are as follows:

CDR-H1: SYWMN (SEQ ID NO:51)
 CDR-H2: TIDSGGRDYASWAKG (SEQ ID NO:52)
 CDR-H3: NWNL (SEQ ID NO:53)

[0124] The light chain variable region CDR sequences of Ab-1 are:

CDR-L1: QSSQSVYDNNWLA (SEQ ID NO:54)
 CDR-L2: DASDLAS (SEQ ID NO:55)
 CDR-L3: QGAYNDVIYA (SEQ ID NO:56)

Ab-B

[0125] Antibody B (also referred to herein as Ab-B and Mab-B) is a mouse antibody which exhibits high affinity binding to sclerostin. The BIAcore binding pattern of Ab-B is shown in Figure 16.

Ab-B Light Chain

[0126] The amino acid sequence of the mature form (signal peptide removed) of the Ab-B LC is:

5
1 QIVLTQSPTI VSASPGEKVT LICSSASSSVS FVDWFQOKPG TSPKRWIYRT
51 SNLGFGVPAR FSGGSGTSH SLTISRMEAE DAATYYCQQR STYPPTFGAG
101 TKLELKRA **DA**PTVSIFPPS **SE**QLTSGGAS **VVC**FLNNFYP **KD**INVKWKID
151 **GS**ERQNGVLN **SW**TDQDSKDS **TY**SMSSTLTL **TK**DEYERHNS **YT**CEATHKTS
201 **TS**PIVKSFNR **NEC** (SEQ ID NO:31)

[0127] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-B LC is:

15
1 CAAATTGTTT TCACCCAGTC TCCAACAATC GTGTCTGCAT CTCCAGGGGA
51 GAAGGTCACC CTAATCTGCA GTGCCAGTTC AAGTGTAAGT TTCGTGGACT
101 GGTTCCAGCA GAAGCCAGGC ACTTCTCCCA AACGCTGGAT TTACAGAACA
151 TCCAACCTGG GTTTTGGAGT CCCTGCTCGC TTCAGTGGCG GTGGATCTGG
20
201 GACCTCTCAC TCTCTCACAA TCAGCCGAAT GGAGGCTGAA GATGCTGCCA
251 CTTATTACTG CCAGCAAAGG AGTACTTACC CACCCACGTT CCGTGCTGGG
301 ACCAAGCTGG AACTGAAACG GGCTGATGCT GCACCAACTG TATCCATCTT
351 CCCACCATCC AGTGAGCAGT TAACATCTGG AGGTGCCTCA GTCGTGTGCT
25
401 TCTTGAACAA CTTCTACCCC AAAGACATCA ATGTCAAGTG GAAGATTGAT
451 GGCAGTGAAC GACAAAATGG CGTCCTGAAC AGTTGGACTG ATCAGGACAG
501 CAAAGACAGC ACCTACAGCA TGAGCAGCAC CCTCACGTTG ACCAAGGACG
551 AGTATGAACG ACATAACAGC TATACCTGTG AGGCCACTCA CAAGACATCA
30
601 ACTTCACCCA TTGTCAAGAG CTTCAACAGG AATGAGTGTT AG (SEQ ID NO:32)

[0128] The amino acid sequence of Ab-B LC including signal peptide is:

35
1 MHFQVQIFSF LLISASVIVS RGQIVLTQSP TIVSASPGEK VTLCSSASSS
51 VSFVDWFQOK PGTSPKRWIY RTSNLGFGVP ARFSGGSGT SHSLTISRME
101 AEDAATYYCQ QRSTYPPTFG AGTKLELKRA DAAPTVSIFP PSSEQLTSGG
151 ASVVCFLNNF YPKDINVKWK IDGSRQNGV LNSWTDQDSK DSTYMSSTL
40
201 TLTKDEYERH NSYTCEATHK TSTSPIVKSF NRNEC (SEQ ID NO:33)

[0129] The nucleic acid sequence of Ab-B LC including signal peptide encoding sequence is:

45
1 ATGCATTTTC AAGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCCTCAGT
51 CATAGTGTCC AGAGGGCAAA TTGTTCTCAC CCAGTCTCCA ACAATCGTGT
101 CTGCATCTCC AGGGGAGAAG GTCACCCTAA TCTGCAGTGC CAGTTCAAGT
151 GTAAGTTTCG TGGACTGGTT CCAGCAGAAG CCAGGCACTT CTCCCAAACG
201 CTGGATTTAC AGAACATCCA ACCTGGGTTT TGGAGTCCCT GCTCGCTTCA
50
251 GTGGCGGTGG ATCTGGGACC TCTCACTCTC TCACAATCAG CCGAATGGAG
301 GCTGAAGATG CTGCCACTTA TTACTGCCAG CAAAGGAGTA CTTACCCACC

55

351 CACGTTCCGGT GCTGGGACCA AGCTGGAACT GAAACGGGCT GATGCTGCAC
 401 CAACTGTATC CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
 451 GCCTCAGTCG TGTGCTTCTT GAACAACCTC TACCCCAAAG ACATCAATGT
 501 CAAGTGGAAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
 551 GGAAGTATCA GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCCTC
 601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
 651 CACTCACAAG ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG
 701 AGTGTTAG (SEQ ID NO:34)

Ab-B Heavy Chain

[0130] The amino acid sequence of the mature form (signal peptide removed) of Ab-B HC:

1 QVTLKESGPG ILQPSOTLSL TCSFSGFSLS TSGMGVGVWIR HPSGKNLEWL
 51 AHIWWDDYKR YNPVLKSRLT ISKDTSNSQV FLKIANVDTA DTATYYCARI
 101 EDEFDYDEEYY AMDYWGQGS VIVSSAKTTP **PSVYPLAPGS AAQTNSMVTL**
 151 **GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW**
 201 **PSETVTCNVA HPASSTKVVDK KIVPRDCGCK PCICTVPEVS SVFIFFPKPK**
 251 **DVLTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS**
 301 **TFRSVSELP I MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV**
 351 **YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPI**
 401 **DTDGSYFVYS KLVNQKSNWE AGNTFTCSVL HEGLHNHTE KSLSHSPGK** (SEQ
 ID NO:35)

[0131] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-B HC:

EP 2 251 351 B1

1 CAGGTTACTC TGAAAGAGTC TGGCCCTGGG ATATTGCAGC CCTCCCAGAC
 51 CCTCAGTCTG ACTTGTTCTT TCTCTGGGTT TTCACTGAGC ACTTCTGGTA
 101 TGGGTGTAGG CTGGATTCTG CACCCATCAG GGAAGAATCT GGAGTGGCTG
 5 GCACACATTT GGTGGGATGA TGTCAAGCGC TATAACCCAG TCCTGAAGAG
 201 CCGACTGACT ATCTCCAAGG ATACCTCCAA CAGCCAGGTA TTCCTCAAGA
 251 TCGCCAATGT GGACACTGCA GATACTGCCA CATACTACTG TGCTCGAATA
 301 GAGGACTTTG ATTACGACGA GGAGTATTAT GCTATGGACT ACTGGGGTCA
 351 AGGAACCTCA GTCATCGTCT CCTCAGCCAA AACGACACCC CCATCTGTCT
 10 ATCCACTGGC CCCTGGATCT GCTGCCCAA CTAACCTCCAT GGTGACCCTG
 451 GGATGCCTGG TCAAGGGCTA TTCCCTGAG CCAGTGACAG TGACCTGGAA
 501 CTCTGGATCC CTGTCCAGCG GTGTGCACAC CTTCCCAGCT GTCCTGCAGT
 551 CTGACCTCTA CACTCTGAGC AGCTCAGTGA CTGTCCCCTC CAGCACCTGG
 15 601 CCCAGCGAGA CCGTCACCTG CAACGTTGCC CACCCGGCCA GCAGACCAA
 651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTTGTAAG CCTTGCATAT
 701 GTACAGTCCC AGAAGTATCA TCTGTCTTCA TCTTCCCCC AAAGCCCAAG
 751 GATGTGCTCA CCATTACTCT GACTCCTAAG GTCACGTGTG TTGTGGTAGA
 20 801 CATCAGCAAG GATGATCCCG AGGTCCAGTT CAGCTGGTTT GTAGATGATG
 851 TGGAGGTGCA CACAGCTCAG ACGCAACCCC GGGAGGAGCA GTTCAACAGC
 901 ACTTTCCGCT CAGTCAGTGA ACTTCCCATC ATGCACCAGG ACTGGCTCAA
 951 TGGCAAGGAG TTCAAATGCA GGGTCAACAG TGCAGCTTTC CCTGCCCCCA
 25 1001 TCGAGAAAAC CATCTCCAA ACCAAAGGCA GACCGAAGGC TCCACAGGTG
 1051 TACACCATT CACCTCCAA GGAGCAGATG GCCAAGGATA AAGTCAGTCT
 1101 GACCTGCATG ATAACAGACT TCTTCCCTGA AGACATTACT GTGGAGTGGC
 1151 AGTGAATGG GCAGCCAGCG GAGAACTACA AGAACACTCA GCCCATCATG
 30 1201 GACACAGATG GCTCTTACTT CGTCTACAGC AAGCTCAATG TGCAGAAGAG
 1251 CAACTGGGAG GCAGGAAATA CTTTCACCTG CTCTGTGTTA CATGAGGGCC
 1301 TGCACAACCA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA
 (SEQ ID NO:36)

[0132] The amino acid sequence of Ab-B HC including signal peptide:

1 MGRLTSSFLL LIVPAYVLSQ VTLKESGPGI LQPSQTLSTL CSFSGFSLST
 51 SGMGVGWIRH PSGKNLEWLA HIWDDVKRY NPVLKSRLTI SKDTSNSQVF
 40 101 LKIANVDTAD TATYYCARIE DFDYDEEYYA MDYWGQGTSV IVSSAKTTPP
 151 SVYPLAPGSA AQTNSMVTLG CLVKGYFPEP VVTWNHSGSL SSGVHTFPAV
 201 LQSDLYTLSS SVTVPSSTWP SETVTCNVAH PASSTKVDDK IVPRDCGCKP
 251 CICTVPEVSS VFIFPPKPKD VLTITLTPKV TCVVVDISKD DPEVQFSWFV
 45 301 DDVEVHTAQT QPREEQFNST FRSVSELPIM HQDWLNGKEF KCRVNSAAFP
 351 APIEKTISK KGRPKAPQVY TIPPPKEQMA KDKVSLTCMI TDDFPEDITV
 401 EWQWNGQPAE NYKNTQPIMD TDGSYFVYSK LNVQKSNWEA GNTFTCSVLH
 451 EGLHNHHTK SLSHSPGK (SEQ ID NO:37)

[0133] The nucleic acid sequence of Ab-B HC including signal peptide encoding sequence:

1 ATGGGCAGGC TTACTTCTTC ATTCTGCTA CTGATTGTCC CTGCATATGT
 51 CCTGTCCCAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT
 101 CCCAGACCCT CAGTCTGACT TGTCTTTTCT CTGGGTTTTTCT ACTGAGCACT
 5 151 TCTGGTATGG GTGTAGGCTG GATTCGTCAC CCATCAGGGA AGAATCTGGA
 201 GTGGCTGGCA CACATTTGGT GGGATGATGT CAAGCGCTAT AACCCAGTCC
 251 TGAAGAGCCG ACTGACTATC TCCAAGGATA CCTCCAACAG CCAGGTATTC
 301 CTCAAGATCG CCAATGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGC
 10 351 TCGAATAGAG GACTTTGATT ACGACGAGGA GTATTATGCT ATGGACTACT
 401 GGGGTCAAGG AACCTCAGTC ATCGTCTCCT CAGCCAAAAC GACACCCCCA
 451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAATA ACTCCATGGT
 501 GACCCTGGGA TGCCTGGTCA AGGGCTATTT CCCTGAGCCA GTGACAGTGA
 551 CCTGGAATC TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
 15 601 CTGCAGTCTG ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCCTCCAG
 651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCAC CCGGCCAGCA
 701 GCACCAAGGT GGACAAGAA ATTGTGCCCA GGGATTGTGG TTGTAAGCCT
 751 TGCATATGTA CAGTCCCAGA AGTATCATCT GTCTTCATCT TCCCCCAA
 20 801 GCCCAAGGAT GTGCTACCA TTACTCTGAC TCCTAAGGTC ACGTGTGTTG
 851 TGGTAGACAT CAGCAAGGAT GATCCCGAGG TCCAGTTCAG CTGGTTTGTA
 901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
 951 CAACAGCACT TTCCGCTCAG TCAGTGAAT TCCCATCATG CACCAGGACT
 25 1001 GGCTCAATGG CAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCTT
 1051 GCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGCAGAC CGAAGGCTCC
 1101 ACAGGTGTAC ACCATTCCAC CTCCCAAGGA GCAGATGGCC AAGGATAAAG
 1151 TCAGTCTGAC CTGCATGATA ACAGACTTCT TCCCTGAAGA CATTACTGTG
 1201 GAGTGGCAGT GGAATGGGCA GCCAGCGGAG AACTACAAGA AACTCAGCC
 30 1251 CATCATGGAC ACAGATGGCT CTACTTTCGT CTACAGCAAG CTCAATGTGC
 1301 AGAAGAGCAA CTGGGAGGCA GGAAATACTT TCACCTGCTC TGTGTTACAT
 1351 GAGGGCCTGC ACAACCACCA TACTGAGAAG AGCCTCTCCC ACTCTCCTGG
 1401 TAAATGA (SEQ ID NO:38)

[0134] The CDR (complementarity determining region) sequences in the variable region of the heavy chain of Ab-B are as follows:

CDR-H1: TSGMGVG (SEQ ID NO:57)
 CDR-H2: HIWDDVKRYNPVLKS (SEQ ID NO:58)
 CDR-H3: EDFDYDEEYYAMDY (SEQ ID NO:59)

[0135] The light chain variable region CDR sequences of Ab-B are:

CDR-L1: SASSSVSFVD (SEQ ID NO:60)
 CDR-L2: RTSNLGF (SEQ ID NO:61)
 CDR-L3: QQRSTYPPT (SEQ ID NO:62)

[0136] Antibodies disclosed herein bind to regions of human sclerostin which are important for the *in vivo* activity of the protein. Binding of an antibody to sclerostin can be correlated with increases in, for example, the bone mineral density achieved by use of the antibody *in vivo* such as described in Examples 5 and 9 (mice) and Example 12 (monkey). Increases in at least one of bone formation, bone mineral content, bone mass, bone quality and bone strength can also be achieved by use of the antibody *in vivo* such as described in Examples 5 and 9 (mice) and Example 12 (monkey). Since the binding of an antibody to sclerostin is primarily determined by its CDR sequences, an antibody for practicing the invention may be generated with all or some of the disclosed CDR sequences in an appropriate framework, wherein the antibody retains the ability to bind specifically to sclerostin, and can be expected to achieve increases in, for example,

bone mineral density. Such antibodies are useful in the treatment of human or animal conditions that are caused by, associated with, or result in at least one of low bone formation, low bone mineral density, low bone mineral content, low bone mass, low bone quality and low bone strength. Methods of constructing and expressing antibodies and fragments thereof comprising CDR's of the present invention are known to those of skill in the art.

[0137] The present disclosure provides an isolated antibody, including Ab-A, or an antigen binding fragment thereof, which specifically binds to sclerostin and wherein the variable domain of the heavy chain comprises at least one CDR having the sequences given in SEQ ID NO:51 for CDR-H1, SEQ ID NO:52 for CDR-H2 and SEQ ID NO:53 for CDR-H3. The antibody or antigen binding fragment thereof may comprise a heavy chain variable domain in which the CDRs consist of at least one of the peptides of SEQ ID NO:51 for CDR-H1, SEQ ID NO:52 for CDR-H2 and SEQ ID NO:53 for CDR-H3.

[0138] When in antibodies of the disclosure a light chain is present the light chain may be any suitable complementary chain and may in particular be selected from a light chain wherein the variable domain comprises at least one CDR having the sequences given in SEQ ID NO:54 for CDR-L1, SEQ ID NO:55 for CDR-L2 and SEQ ID NO:56 for CDR-L3. The antibody or antigen binding fragment thereof may comprise a light chain variable domain in which the CDRs consist of at least one of the peptides of SEQ ID NO:54 for CDR-L1, SEQ ID NO:55 for CDR-L2 and SEQ ID NO:56 for CDR-L3.

[0139] The present disclosure further relates to an isolated antibody, including Ab-B, or an antigen binding fragment hereof, which specifically binds to sclerostin and wherein the variable domain of the heavy chain comprises at least one CDR having the sequences given in SEQ ID NO:57 for CDR-H1, SEQ ID NO:58 for CDR-H2 and SEQ ID NO:59 for CDR-H3. The antibody or antigen binding fragment thereof may comprise a heavy chain variable domain in which the CDRs consist of at least one of the peptides of SEQ ID NO:57 for CDR-H1, SEQ ID NO:58 for CDR-H2 and SEQ ID NO:59 for CDR-H3.

[0140] When in antibodies of the disclosure a light chain is present the light chain may be any suitable complementary chain and may in particular be selected from a light chain wherein the variable domain comprises at least one CDR having the sequences given in SEQ ID NO:60 for CDR-L1, SEQ ID NO:61 for CDR-L2 and SEQ ID NO:62 for CDR-L3. The antibody or antigen binding fragment thereof may comprise a light chain variable domain in which the CDRs consist of at least one of the peptides of SEQ ID NO:60 for CDR-L1, SEQ ID NO:61 for CDR-L2 and SEQ ID NO:62 for CDR-L3.

[0141] The present disclosure still further relates to an isolated antibody, including Ab-C, or an antigen binding fragment hereof, which specifically binds to sclerostin and wherein the variable domain of the heavy chain comprises at least one CDR having the sequences given in SEQ ID NO:45 for CDR-H1, SEQ ID NO:46 for CDR-H2 and SEQ ID NO:47 for CDR-H3. The antibody or antigen binding fragment thereof may comprise a heavy chain variable domain in which the CDRs consist of at least one of the peptides of SEQ ID NO:45 for CDR-H1, SEQ ID NO:46 for CDR-H2 and SEQ ID NO:47 for CDR-H3.

[0142] When in antibodies of the disclosure a light chain is present the light chain may be any suitable complementary chain and may in particular be selected from a light chain wherein the variable domain comprises at least one CDR having the sequences given in SEQ ID NO:48 for CDR-L1, SEQ ID NO:49 for CDR-L2 and SEQ ID NO:50 for CDR-L3. The antibody or antigen binding fragment thereof may comprise a light chain variable domain in which the CDRs consist of at least one of the peptides of SEQ ID NO:48 for CDR-L1, SEQ ID NO:49 for CDR-L2 and SEQ ID NO:50 for CDR-L3.

[0143] The present disclosure also relates to an isolated antibody, including Ab-D, or an antigen binding fragment hereof, which specifically binds to sclerostin and wherein the variable domain of the heavy chain comprises at least one CDR having the sequences given in SEQ ID NO:39 for CDR-H1, SEQ ID NO:40 for CDR-H2 and SEQ ID NO:41 for CDR-H3. The antibody or antigen binding fragment thereof may comprise a heavy chain variable domain in which the CDRs consist of at least one of the peptides of SEQ ID NO:39 for CDR-H1, SEQ ID NO:40 for CDR-H2 and SEQ ID NO:41 for CDR-H3.

[0144] When in antibodies of the disclosure a light chain is present the light chain may be any suitable complementary chain and may in particular be selected from a light chain wherein the variable domain comprises at least one CDR having the sequences given in SEQ ID NO:42 for CDR-L1, SEQ ID NO:43 for CDR-L2 and SEQ ID NO:44 for CDR-L3. The antibody or antigen binding fragment thereof may comprise a light chain variable domain in which the CDRs consist of at least one of the peptides of SEQ ID NO:42 for CDR-L1, SEQ ID NO:43 for CDR-L2 and SEQ ID NO:44 for CDR-L3.

[0145] Additional anti-sclerostin antibodies are described below. For some of the amino acid sequences the complementarity-determining regions (CDRs) are boxed-shaded and the constant regions are in bold-italics.

Ab-2

[0146] The sequences of the Antibody 2 (also referred to as Ab-2) LC and HC are as follows:

Ab-2 Light Chain:

[0147] Amino acid sequence of the mature form (signal peptide removed) of the Ab-2 LC:

1 QIVLSQSPAI LSTSPGEKVT MTCRASSSVY YMHYQKPG SSPKPWIY AT
 51 SNLASGVPVR FSGSGSGTSY SLTITRVEAE DAATYYCQQW SSDPLTFGAG
 101 TKLELKRA DA APTVSIFPPS SEQLTSGGAS VVCFLNNFYP KDINVKWKID
 151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
 201 TSPIVKSFNR NEC (SEQ ID NO:117)

[0148] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-2 LC:

1 CAAATTGTTC TCTCCCAGTC TCCAGCAATC CTGTCTACAT CTCCAGGGGA
 51 GAAGGTCACA ATGACTTGCA GGGCCAGCTC AAGTGTATAT TACATGCACT
 101 GGTACCAGCA GAAGCCAGGA TCCTCCCCCA AACCTGGAT TTATGCCACA
 151 TCCAACCTGG CTTCTGGAGT CCCTGTTCGC TTCAGTGGCA GTGGGTCTGG
 201 GACCTCTTAC TCTCTCACA TCACCAGAGT GGAGGCTGAA GATGCTGCCA
 251 CTTATTACTG CCAGCAGTGG AGTAGTGACC CACTCACGTT CGGTGCTGGG

301 ACCAAGCTGG AGCTGAAACG GGCTGATGCT GCACCAACTG TATCCATCTT
 351 CCCACCATCC AGTGAGCAGT TAACATCTGG AGGTGCCTCA GTCGTGTGCT
 401 TCTTGAACAA CTTCTACCCC AAAGACATCA ATGTCAAGTG GAAGATTGAT
 451 GGCAGTGAAC GACAAAATGG CGTCCTGAAC AGTTGGACTG ATCAGGACAG
 501 CAAAGACAGC ACCTACAGCA TGAGCAGCAC CCTCACGTTG ACCAAGGACG
 551 AGTATGAACG ACATAACAGC TATACCTGTG AGGCCACTCA CAAGACATCA
 601 ACTTCACCCA TTGTCAAGAG CTTCAACAGG AATGAGTGTT AG (SEQ ID
 NO:118)

[0149] Amino acid sequence of the Ab-2 LC including signal peptide:

1 MDFVQVIFSF LLISASVIMS RGQIVLSQSP AILSTSPGEK VTMTCRASSS
 51 VYYMHYQK PGSSPKWIY ATSNLASGVP VRFSGSGSGT SYSLTITRVE
 101 AEDAATYYCQ QWSSDPLTFG AGTKLELKRA DAAPTVSIFP PSSEQLTSGG
 151 ASVVCFLNNF YPKDINVKWK IDGSERQNGV LNSWTDQDSK DSTYSMSSTL
 201 TLTKDEYERH NSYTCEATHK TSTSPIVKSF NRNEC (SEQ ID NO:119)

[0150] Nucleic acid sequence of the Ab-2 LC including signal peptide encoding sequence:

1 ATGGATTTTC AAGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCTTCAGT
 51 CATTATGTCC AGGGGACAAA TTGTTCTCTC CCAGTCTCCA GCAATCCTGT
 101 CTACATCTCC AGGGGAGAAG GTCACAATGA CTTGCAGGGC CAGCTCAAGT
 151 GTATATTACA TGCACTGGTA CCAGCAGAAG CCAGGATCCT CCCCCAAACC
 201 CTGGATTTAT GCCACATCCA ACCTGGCTTC TGGAGTCCCT GTTCGCTTCA
 251 GTGGCAGTGG GTCTGGGACC TCTTACTCTC TCACAATCAC CAGAGTGGAG
 301 GCTGAAGATG CTGCCACTTA TTACTGCCAG CAGTGGAGTA GTGACCCACT
 351 CACGTTCGGT GCTGGGACCA AGCTGGAGCT GAAACGGGCT GATGCTGCAC
 401 CAACTGTATC CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
 451 GCCTCAGTCG TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT
 501 CAAGTGGAAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
 551 GGA CTGATCA GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCTC
 601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
 651 CACTCACAAG ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG
 701 AGTGTTAG (SEQ ID NO:120)

Ab-2 Heavy Chain

[0151] Amino acid sequence of the mature form (signal peptide removed) of the Ab-2 HC:

1 EVQVQQSGPE LVKPGASVKL SCTASGFNIK ~~DYFIHWVKQR~~ PEQGLEWIGR
 51 ~~EDPEDGESDY~~ ~~APKEFDKAIM~~ TADTSSNTAY LQLRSLTSED TAIYYCERED
 101 ~~YDGTYYTFPY~~ WGQGT LTVS ~~AAKTTTPSVY~~ ~~PLAPGSAAQT~~ NSMVTLGCLV
 151 ~~KGYFPEPVTV~~ TWNSGSLSSG ~~VHTFPAVLQS~~ DLYTLSSSVT VPSSTWPSET
 201 VTCNV AHPAS ~~STKVDDKKIVP~~ RDCGCKPCIC TVPEVSSVFI FPPKPKDVLV
 251 ITLTPKVTCV VVDISKDDPE ~~VQFSWFVDDV~~ EVHTAQTPR ~~EEQFNSTFRS~~
 301 ~~VSELPIMHQD~~ WLNGKEFKCR ~~VNSAAFPAPI~~ EKTISKTKGR PKAPQVYTIP
 351 ~~PPKEQMAKDK~~ VSLTCMITDF ~~FPEDITVEWQ~~ WNGQPAENYK NTQPIMDTDG
 401 SYFIYSKLVN ~~QKSNWEAGNT~~ FTCSVLHEGL HNHHTEKSLS HSPGK (SEQ ID
 NO:121)

[0152] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-2 HC:

1 GAGGTTTCAGG TGCAGCAGTC TGGGCCAGAA CTTGTGAAGC CAGGGGCCTC
 51 AGTCAAGTTG TCCTGCACAG CTTCTGGCTT CAACATTAAA GACTACTTTA
 101 TACACTGGGT GAAGCAGAGG CCTGAACAGG GCCTGGAGTG GATTGGAAGG
 5 151 CTTGATCCTG AGGATGGTGA AAGTGATTAT GCCCCGAAGT TCCAGGACAA
 201 GGCCATTATG ACAGCAGACA CATCATCCAA CACAGCCTAT CTTGAGCTCA
 251 GAAGCCTGAC ATCTGAGGAC ACTGCCATCT ATTATTGTGA GAGAGAGGAC
 301 TACGATGGTA CCTACACCTT TTTTCCTTAC TGGGGCCAAG GGACTCTGGT
 10 351 CACTGTCTCT GCAGCCAAAA CGACACCCCC ATCTGTCTAT CCACTGGCCC
 401 CTGGATCTGC TGCCCAAAC TAACTCCATGG TGACCCTGGG ATGCCTGGTC
 451 AAGGGCTATT TCCCTGAGCC AGTGACAGTG ACCTGGAAC TGGATCCCT
 501 GTCCAGCGGT GTGCACACCT TCCCAGCTGT CCTGCAGTCT GACCTCTACA
 551 CTCTGAGCAG CTCAGTGA CTGCCCCCTCCA GCACCTGGCC CAGCGAGACC
 15 601 GTCACCTGCA ACGTTGCCCA CCCGGCCAGC AGCACCAAGG TGGACAAGAA
 651 AATTGTGCCC AGGGATTGTG GTTGTAAGCC TTGCATATGT ACAGTCCCAG
 701 AAGTATCATC TGTCTTCATC TTCCCCCAA AGCCCAAGGA TGTGCTCACC
 751 ATTACTCTGA CTCCTAAGGT CACGTGTGTT GTGGTAGACA TCAGCAAGGA
 20 801 TGATCCCGAG GTCCAGTTCA GCTGGTTTGT AGATGATGTG GAGGTGCACA
 851 CAGCTCAGAC GCAACCCCGG GAGGAGCAGT TCAACAGCAC TTTCCGCTCA
 901 GTCAGTGAAC TTCCCATCAT GCACCAGGAC TGGCTCAATG GCAAGGAGTT
 951 CAAATGCAGG GTCAACAGTG CAGCTTTCCC TGCCCCCATC GAGAAAACCA
 25 1001 TCTCCAAAAC CAAAGGCAGA CCGAAGGCTC CACAGGTGTA CACCATTCCA
 1051 CCTCCCAAGG AGCAGATGGC CAAGGATAAA GTCAGTCTGA CCTGCATGAT
 1101 AACAGACTTC TTCCCTGAAG ACATTACTGT GGAGTGGCAG TGAATGGGC
 1151 AGCCAGCGGA GAACTACAAG AACACTCAGC CCATCATGGA CACAGATGGC
 30 1201 TCTTACTTCA TCTACAGCAA GCTCAATGTG CAGAAGAGCA ACTGGGAGGC
 1251 AGGAAATACT TTCACCTGCT CTGTGTTACA TGAGGGCCTG CACAACCACC
 1301 ATACTGAGAA GAGCCTCTCC CACTCTCCTG GTAAATGA (SEQ ID NO:122)

[0153] Amino acid sequence of the Ab-2 HC including signal peptide:

1 MKCSWVIFFL MAVVTGVNSE VQVQQSGPEL VKPGASVKLS CTASGFNIKD
 51 YFIHWVKQRP EQGLEWIGRL DPEDGESDYA PKFQDKAIMT ADTSSNTAYL
 101 QLRSLTSEDY AIYYCEREDY DGTYTFFPYW GQGTLVTVSA AKTTPPSVYP
 40 151 LAPGSAAQTN SMVTLGCLVK GYFPEPVTVT WNSGSLSSGV HTFPAVLQSD
 201 LYTLSSSVTV PSSTWPSETV TCNVAHPASS TKVDKKIVPR DCGCKPCICT
 251 VPEVSSVFIF PPKPKDVLTI TLPKVTCTVV VDISKDDPEV QFSWFVDDVE
 301 VHQAQTQPRE EQFNSTFRSV SELPIMHQDW LNGKEFKCRV NSAAFPAPIE
 45 351 KTISKTKGRP KAPQVYTIPP PKEQMAKDKV SLTCMITDFF PEDITVEWQW
 401 NGQPAENYKN TQPIMDTDGS YFIYSKLNQV KSNWEAGNTF TCSVLHEGLH
 451 NHHTEKSLSH SPGK (SEQ ID NO:123)

[0154] Nucleic acid sequence of the Ab-2 HC including signal peptide encoding sequence:

1 ATGAAATGCA GCTGGGTCAT CTTCTTCCTG ATGGCAGTGG TTACAGGGGT
 51 CAATTCAGAG GTTCAGGTGC AGCAGTCTGG GCCAGAACTT GTGAAGCCAG
 101 GGGCCTCAGT CAAGTTGTCC TGCACAGCTT CTGGCTTCAA CATTAAAGAC
 151 TACTTTATAC ACTGGGTGAA GCAGAGGCCT GAACAGGGCC TGGAGTGGAT
 201 TGGAAGGCTT GATCCTGAGG ATGGTGAAAG TGATTATGCC CCGAAGTTCC
 251 AGGACAAGGC CATTATGACA GCAGACACAT CATCCAACAC AGCCTATCTT
 301 CAGCTCAGAA GCCTGACATC TGAGGACACT GCCATCTATT ATTGTGAGAG
 351 AGAGGACTAC GATGGTACCT ACACCTTTT TCCTTACTGG GGCCAAGGGA
 401 CTCTGGTCAC TGTCTCTGCA GCCAAAACGA CACCCCATC TGTCTATCCA
 451 CTGGCCCCTG GATCTGCTGC CCAAATAAC TCCATGGTGA CCCTGGGATG

501 CCTGGTCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAAGTCTG
 551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCCT GCAGTCTGAC
 601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCCTCCAGCA CCTGGCCCAG
 651 CGAGACCGTC ACCTGCAACG TTGCCACCC GGCCAGCAGC ACCAAGGTGG
 701 ACAAGAAAAT TGTGCCCAGG GATTGTGGTT GTAAGCCTTG CATATGTACA
 751 GTCCCAGAAG TATCATCTGT CTTCATCTC CCCCCAAAGC CCAAGGATGT
 801 GCTCACCATT ACTCTGACTC CTAAGGTCAC GTGTGTTGTG GTAGACATCA
 851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTTTGTAGA TGATGTGGAG
 901 GTGCACACAG CTCAGACGCA ACCCCGGGAG GAGCAGTTCA ACAGCACTTT
 951 CCGCTCAGTC AGTGAAGTTC CCATCATGCA CCAGGACTGG CTCAATGGCA
 1001 AGGAGTTCAA ATGCAGGGTC AACAGTGCAG CTTTCCTGTC CCCCATCGAG
 1051 AAAACCATCT CCAAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
 1101 CATTCCACCT CCCAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
 1151 GCATGATAAC AGACTTCTTC CCTGAAGACA TTACTGTGGA GTGGCAGTGG
 1201 AATGGGCAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
 1251 AGATGGCTCT TACTTCATCT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
 1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTTACATGA GGGCCTGCAC
 1351 AACCACCATA CTGAGAAGAG CCTCTCCAC TCTCCTGGTA AATGA (SEQ ID
 NO:124)

Ab-3

[0155] The sequences of the Antibody 3 (also referred to herein as Ab-3) LC and HC are as follows:

Ab-3 Light Chain

[0156] Amino acid sequence of the mature form (signal peptide removed) of the Ab-3 LC:

1 EIVLTQSPAL MAASPGEKVT ITCSVSSTIS SNHLHWFOQK SDTSPKPWIY
 51 GTSNLEASGVP VRFSGSGSGT SYSLTISSME AEDAATYYCQ QWSSYPLTFG
 101 AGTKLELRR *DAAPT*VSIFP *PSSEQL*TSGG *ASVVC*FLNNF *YPKD*INVKWK
 151 *IDGSE*RQNGV *LNSWTD*QDSK *DSTYS*MSSTL *TLTKDE*YERH NSYTCEATHK
 201 *TSTSP*IVKSF NRNEC (SEQ ID NO:125)

[0157] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-3 LC:

1 GAAATTGTGC TCACCCAGTC TCCAGCACTC ATGGCTGCAT CTCCGGGGGA
 51 GAAGGTCACC ATCACCTGCA GTGTCAGTTC AACTATAAGT TCCAACCACT
 101 TGCACTGGTT CCAGCAGAAG TCAGACACCT CCCCCAAACC CTGGATTAT
 5 151 GGCACATCCA ACCTGGCTTC TGGAGTCCCT GTTCGCTTCA GTGGCAGTGG
 201 ATCTGGGACC TCTTATTCTC TCACAATCAG CAGCATGGAG GCTGAGGATG
 251 CTGCCACTTA TTA CTGTCAA CAGTGGAGTA GTTACCCACT CACGTTCCGGC
 301 GCTGGGACCA AGCTGGAGCT GAGACGGGCT GATGCTGCAC CAACTGTATC
 10 351 CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT GCCTCAGTCG
 401 TGTGCTTCTT GAACAACCTC TACCCCAAAG ACATCAATGT CAAGTGGAAG
 451 ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT GGA CTGATCA
 501 GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCCTC ACGTTGACCA
 15 551 AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC CACTCACAAG
 601 ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG AGTGTTAG (SEQ
 ID NO:126)

[0158] Amino acid sequence of the Ab-3 LC including signal peptide:

1 MDFHVQIFS F MLISVTVILS SGEIVLTQSP ALMAASPGEK VTITCSVSST
 51 ISSNHLHW FQ QKSDTSPKPW IYGTSNLASG VPVRFSGSGS GTSYSLTISS
 101 MEAEDAATY Y CQWSSYPLT FGAGTKLELR RADAAPT VSI FPPSSEQ LTS
 25 151 GGASVVCFLN NFYPKDINVK WKIDG SERQN GVLNSWTDQD SKDSTYS MSS
 201 TLTLTKDEYE RHNSYTCEAT HKTSTSPIVK SFNRNEC (SEQ ID NO:127)

[0159] Nucleic acid sequence of the Ab-3 LC including signal peptide encoding sequence:

1 ATGGATTTTC ATGTGCAGAT TTTCAGCTTC ATGCTAATCA GTGTCACAGT
 51 CATTTTGTCC AGTGGAGAAA TTGTGCTCAC CCAGTCTCCA GCACTCATGG
 101 CTGCATCTCC GGGGGAGAAG GTCACCATCA CCTGCAGTGT CAGTTCAACT
 35 151 ATAAGTTCCA ACCACTTGCA CTGGTTCCAG CAGAAGTCAG ACACCTCCCC
 201 CAAACCCTGG ATTTATGGCA CATCCAACCT GGCTTCTGGA GTCCCTGTTC
 251 GCTTCAGTGG CAGTGGATCT GGGACCTCTT ATTCTCTCAC AATCAGCAGC
 301 ATGGAGGCTG AGGATGCTGC CACTTATTAC TGTCAACAGT GGAGTAGTTA
 40 351 CCCACTCACG TTCGGCGCTG GGACCAAGCT GGAGCTGAGA CGGGCTGATG
 401 CTGCACCAAC TGTATCCATC TTCCACCAT CCAGTGAGCA GTTAACATCT
 451 GGAGGTGCCT CAGTCGTGTG CTCTTGAAC AACTTCTACC CCAAAGACAT
 501 CAATGTCAAG TGGAAGATTG ATGGCAGTGA ACGACAAAAT GGCCTCCTGA
 55 551 ACAGTTGGAC TGATCAGGAC AGCAAAGACA GCACCTACAG CATGAGCAGC
 601 ACCCTCACGT TGACCAAGGA CGAGTATGAA CGACATAACA GCTATACCTG
 651 TGAGGCCACT CACAAGACAT CAACTTCACC CATTGTCAAG AGCTTCAACA
 701 GGAATGAGTG TTAG (SEQ ID NO:128)

Ab-3 Heavy Chain

[0160] Amino acid sequence of the mature form (signal peptide removed) of the Ab-3 HC:

1 EVQLQQSGAE LVRPGALVKL SCTASDFNIK DFYLHWMRQR PEQGLDWIGR
 51 IDPENGDTLY DPKFQDKATL TDTSSNTAY LQLSGLTSET TAVYYCSREA
 101 DYFHDGTSYW YFDVWGAGTT ITVSSAKTTP PSVYPLAPGS AAQTNSMVTL
 151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
 201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
 251 DVLITITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
 301 TFRSVSELPI MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
 351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIM
 401 DTDGSYFIYS KLVNQKSNWE AGNTFTCSVL HEGLHNHHTE KSLSHSPGK (SEQ
 ID NO:129)

[0161] nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-3 HC:

1 GAGGTTTCAGC TGCAGCAGTC TGGGGCTGAA CTTGTGAGGC CAGGGGCCTT
 51 AGTCAAGTTG TCCTGCACAG CTTCTGACTT CAACATTAAA GACTTCTATC
 101 TACACTGGAT GAGGCAGCGG CCTGAACAGG GCCTGGACTG GATTGGAAGG
 151 ATTGATCCTG AGAATGGTGA TACTTTATAT GACCCGAAGT TCCAGGACAA
 201 GGCCACTCTT ACAACAGACA CATCCTCCAA CACAGCCTAC CTGCAGCTCA
 251 GCGGCCTGAC ATCTGAGACC ACTGCCGTCT ATTACTGTTC TAGAGAGGCG
 301 GATTATTTCC ACGATGGTAC CTCCTACTGG TACTTCGATG TCTGGGGCGC
 351 AGGGACCACA ATCACCCTCT CCTCAGCCAA AACGACACCC CCATCTGTCT
 401 ATCCACTGGC CCCTGGATCT GCTGCCCAA CTAACCTCAT GGTGACCCTG
 451 GGATGCCTGG TCAAGGGCTA TTTCCCTGAG CCAGTGACAG TGACCTGGAA
 501 CTCTGGATCC CTGTCCAGCG GTGTGCACAC CTTCCCAGCT GTCCTGCAGT
 551 CTGACCTCTA CACTCTGAGC AGCTCAGTGA CTGTCCCCTC CAGCACCTGG

 601 CCCAGCGAGA CCGTCACCTG CAACGTTGCC CACCCGGCCA GCAGCACCAA
 651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTTGTAAG CCTTGCATAT
 701 GTACAGTCCC AGAAGTATCA TCTGTCTTCA TCTTCCCCC AAAGCCCAAG
 751 GATGTGCTCA CCATTACTCT GACTCCTAAG GTCACGTGTG TTGTGGTAGA
 801 CATCAGCAAG GATGATCCCG AGGTCCAGTT CAGCTGGTTT GTAGATGATG
 851 TGGAGGTGCA CACAGCTCAG ACGCAACCC GGGAGGAGCA GTTCAACAGC
 901 ACTTCCGCT CAGTCAGTGA ACTTCCCATC ATGCACCAGG ACTGGCTCAA
 951 TGGCAAGGAG TTCAAATGCA GGGTCAACAG TGCAGCTTTC CCTGCCCCCA
 1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGCA GACCGAAGGC TCCACAGGTG
 1051 TACACCATTC CACCTCCCAA GGAGCAGATG GCCAAGGATA AAGTCAGTCT
 1101 GACCTGCATG ATAACAGACT TCTTCCCTGA AGACATTACT GTGGAGTGGC
 1151 AGTGGAATGG GCAGCCAGCG GAGAACTACA AGAACACTCA GCCCATCATG
 1201 GACACAGATG GCTCTTACTT CATCTACAGC AAGCTCAATG TGCAGAAGAG
 1251 CAACTGGGAG GCAGGAAATA CTTTCACCTG CTCTGTGTGA CATGAGGGCC
 1301 TGCACAACCA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA
 (SEQ ID NO:130)

[0162] Amino acid sequence of the Ab-3 HC including signal peptide:

1 MKCSWVIFFL MAVVTGVNSE VQLQQSGAEL VRPGALVKLS CTASDFNIKD
 51 FYLHWMRQRP EQGLDWIGRI DPENGDLYD PKFQDKATLT TDTSSNTAYL
 101 QLSGLTSETT AVYYCSREAD YFHDGTSYWY FDVWGAGTTI TVSSAKTTPP
 151 SVYPLAPGSA AQNSMVTLG CLVKGYFPEP VTVTWNSGSL SSGVHTFPAV
 201 LQSDLYTLSS SVTVPSSTWP SETVTCNVAH PASSTKVDDK IVPRDCGCKP
 251 CICTVPEVSS VFIFPPKPKD VLTITLTPKV TCVVVDISKD DPEVQFSWFV
 301 DDVEVHTAQT QPREEQFNST FRSVSELPIM HQDWLNGKEF KCRVNSAAFP
 351 APIEKTISK KGRPKAPQVY TIPPPKEQMA KDKVSLTCMI TDFFPEDITV
 401 EWQWNGQPAE NYKNTQPIMD TDGSYFIYSK LNVQKSNWEA GNTFTCSVLH
 451 EGLHNHHTK SLSHSPGK (SEQ ID NO:131)

[0163] Nucleic acid sequence of the Ab-3 HC including signal peptide encoding sequence:

1 ATGAAATGCA GCTGGGTCAT CTTCTTCCTG ATGGCAGTGG TTACAGGGGT
 51 CAATTCAGAG GTTCAGCTGC AGCAGTCTGG GGCTGAACTT GTGAGGCCAG
 101 GGGCCTTAGT CAAGTTGTCC TGCACAGCTT CTGACTTCAA CATTAAAGAC
 151 TTCTATCTAC ACTGGATGAG GCAGCGGCCT GAACAGGGCC TGGACTGGAT
 201 TGGAAGGATT GATCCTGAGA ATGGTGATAC TTTATATGAC CCGAAGTTC
 251 AGGACAAGGC CACTCTTACA ACAGACACAT CCTCCAACAC AGCCTACCTG
 301 CAGCTCAGCG GCCTGACATC TGAGACCACT GCCGTCTATT ACTGTTCTAG
 351 AGAGGCGGAT TATTTCCACG ATGGTACCTC CTAAGGTAC TTCGATGTCT
 401 GGGGCGCAGG GACCACAATC ACCGTCTCCT CAGCCAAAAC GACACCCCCA
 451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAATA ACTCCATGGT
 501 GACCCTGGGA TGCCTGGTCA AGGGCTATTT CCCTGAGCCA GTGACAGTGA
 551 CCTGGAATC TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
 601 CTGCAGTCTG ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCCTCCAG
 651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCAC CCGGCCAGCA
 701 GCACCAAGGT GGACAAGAAA ATTGTGCCA GGGATTGTGG TTGTAAGCCT
 751 TGCATATGTA CAGTCCCAGA AGTATCATCT GTCTTCATCT TCCCCCAAA
 801 GCCCAAGGAT GTGCTCACCA TTAAGTCTGAC TCCTAAGGTC ACGTGTGTG
 851 TGGTAGACAT CAGCAAGGAT GATCCCGAGG TCCAGTTCAG CTGGTTTGT
 901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
 951 CAACAGCACT TTCCGCTCAG TCAGTGAAGT TCCCATCATG CACCAGGACT

 1001 GGCTCAATGG CAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCCT
 1051 GCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGCAGAC CGAAGGCTCC
 1101 ACAGGTGTAC ACCATTCCAC CTCCCAAGGA GCAGATGGCC AAGGATAAAG
 1151 TCAGTCTGAC CTGCATGATA ACAGACTTCT TCCCTGAAGA CATTACTGTG
 1201 GAGTGGCAGT GGAATGGGCA GCCAGCGGAG AACTACAAGA AACTCAGCC
 1251 CATCATGGAC ACAGATGGCT CTTACTTCAT CTACAGCAAG CTCAATGTGC
 1301 AGAAGAGCAA CTGGGAGGCA GGAAATACTT TCACCTGCTC TGTGTTACAT
 1351 GAGGGCCTGC ACAACCACCA TACTGAGAAG AGCCTCTCCC ACTCTCCTGG
 1401 TAAATGA (SEQ ID NO:132)

Ab-4

[0164] The sequences of the Antibody 4 (also referred to herein as Ab-4) LC and HC are as follows:

Ab-4 Light Chain:

[0165] Amino acid sequence of the mature form (signal peptide removed) of the Ab-4 LC:

5
1 DIQMTQITSS LSASLGDRVS ISCRASQDIS NYLNWYQQKP DGTFKLLIFY
51 TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDTLPYTFGG
101 GTKLEIKRAD APTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:133)

[0166] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-4 LC:

15
1 GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
101 ACTGGTATCA GCAGAAACCA GATGGAACCT TAAACTCCT TATCTTCTAC
151 ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAAGT GCAGTGGGTC
201 TGGAACAGAT TATTCTCTCA CCATTACAA CCTGGAGCAA GAAGATTTTG
251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
25 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
30 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
NO:134)

[0167] Amino acid sequence of the Ab-4 LC including signal peptide:

35
1 MMSSAQFLGL LLLCFQGTRC DIQMTQITSS LSASLGDRVS ISCRASQDIS
51 NYLNWYQQKP DGTFKLLIFY TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ
101 EDFATYFCQQ GDTLPYTFGG GTKLEIKRAD APTVSIFPP SSEQLTSGGA
151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
40 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:135)

[0168] Nucleic acid sequence of the Ab-4 LC including signal peptide encoding sequence:

45
1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT

101 CTCTGGGAGA CAGGGICTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
 151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAACCTT TTAAACTCCT
 201 TATCTTCTAC ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTTCAGTG
 251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
 301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
 351 TTTTCGGAGGG GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GTTAG (SEQ ID NO:136)

Ab-4 Heavy Chain:

[0169] Amino acid sequence of the mature form (signal peptide removed) of the Ab-4 HC:

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWVKQN QGKTLIEWIG
 51 INPNSGGAGY NQKFKGKATL TVDKSSTAY MELRSLTSED SAVYYCAREG
 101 YDDIYDDWYF DVWGAGTTVT VSSAKTTPPS VYPLAPGSAA QTNSMVTLGC
 151 LVKGYFPEPV TVTWNSGSL SSGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
 201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAAFPA PIEKTISKTK GRPKAPQVYT
 351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID
 NO:137)

[0170] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-4 HC:

1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA TACATTCACT GACTACAACA
 101 TGCACTGGGT GAAGCAGAAC CAAGGAAAGA CCCTAGAGTG GATAGGAGAA
 5 151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAGT TCAAGGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 10 351 CACGGTCACC GTCTCCTCAG CCAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAAGTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
 15 601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
 701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 20 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
 25 1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC

1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
 1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
 30 1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
 1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
 1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
 1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID
 35 NO:138)

[0171] Amino acid sequence of the Ab-4 HC including signal peptide:

1 MGWSWTFLL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
 51 YNMHWVKQNN GKTLIEWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
 101 ELRSLTSEDS AVYYCARLGY DDIYDDWYFD VWGAGTTVTV SSAKTTPPSV
 151 YPLAPGSAAQ TNSMVTGLCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
 40 201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTPQ REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMITD FFPEDITVEW
 401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
 50 451 LHNHHTKSL SHSPGK (SEQ ID NO:139)

[0172] Nucleic acid sequence of the Ab-4 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAACCTG AACAGTCTGG ACCTGAACTA ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCACTGAC
 151 TACAACATGC ACTGGGTGAA GCAGAACCAA GGAAAGACCC TAGAGTGGAT
 201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA
 251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 351 ATTGGGCTAC GATGATATCT ACGACGACTG GTACTTCGAT GTCTGGGGCG
 401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CTTCCCAGC TGTCTGCAG
 601 TCTGACCTCT AACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
 801 GGATGTGCTC ACCATTACTC TGAATCCTAA GGTCACGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGAATG GGCAGCCAGC GGAGAACTAC AAGAACAATC AGCCCATCAT
 1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAATG

1401 A (SEQ ID NO:140)

[0173] Ab-4 was humanized to generate Ab-5.

Ab-5

[0174] The sequences of the Antibody 5 (also referred to herein as Ab-5) LC and HC are as follows:

Ab-5 Light Chain:

[0175] Amino acid sequence of the mature form (signal peptide removed) of the Ab-5 LC:

1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKP GKAPKLLIYY
 51 TSRLLESGVPS RFGSGSGTD FTLTISSLQP EDFATYYCQQ GDILPYTFGG
 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNIFY PREAKVQWKV
 151 DNALQSGNSQ ESVTEQDSKD STYLSSTLT LSKADYEKHK VYACEVTHQG
 201 LSSPVTKSFN RGEK (SEQ ID NO:141)

[0176] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-5 LC:

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCCGCAT CCGTAGGCCGA
 51 CCGCGTAACC ATAACATGTA GAGCATCTCA AGATATTTCC AACTATTTGA
 101 ATTGGTACCA AAAAAACCC GGCAAAGCAC CTAAACTCCT CATTACTAT
 5 151 ACATCAAGAC TCCTCTCCGG CGTTCCATCA CGATTCTCAG GCTCCGGCTC
 201 CGGCACAGAT TTCACACTCA CTATTTCCTC CCTCCAACCA GAAGATTTTG
 251 CAACCTATTA CTGTCAACAA GGCATAACAC TCCCATAACAC ATTCGGCGGC
 301 GGCACAAAAG TTGAAATTAA ACGTACGGTG GCTGCACCAT CTGTCTTCAT
 10 351 CTTCCCGCCA TCTGATGAGC AGTTGAAATC TGGAAGTACC TCTGTTGTGT
 401 GCCTGCTGAA TAACTTCTAT CCCAGAGAGG CCAAAGTACA GTGGAAGGTG
 451 GATAACGCCC TCCAATCGGG TAACTCCCAG GAGAGTGTCA CAGAGCAGGA
 501 CAGCAAGGAC AGCACCTACA GCCTCAGCAG CACCCTGACG CTGAGCAAAG
 15 551 CAGACTACGA GAAACACAAA GTCTACGCCT GCGAAGTCAC CCATCAGGGC
 601 CTGAGCTCGC CCGTCACAAA GAGCTTCAAC AGGGGAGAGT GT (SEQ ID
 NO:142)

[0177] Amino acid sequence of the Ab-5 LC including signal peptide:

1 MDMRVPAQLL GLLLLWLRGA RCDIQMTQSP SLSASVGDR VTITCRASQD
 51 ISNYLNWYQQ KPGKAPKLLI YYTSRLLSGV PSRFSGSGSG TDFTLTISL
 101 QPEDFATYYC QQGDTLPYTF GGGTKVEIKR TVAAPSVFIF PPSDEQLKSG
 25 151 TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYLSST
 201 LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC (SEQ ID NO:143)

[0178] Nucleic acid sequence of the Ab-5 LC including signal peptide encoding sequence:

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TACTCTGGCT
 51 CCGAGGTGCC AGATGTGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTCT
 101 CCGCATCCGT AGGCGACCGC GTAACCATAA CATGTAGAGC ATCTCAAGAT
 35 151 ATTTCCAAC TTTGAATTG GTACCAACAA AAACCCGGCA AAGCACCTAA
 201 ACTCCTCATT TACTATACAT CAAGACTCCT CTCCGGCGTT CCATCACGAT
 251 TCTCAGGCTC CGGCTCCGGC ACAGATTTC CACTCACTAT TTCCTCCCTC
 301 CAACCAGAAG ATTTTGCAAC CTATTACTGT CAACAAGGCG ATACACTCCC
 40 351 ATACACATTC GCGGCGGCA CAAAAGTTGA AATTAAACGT ACGGTGGCTG
 401 CACCATCTGT CTTATCTTC CCGCCATCTG ATGAGCAGTT GAAATCTGGA
 451 ACTGCCTCTG TTGTGTGCCT GCTGAATAAC TTCTATCCCA GAGAGGCCAA
 45 501 AGTACAGTGG AAGGTGGATA ACGCCCTCCA ATCGGGTAAC TCCCAGGAGA
 551 GTGTCACAGA GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC
 601 CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA
 651 AGTCACCCAT CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGGG
 50 701 GAGAGTGT (SEQ ID NO:144)

Ab-5 Heavy Chain:

[0179] Amino acid sequence of the mature form (signal peptide removed) of the Ab-5 HC:

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
 51 INPNSGGAGY NQKFKGRVTM TTDSTSTAY MELRSLRSDD TAVYYCARLG
 101 YDDIYDDWYF DVWGQGT T VTSASTKGPS VFPLAPCSRS TSESTAALGC
 151 LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSNFG
 201 TQTYTCNV DH KPSNTKVDKT VERKCCVECP PCPAPPVAGP SVFLFPPKPK
 251 DTL MISRTPE VTCVVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS
 301 TFRVVS VLT V VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGQPREPQV
 351 YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTT PML
 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSV M HEALHNHYTQ KSLSLSPGK (SEQ
 ID NO:145)

[0180] Amino acid sequence of the mature form (signal peptide removed) of the Ab-5 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
 51 INPNSGGAGY NQKFKGRVTM TTDSTSTAY MELRSLRSDD TAVYYCARLG
 101 YDDIYDDWYF DVWGQGT T VTSASTKGPS VFPLAPCSRS TSESTAALGC
 151 LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSNFG
 201 TQTYTCNV DH KPSNTKVDKT VERKCCVECP PCPAPPVAGP SVFLFPPKPK
 251 DTL MISRTPE VTCVVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS
 301 TFRVVS VLT V VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGQPREPQV
 351 YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTT PML
 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSV M HEALHNHYTQ KSLSLSPG (SEQ
 ID NO:392)

[0181] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-5 HC:

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTAAAAAAC CAGGAGCAAG
 51 CGTTAAAGTT TCTTGTAAG CAAGCGGATA TACATTTACA GATTACAACA
 101 TGCATTGGGT AAGACAAGCG CCAGGACAAG GATTGGAATG GATGGGCGAA
 151 ATTAACCCTA ATAGTGGAGG AGCAGGCTAC AATCAAAAAT TCAAAGGGAG
 201 AGTTACAATG ACAACAGACA CAAGCACTTC AACAGCATAT ATGGAAGTGC
 251 GATCACTTAG AAGCGACGAT ACAGCTGTAT ACTATTGCGC ACGACTTGGG
 301 TATGATGATA TATATGATGA CTGGTATTC GATGTTTGGG GCCAGGGAAC
 351 AACAGTTACC GTCTCTAGTG CCTCCACCAA GGGCCCATCG GTCTTCCCCC
 401 TGGCGCCCTG CTCCAGGAGC ACCTCCGAGA GCACAGCGGC CCTGGGCTGC
 451 CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT GGAAGTCAAG
 501 CGCTCTGACC AGCGGCGTGC ACACCTTCCC AGCTGTCCTA CAGTCCTCAG
 551 GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG CAACTTCGGC
 601 ACCCAGACCT ACACCTGCAA CGTAGATCAC AAGCCCAGCA ACACCAAGGT
 651 GGACAAGACA GTTGAGCGCA AATGTTGTGT CGAGTGCCCA CCGTGCCAG
 701 CACCACCTGT GGCAGGACCG TCAGTCTTCC TCTTCCCCC AAAACCAAG

751 GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACGTGCG TGGTGGTGGGA
 801 CGTGAGCCAC GAAGACCCCG AGGTCCAGTT CAACTGGTAC GTGGACGGCG
 851 TGGAGGTGCA TAATGCCAAG ACAAAGCCAC GGGAGGAGCA GTTCAACAGC
 901 ACGTTCCGTG TGGTCAGCGT CCTCACCGTT GTGCACCAGG ACTGGCTGAA
 951 CGGCAAGGAG TACAAGTGCA AGGTCTCCAA CAAAGGCCTC CCAGCCCCCA
 1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGGC AGCCCCGAGA ACCACAGGTG
 1051 TACACCCTGC CCCCATCCCG GGAGGAGATG ACCAAGAACC AGGTCAGCCT
 1101 GACCTGCCTG GTCAAAGGCT TCTACCCAG CGACATCGCC GTGGAGTGGG
 1151 AGAGCAATGG GCAGCCGGAG AACAACTACA AGACCACACC TCCCATGCTG
 1201 GACTCCGACG GCTCCTTCTT CCTCTACAGC AAGCTCACCG TGGACAAGAG
 1251 CAGGTGGCAG CAGGGGAACG TCTTCTCATG CTCCGTGATG CATGAGGCTC
 1301 TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC GGGTAAA (SEQ
 ID NO:146)

[0182] Amino acid sequence of the Ab-5 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASGYTFTD
 51 YNMHWVRQAP GQGLEWMGEI NPNSGGAGYN QKFKGRVTMT TDTSTSTAYM
 101 ELRSLRSDDT AVYYCARLGY DDIYDDWYFD VWGQGTTVTV SSASTKGPSV
 151 FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ
 201 SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVECPP
 251 CPAPPVAGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVQFNWYV
 301 DGVEVHNAKT KPREEQFNST FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP
 351 APIEKTISKI KGQPREPQVY TLPPSREEMT KNQVSLTCLV KGFYPSDIAV
 401 EWESNGQPEN NYKTTTPMLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH
 451 EALHNHYTQK SLSLSPGK (SEQ ID NO:147)

[0183] Nucleic acid sequence of the Ab-5 HC including signal peptide encoding sequence:

1 ATGGA CTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACTCCGAG GTGCAGCTGG TGCAGAGCGG CGCCGAGGTA AAAAAACCAG
 101 GAGCAAGCGT TAAAGTTTCT TGTAAGCAA GCGGATATAC ATTTACAGAT
 151 TACAACATGC ATTTGGGTAAG ACAAGCGCCA GGACAAGGAT TGGAATGGAT
 201 GGGCGAAATT AACCTAATA GTGGAGGAGC AGGCTACAAT CAAAAATTCA
 251 AAGGGAGAGT TACAATGACA ACAGACACAA GCACTTCAAC AGCATATATG
 301 GAACTGCGAT CACTTAGAAG CGACGATACA GCTGTATACT ATTGCGCACG
 351 ACTTGGGTAT GATGATATAT ATGATGACTG GTATTTTCGAT GTTTGGGGCC
 401 AGGGAACAAC AGTTACCGTC TCTAGTGCCT CCACCAAGGG CCCATCGGTC
 451 TTCCCCCTGG CGCCCTGCTC CAGGAGCACC TCCGAGAGCA CAGCGGCCCT
 501 GGGCTGCCTG GTCAAGGACT ACTTCCCCGA ACCGGTGACG GTGTCGTGGA
 551 ACTCAGGCGC TCTGACCAGC GCGGTGCACA CCTTCCCAGC TGTCTACAG
 601 TCCTCAGGAC TCTACTCCCT CAGCAGCGTG GTGACCGTGC CCTCCAGCAA
 651 CTTCGGCACC CAGACCTACA CCTGCAACGT AGATCACAAG CCCAGCAACA
 701 CCAAGGTGGA CAAGACAGTT GAGCGCAAAT GTTGTGTCGA GTGCCACCG
 751 TGCCAGCAC CACCTGTGGC AGGACCGTCA GTCTTCCTCT TCCCCCAA
 801 ACCCAAGGAC ACCCTCATGA TCTCCCGGAC CCCTGAGGTC ACGTGCGTGG
 851 TGGTGGACGT GAGCCACGAA GACCCCGAGG TCCAGTTCAA CTGGTACGTG
 901 GACGGCGTGG AGGTGCATAA TGCCAAGACA AAGCCACGGG AGGAGCAGTT
 951 CAACAGCACG TTCCGTGTGG TCAGCGTCCT CACCGTTGTG CACCAGGACT
 1001 GGCTGAACGG CAAGGAGTAC AAGTGCAAGG TCTCCAACAA AGGCCTCCCA
 1051 GCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGGCAGC CCGAGAACC

 1101 ACAGGTGTAC ACCCTGCCCC CATCCCGGGA GGAGATGACC AAGAACCAGG
 1151 TCAGCCTGAC CTGCCTGGTC AAAGGCTTCT ACCCCAGCGA CATCGCCGTG
 1201 GAGTGGGAGA GCAATGGGCA GCCGGAGAAC AACTACAAGA CCACACCTCC
 1251 CATGCTGGAC TCCGACGGCT CCTTCTTCCT CTACAGCAAG CTCACCGTGG
 1301 ACAAGAGCAG GTGGCAGCAG GGAACGTCT TCTCATGCTC CGTGATGCAT
 1351 GAGGCTCTGC ACAACCACTA CACGCAGAAG AGCCTCTCCC TGTCTCCGGG
 1401 TAAA (SEQ ID NO:148)

Ab-5 Variable domains:

[0184] Ab-5 light chain variable domain amino acid sequence (without signal sequence):

1 DIQMTQSPSS LSASVGDRVIT ITCRASQDISNYLNWYQOKP GKAPKLLIYY
 51 TSREL SGVPS RFGSGSGTD FTLTISSLPQ EDFATYYCQQ GDTLPYTFGG
 101 GTKVEIK (SEQ ID NO:376)

[0185] Ab-5 light chain variable domain DNA sequence (without signal sequence):

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCCGCAT CCGTAGGCGA
 51 CCGCGTAACC ATAACATGTA GAGCATCTCA AGATATTTC AACTATTGTA
 101 ATTGGTACCA AAAAAACCC GGCAAAGCAC CTAAACTCCT CATTACTAT
 151 ACATCAAGAC TCCTCTCCGG CGTTCCATCA CGATTCTCAG GCTCCGGCTC
 201 CGGCACAGAT TTCACACTCA CTATTTCCTC CCTCCAACCA GAAGATTTTG
 251 CAACCTATTA CTGTCAACAA GCGGATACAC TCCCATACAC ATTCGGCGGC
 301 GGCACAAAAG TTGAAATTAA A (SEQ ID NO:377)

EP 2 251 351 B1

[0186] Ab-5 heavy chain variable domain amino acid sequence (without signal sequence):

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
51 INPNSGGAGY NQKFKGRVTM TTDSTSTAY MELRSLRSDD TAVYYCARLG
101 YDDIYDDWYF DVWGQGTTVT VSS (SEQ ID NO:378)

[0187] Ab-5 heavy chain variable domain DNA sequence (without signal sequence):

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTAAAAAAAC CAGGAGCAAG
51 CGTTAAAGTT TCTTGTAAG CAAGCGGATA TACATTTACA GATTACAACA
101 TGCATTGGGT AAGACAAGCG CCAGGACAAG GATTGGAATG GATGGGCGAA
151 ATTAACCCTA ATAGTGGAGG AGCAGGCTAC AATCAAAAAT TCAAAGGGAG
201 AGTTACAATG ACAACAGACA CAAGCACTTC AACAGCATAT ATGGAAGTGC
251 GATCACTTAG AAGCGACGAT ACAGCTGTAT ACTATTGCGC ACGACTTGGG
301 TATGATGATA TATATGATGA CTGGTATTC GATGTTTGGG GCCAGGGAAC
351 AACAGTTACC GTCTCTAGT (SEQ ID NO:379)

[0188] The CDR (complementarity determining region) sequences in the variable region of the heavy chain of Ab-5 are as follows:

CDR-H1: DYNMH (SEQ ID NO:245)
CDR-H2: EINPNSGGAGYNQKFKG (SEQ ID NO:246)
CDR-H3: LGYDDIYDDWYFDV (SEQ ID NO:247)

[0189] The light chain variable region CDR sequences of Ab-5 are:

CDR-L1: RASQDISNYLN (SEQ ID NO:78)
CDR-L2: YTSRLLS (SEQ ID NO:79)
CDR-L3: QQGDTLPYT (SEQ ID NO:80)

Ab-6

[0190] The sequences of the Antibody 6 (also referred to herein as Ab-6) LC and HC are as follows:

Ab-6 Light Chain

[0191] Amino acid sequence of the mature form (signal peptide removed) of the Ab-6 LC:

1 DIQMTQTTSS LSASLGDRVT ISCRASQDIS NYLNWFQQKP DGTLKLLIFY
51 TSRLHSGVPS RFGSGSGTD YSLTISNLEQ EDIATYFCQQ GDTEPYTFGG
101 GTKLEIRRAD AAPTYSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVWKI
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:149)

[0192] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-6 LC:

1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
 51 CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC AATTATTTAA
 101 ACTGGTTTCA GCAGAAACCA GATGGAAGTC TTAAACTCCT GATCTTCTAC
 5 151 ACATCAAGAT TACTCTCAGG AGTTCCATCA AGGTTCAAGT GCAGTGGGTC
 201 TGGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAGCAA GAAGATATTG
 251 CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC GTTCGGGGGG
 301 GGGACCAAGC TGGAAATAAG ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 10 351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
 15 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
 NO:150)

[0193] Amino acid sequence of the Ab-6 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTTSS LSASLGDRVT ISCRASQDIS
 51 NYLWNFQQKP DGTLKLLIFY TSRLHSGVPS RFGSGSGTD YSLTISNLEQ
 101 EDIATYFCQQ GDTPYTFGG GTKLEIRRAD APTVSIFPP SSEQLTSGGA
 25 151 SVVCFLNNFY PKDINVWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:151)

[0194] Nucleic acid sequence of the Ab-6 LC including signal peptide encoding sequence:

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
 51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
 101 CTCTGGGAGA CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC
 35 151 AATTATTTAA ACTGGTTTCA GCAGAAACCA GATGGAAGTC TTAAACTCCT
 201 GATCTTCTAC ACATCAAGAT TACTCTCAGG AGTTCCATCA AGGTTCAAGT
 251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAGCAA
 301 GAAGATATTG CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC
 40 351 GTTCGGGGGG GGGACCAAGC TGGAAATAAG ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
 45 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GTTAG (SEQ ID NO:152)

Ab-6 Heavy Chain:

[0195] Amino acid sequence of the mature form (signal peptide removed) of the Ab-6 HC:

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHVVKQN QGKSLEWIGE
 51 INPNSGGSGY NQKFKGKATL TVDKSSSTAY MELRSLTSED SAVYYCARLV
 101 YDGSYEDWYE DVWGAGTTVT VSSAKTTPPS VYPLAPGSAA QTNSMVTLGC
 151 LVKGYFPEPV TWTWNSGSLG SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
 201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAFAPIEKTISKTK GRPKAPQVYT
 351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTSKS LSHSPGK (SEQ ID
 NO:153)

[0196] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-6 HC:

1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA CACATTCAC TACTACAACA
 101 TGCCTGGGT GAAACAGAAC CAAGGAAAGA GCCTAGAGTG GATAGGAGAA
 151 ATTAATCCTA ACAGTGGTGG TAGTGGCTAC AACCAAAAGT TCAAAGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCTTCCAG CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGTC
 301 TACGATGGCA GCTACGAGGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCCTCAG CCAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAAGTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
 601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCAGGG ATTGTGTTG TAAGCCTTGC ATATGTACAG
 701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCGGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAAGTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
 1001 AAACCATCTC CAAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
 1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
 1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
 1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
 1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
 1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
 1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID
 NO:154)

[0197] Amino acid sequence of the Ab-6 HC including signal peptide:

1 MGWSWTFLEFL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
 51 YNMHIWVKQNQ GKSLEWIGEI NPNSGGSGYN QKFKGKATLT VDKSSSTAYM
 101 ELRSLTSEDS AVYYCARLVY DGSYEDWYFD VWGAGTTVTV SSAKTTPPSV
 5 151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
 201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTQP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 10 351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMITD FFPEDITVEW
 401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
 451 LHNHHTEKSL SHSPGK (SEQ ID NO:155)

[0198] Nucleic acid sequence of the Ab-6 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCAGTAC
 20 151 TACAACATGC ACTGGGTGAA ACAGAACCAA GGAAAGAGCC TAGAGTGGAT
 201 AGGAGAAATT AATCCTAACA GTGGTGGTAG TGGCTACAAC CAAAAGTTCA
 251 AAGGCAAGGC CACATTGACT GTAGACAAGT CTTCCAGCAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 351 ATTGGTCTAC GATGGCAGCT ACGAGGACTG GTACTTCGAT GTCTGGGGCG
 25 401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGA CA GTGACCTGGA
 551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
 30 601 TCTGACCTCT AACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
 35 801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTCACGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 40 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGGAAATG GGCAGCCAGC GGAGAACTAC AAGAACACTC AGCCCATCAT

1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAATG
 50 1401 A (SEQ ID NO:156)

Ab-7

[0199] The sequences of the Antibody 7 (also referred to herein as Ab-7) LC and HC are as follows:

Ab-7 Light Chain:

[0200] Amino acid sequence of the mature form (signal peptide removed) of the Ab-7 LC:

5 1 DIQMTQTTSS LSASLGDRVT ICCRASQVIT NYLYWYQQKP DGTFKLLIYY
 51 TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GDTLPYTFGG
 101 GTKLEIKRAD APTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
 151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:157)

[0201] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-7 LC:

15 1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
 51 CAGAGTCACC ATCTGTTGCA GGGCAAGTCA GGTCATTACC AATTATTTAT
 101 ACTGGTATCA GCAGAAACCA GATGGAACCTT TTAAACTCCT GATCTACTAC
 151 ACATCAAGAT TACTCTCAGG AGTCCCACATCA AGGTTTCAGTG GCAGTGGGTC
 201 TGGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAACAG GAAGATATTG
 251 CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC GTTCGGAGGG
 301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GT (SEQ ID
 NO:158)

[0202] Amino acid sequence of the Ab-7 LC including signal peptide:

35 1 MMSSAQFLGL LLLCFQGTRC DIQMTQTTSS LSASLGDRVT ICCRASQVIT
 51 NYLYWYQQKP DGTFKLLIYY TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ
 101 EDIATYFCQQ GDTLPYTFGG GTKLEIKRAD APTVSIFPP SSEQLTSGGA
 151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
 40 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:159)

[0203] Nucleic acid sequence of the Ab-7 LC including signal peptide encoding sequence:

45 1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
 51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
 101 CTCTGGGAGA CAGAGTCACC ATCTGTTGCA GGGCAAGTCA GGTCATTACC
 151 AATTATTTAT ACTGGTATCA GCAGAAACCA GATGGAACCTT TTAAACTCCT
 50 201 GATCTACTAC ACATCAAGAT TACTCTCAGG AGTCCCACATCA AGGTTTCAGTG
 251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAACAG
 301 GAAGATATTG CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC

351 GTTCGGAGGG GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCAGC
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GT (SEQ ID NO:160)

Ab-7 Heavy Chain:

[0204] Amino acid sequence of the mature form (signal peptide removed) of the Ab-7 HC:

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWMKQN QGKSLEWIGE
 51 INPNSGGAGY NQQFKGKATL TVDKSSRTAY MELRSLTSED SAVYYCARLG
 101 YYGNYEDWYF DYWGAGTTVT VSSAKTTPPS VYPLAPGSAA QTNSMVTLCG
 151 LVKGYFPEPV TVTWNSGSL SSGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
 201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQEQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAAFPA PIEKTISKTK GRPKAPQVYT
 351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID
 NO:161)

[0205] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-7 HC:

1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA CACATTCAC TACTACAACA
 101 TGCAGTGGAT GAAGCAGAAC CAAGGAAAGA GCCTAGAATG GATAGGAGAA
 5 151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGCAGT TCAAAGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAG GACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACGTTGGTA ATTACGAGGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 10 351 CACGGTCACC GTCTCCTCAG CCAAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAAGTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
 15 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
 601 GAGACCGTCA CCTGCAACGT TGCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
 701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 20 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
 25 1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
 1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
 1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
 1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
 30 1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
 1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA

1301 ACCACCATACTGAGAAGAGC CTCTCCCACT CTCCTGGTAA A (SEQ ID
 NO:162)

[0206] Amino acid sequence of the Ab-7 HC including signal peptide:

1 MGWSWTFLL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
 51 YNMHWKQNN GKSLEWIGEI NPNSGGAGYN QQFKGKATLT VDKSSRTAYM
 101 ELRSLTSEDS AVYYCARLGY VGNVEDWYFD VWGAGTTVTV SSAKTPPSV
 151 YPLAPGSAAQ TNSMVTGLCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
 201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
 45 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTPQ REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMITD FFPEDITVEW
 401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
 50 451 LHNHHTKSL SHSPGK (SEQ ID NO:163)

[0207] Nucleic acid sequence of the Ab-7 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGA~~ACTA~~ ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCACTGAC
 5 151 TACAACATGC ACTGGATGAA GCAGAACCAA GGAAAGAGCC TAGAATGGAT
 201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGCAGTTCA
 251 AAGGCAAGGC CACATTGACT GTAGACAAGT CCTCCAGGAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 10 351 ATTGGGCTAC GTTGGTAATT ACGAGGACTG GTACTTCGAT GTCTGGGGCG
 401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 15 551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
 601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGA~~CAA~~ GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
 20 801 GGATGTGCTC ACCATTACTC TGA~~CT~~CCTAA GGTCACGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TG~~T~~AGATGAT
 901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 25 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 30 1201 CAGTGGAATG GGCAGCCAGC GGAGAACTAC AAGAACA~~CTC~~ AGCCCATCAT
 1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCAC~~TCTC~~ CTGGTAAA
 35 (SEQ ID NO:164)

Ab-8

[0208] The sequences of the Antibody 8 (also referred to herein as Ab-8) LC and HC are as follows:

Ab-8 Light Chain:

[0209] Amino acid sequence of the mature form (signal peptide removed) of the Ab-8 LC:

1 DIQMTQTTSS LSASLGDRVS ISCRASQDIS NYLNWYQOKP DGTFKLLIFY
 51 [TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDILPYTFGG
 101 GTKLEIKRAD *AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI*
 151 *DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT*
 201 *STSPIVKSFN RNEC* (SEQ ID NO:165)

[0210] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-8 LC:

1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
 51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
 101 ACTGGTATCA GCAGAAACCA GATGGAACCT TTAAACTCCT TATCTTCTAC
 5 151 ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTTCAGTG GCAGTGGGTC
 201 TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA GAAGATTTTG
 251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
 301 GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 10 351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
 15 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
 NO:166)

[0211] Amino acid sequence of the Ab-8 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTTSS LSASLGDRVS ISCRASQDIS
 51 NYLNWYQQKP DGTFKLLIFY TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ
 101 EDFATYFCQQ GDTLPYTFGG GTKLEIKRAD APTVSIFPP SSEQLTSGGA
 25 151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:167)

[0212] Nucleic acid sequence of the Ab-8 LC including signal peptide encoding sequence:

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
 51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
 101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
 35 151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAACCT TTAAACTCCT
 201 TATCTTCTAC ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTTCAGTG
 251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
 301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
 40 351 TTTCGGAGGG GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
 45 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GTTAG (SEQ ID NO:168)

Ab-8 Heavy Chain:

[0213] Amino acid sequence of the mature form (signal peptide removed) of the Ab-8 HC:

1 EVQLQDSGPE LMKPGASVKM SCKASGYTFT DYNMHWVKQN QGKTLDWIGE
 51 INPNSGGAGY NQKFKGKATL TVDKSSTTAY MELRSLTSED SAVYYCARLG
 101 YDDIYDDWYF DVWGAGTTVT VSSAKTTPPS VYPLAPGSAA QTNMVTLG
 151 LVKGYFPEPV TWTWNSGSL SSVHTFPAVL QSDLYTLSSS VTPSSTWPS
 201 ETVTCNVAHP ASSTKVDDKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAFAPIEKTISKTK GRPKAPQVYT
 351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTTEKS LSHSPGK (SEQ ID
 NO:169)

[0214] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-8 HC:

1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGCAAGG CTCTGGGATA TACATTCAC TACTACAACA
 101 TGCACTGGGT GAAGCAGAAC CAAGGAAAGA CCCTAGACTG GATAGGAGAA
 151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAGT TCAAGGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCTCCAC CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCCTCAG CCAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAAGTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
 601 GAGACCGTCA CCTGCAACGT TGCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCCAGGG ATTGTGGTGT TAAGCCTTGC ATATGTACAG
 701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAGAGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTGTTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAA TGCAGGGTCA ACAGTGACG TTTCCCTGCC CCCATCGAGA
 1001 AAACCATCTC CAAAACCAA GGCAGACCGA AGGCTCCACA GGTGTACACC
 1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
 1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
 1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
 1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
 1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
 1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID
 NO:170)

[0215] Amino acid sequence of the Ab-8 HC including signal peptide:

1 MGWSWTFLL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
 51 YNMHWVKQNN GKTLDWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
 101 ELRLTSEDS AVYYCARLGY DDIYDDWYFD VWGAGTTVTV SSAKTTPPSV
 151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ

201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMITD FFPEDITVEW
 401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
 451 LHNHTEKSL SHSPGK (SEQ ID NO:171)

[0216] Nucleic acid sequence of the Ab-8 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAACGTC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCAGTGAC
 151 TACAACATGC ACTGGGTGAA GCAGAACCAA GGAAAGACCC TAGACTGGAT
 201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA
 251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 351 ATTGGGCTAC GATGATATCT ACGACGACTG GACTTCGAT GTCTGGGGCG
 401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 551 ACTCTGGATC CTTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCTGCAG
 601 TCTGACCTCT AACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCCA
 801 GGATGTGCTC ACCATTACTC TGAATCCTAA GGTCACGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCGCG TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGGAAATG GGCAGCCAGC GGAGAACTAC AAGAACAATC AGCCCATCAT
 1251 GGACAAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCCTCTC CTGGTAAATG
 1401 A (SEQ ID NO:172)

Ab-9

[0217] The sequences of the Antibody 9 (also referred to herein as Ab-9) LC and HC are as follows:

Ab-9 Light Chain:

[0218] Amino acid sequence of the mature form (signal peptide removed) of the Ab-9 LC:

5
1 DIQMTQITSS LSASLGDRVS ISCRASQDIS NYLNWYQQKP DGTFKLLIFY
51 TSRLFSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDTLPYTFGG
101 GTKVEIKRAD APTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVWKI
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:173)

[0219] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-9 LC:

15
1 GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
101 ATTGGTATCA GCAGAAACCA GATGGAACCTT TTAAACTCCT TATCTTCTAC
151 ACATCAAGAT TATTTTCAGG AGTCCCATCA AGGTTCAAGTGC GAGTGGGTC
20
201 TGGAACAGAT TATTCTCTCA CCATTACAA CCTGGAGCAA GAAGATTTTG
251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
301 GGGACCAAGG TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCACCA TCCAGTGAGC AGTTAATATC TGGAGGTGCC TCAGTCGTGT
25
401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
30
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GT (SEQ ID
NO:174)

[0220] Amino acid sequence of the Ab-9 LC including signal peptide:

35
1 MMSSAQFLGL LLLCFQGTRC DIQMTQITSS LSASLGDRVS ISCRASQDIS
51 NYLNWYQQKP DGTFKLLIFY TSRLFSGVPS RFSGSGSGTD YSLTIYNLEQ
101 EDFATYFCQQ GDTLPYTFGG GTKVEIKRAD APTVSIFPP SSEQLTSGGA
151 SVVCFLNNFY PKDINVWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
40
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:175)

[0221] Nucleic acid sequence of the Ab-9 LC including signal peptide encoding sequence:

45

50

55

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
 51 TACCAGATGT GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT
 101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
 5 151 AATTATTTAA ATTGGTATCA GCAGAAACCA GATGGAACCTT TTAAACTCCT
 201 TATCTTCTAC ACATCAAGAT TATTTTCAGG AGTCCCATCA AGGTTCACTG
 251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
 301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
 10 351 TTTCGGAGGG GGGACCAAGG TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
 15 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GT (SEQ ID NO:176)

20 Ab-9 Heavy Chain:

[0222] Amino acid sequence of the mature form (signal peptide removed) of the Ab-9 HC:

25 1 EVQLQQSGPE LMKPGTSVKM SCKASGYTFT DYNMHWVKQT QGKILEWIGE
 51 INPNSGGAGY NQKFKGKATL TVDKSSTTAY MELRSLTSED SAVYYCAKLG
 101 YDDIYDDWYF DVWGAGTTVT VSSAKTTAPS VYPLAPVCGD TTGSSVTLGC
 151 LVKGYFPEPV TLTWNSGSL SSVHTFPALL QSGLYTLSSS VTVTTWPSQT
 201 ITCNVAHPAS STKVDDKIEP RGSPTHKPCP PCPAPNLLGG PSVFIFPPKI
 30 251 KDVLMISLSP MVTCTVVDVS EDDPDVHVSW FVNNVEVHTA QTQTHREDYN

 301 STIRVVSALP IQHQDWMSGK EFKCKVNNKA LPAPIERTIS KPKGPVRAPO
 351 VYVLPPEEE MTKKQVTLTC MITDFMPEDI YVEWTNNGQT ELNYKNTEPV
 401 LDSDGSYFMY SKLRVEKKNW VERNYSYSCSV VHEGLHNHHT TKSFSRTPGK
 (SEQ ID NO:177)

40 [0223] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-9 HC:

1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGACTTC
 51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA TACATTCACT GACTACAACA
 101 TGCACTGGGT GAAGCAGACC CAAGGAAAGA CCCTAGAGTG GATAGGAGAA
 5 151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAAGAAGT TCAAGGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAAATTGGGC
 301 TACGATGATA TCTACGACGA CTGGTATTTT GATGTCTGGG GCGCAGGGAC
 10 351 CACGGTCACC GTCTCCTCAG CCAAAACAAC AGCCCCATCG GTCTATCCAC
 401 TGGCCCCTGT GTGTGGAGAT ACAACTGGCT CCTCGGTGAC TCTAGGATGC
 451 CTGGTCAAGG GTTATTTCCC TGAGCCAGTG ACCTTGACCT GGAAGCTCTGG
 501 ATCCCTGTCC AGTGATGTGC ACACCTTCCC AGCTCTCCTG CAGTCTGGCC
 15 551 TCTACACCTT CAGCAGCTCA GTGACTGTAA CCACCTGGCC CAGCCAGACC
 601 ATCACCTGCA ATGTGGCCCA CCCGGCAAGC AGCACCAAAG TGGACAAGAA
 651 AATTGAGCCC AGAGGGTCCC CAACACATAA ACCCTGTCCT CCATGCCCAG
 701 CTCCTAACCT CTGGGTGGA CCATCCGTCT TCATCTTCCC TCCAAAGATC
 20 751 AAGGATGTAC TCATGATCTC CCTGAGCCCC ATGGTCACGT GTGTGGTGGT
 801 GGATGTGAGC GAGGATGACC CAGATGTCCA TGTCAGCTGG TTCGTGAACA
 851 ACGTGGAAGT ACACACAGCT CAGACACAAA CCCATAGAGA GGATTACAAC
 901 AGTACTATCC GGGTGGTCAG TGCCCTCCCC ATCCAGCACC AGGACTGGAT
 951 GAGTGGCAAG GAGTTCAAAT GCAAGGTCAA CAACAAAGCC CTCCCAGCGC
 25 1001 CCATCGAGAG AACCATCTCA AAACCCAAAG GGCCAGTAAG AGCTCCACAG
 1051 GTATATGTCT TGCCTCCACC AGAAGAAGAG ATGACTAAGA AACAGGTCAC
 1101 TCTGACCTGC ATGATCACAG ACTTCATGCC TGAAGACATT TACGTGGAGT
 1151 GGACCAACAA CGGGCAAACA GAGCTAAACT ACAAGAACAC TGAACCAGTC
 30 1201 CTGGACTCTG ATGGTTCTTA CTTTCATGTAC AGCAAGCTGA GAGTGGAAAA
 1251 GAAGAACTGG GTGGAAAGAA ATAGCTACTC CTGTTCAAGT GTCCACGAGG
 1301 GTCTGCACAA TCACCACACG ACTAAGAGCT TCTCCCGGAC TCCGGGTAAA
 (SEQ ID NO:178)

[0224] Amino acid sequence of the Ab-9 HC including signal peptide:

1 MGWSWIFLFL LSGTAGVLSE VQLQQSGPEL MKPGTSVKMS CKASGYTFTD
 51 YNMHWVKQTQ GKTLEWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
 101 ELRSLTSEDS AVYYCAKLG YDDIYDDWYFD VWGAGTTVTV SSAKTTAPSV
 151 YPLAPVCGDT TGSSVTLGCL VKGYFPEPVT LTWNSGSLSS DVHTFPALLQ
 201 SGLYTLSSSV TVTTWPSQTI TCNVAHPASS TKVDKKEPR GSPTHKPCPP
 251 CPAPNLLGGP SVFIFPPKIK DVLMLSLSPM VTCVVVDVSE DDPDVHVSWF
 45 301 VNNVEVHTAQ TQTHREDYNS TIRVVSALPI QHQDWMSGKE FKCKVNNKAL
 351 PAPIERTISK PKGPVRAPQV YVLPPEEEM TTKQVTLTCM ITDFMPEDIY
 401 VEWTNNGQTE LNYKNTEPVL DSDGSYFMYS KLRVEKKNWV ERNSYSCSVV
 451 HEGLHNHHTT KSFSRTPGK (SEQ ID NO:179)

[0225] Nucleic acid sequence of the Ab-9 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
 55 51 CCTCTCTGAG GTCCAACCTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG

101 GGACTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCACTGAC
 151 TACAACATGC ACTGGGTGAA GCAGACCCAA GGAAAGACCC TAGAGTGGAT
 201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA
 251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAA
 351 ATTGGGCTAC GATGATATCT ACGACGACTG GTATTTTCGAT GTCTGGGGCG
 401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACAACAGC CCCATCGGTC
 451 TATCCACTGG CCCCTGTGTG TGGAGATACA ACTGGCTCCT CGGTGACTCT
 501 AGGATGCCTG GTCAAGGGTT ATTTCCCTGA GCCAGTGACC TTGACCTGGA
 551 ACTCTGGATC CCTGTCCAGT GATGTGCACA CTTCCCAGC TCTCCTGCAG
 601 TCTGGCCTCT ACACCCTCAG CAGCTCAGTG ACTGTAACCA CCTGGCCCAG
 651 CCAGACCATC ACCTGCAATG TGGCCCAACC GGCAAGCAGC ACCAAAGTGG
 701 ACAAGAAAAT TGAGCCCAGA GGGTCCCCAA CACATAAACC CTGTCCTCCA
 751 TGCCCAGCTC CTAACCTCTT GGGTGGACCA TCCGTCTTCA TCTTCCCTCC
 801 AAAGATCAAG GATGTACTCA TGATCTCCCT GAGCCCCATG GTCACGTGTG
 851 TGGTGGTGGA TGTGAGCGAG GATGACCCAG ATGTCCATGT CAGCTGGTTC
 901 GTGAACAACG TGGAAGTACA CACAGCTCAG ACACAAACCC ATAGAGAGGA
 951 TTACAACAGT ACTATCCGGG TGGTCAGTGC CCTCCCCATC CAGCACCAGG
 1001 ACTGGATGAG TGGCAAGGAG TTCAAATGCA AGGTCAACAA CAAAGCCCTC
 1051 CCAGCGCCCA TCGAGAGAAC CATCTCAAAA CCCAAAGGGC CAGTAAGAGC
 1101 TCCACAGGTA TATGTCTTGC CTCCACCAGA AGAAGAGATG ACTAAGAAAC
 1151 AGGTCACTCT GACCTGCATG ATCACAGACT TCATGCCTGA AGACATTAC
 1201 GTGGAGTGGA CCAACAACGG GCAAACAGAG CTAAACTACA AGAACACTGA
 1251 ACCAGTCCTG GACTCTGATG GTTCTTACTT CATGTACAGC AAGCTGAGAG
 1301 TGGAAAAGAA GAACTGGGTG GAAAGAAATA GCTACTCCTG TTCAGTGGTC
 1351 CACGAGGGTC TGCACAATCA CCACACGACT AAGAGCTTCT CCCGGACTCC
 1401 GGGTAAA (SEQ ID NO:180)

Ab-10

[0226] The sequences of the Antibody 10 (also referred to herein as Ab-10) LC and HC are as follows:

Ab-10 Light Chain:

[0227] Amino acid sequence of the mature form (signal peptide removed) of the Ab-10 LC:

1 DIQMTQTTSS LSASLGDRVS ISCRASQDIS NYLNWYQQKP DGTFKLLIFY
 51 TSRLSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDILPYTFGG
 101 GTKLEIKRAD APTVSIFPL SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
 151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:181)

[0228] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-10 LC:

1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
 51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
 101 ACTGGTATCA GCAGAAACCA GATGGAACCTT TTAAACTCCT TATCTTCTAC
 5 151 ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAAGT GCAGTGGGTC
 201 TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA GAAGATTTTG
 251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
 301 GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 10 351 CTTCCCACTA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT

451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
 15 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
 NO:182)

[0229] Amino acid sequence of the Ab-10 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTTSS LSASLGDRVS ISCRASQDIS
 25 51 NYLNWYQQKP DGTFLKLLIFY TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ
 101 EDFATYFCQQ GDTLPYTFGG GTKLEIKRAD APTVSIFPL SSEQLTSGGA
 151 SVVCFLNNFY PKDINVWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:183)

[0230] Nucleic acid sequence of the Ab-10 LC including signal peptide encoding sequence:

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
 35 51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
 101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
 151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAACCTT TTAAACTCCT
 201 TATCTTCTAC ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAAGT
 40 251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
 301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
 351 TTTCGGAGGG GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCCACTA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 45 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 50 701 GTTAG (SEQ ID NO:184)

Ab-10 Heavy Chain:

[0231] Amino acid sequence of the mature form (signal peptide removed) of the Ab-10 HC:

1 EVQLQDSGPE LMKPGASVKM SCKASGYTFT DYNMHVVKQN QGKTLIEWIG
 51 INPNSGGAGY NQKFKGKATL TVDKSSTTAY MELRSLTSED SAVYYCARLG
 101 YDDIYDDWYF DVWGAGTTVT VSSAKTTPPS VYPLAPGSAA QTNSMVTLGC
 151 LVKGYFPEPV TWTWNSGSLG SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
 201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAFAFPA PIEKTISKTK GRPKAPQVYT
 351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID
 NO:185)

[0232] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-10 HC:

1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA TACATTCAC TACTACAACA
 101 TGCAC TGGGT GAAGCAGAAC CAAGGAAAGA CCCTAGAATG GATAGGAGAA
 151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAGT TCAAGGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCCTCAG CAAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAACTAAT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACCTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
 601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
 701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAA TGCAGGGTCA ACAGTGCAGC TTTCCTGCC CCCATCGAGA
 1001 AAACCATCTC CAAAACCAA GGCAGACCGA AGGCTCCACA GGTGTACACC
 1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
 1101 CATGATAACA GACTTCTTCC CTGAAGAAT TACTGTGGAG TGGCAGTGGA
 1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
 1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
 1251 GGAGGCAGGA AATACTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
 1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID
 NO:186)

[0233] Amino acid sequence of the Ab-10 HC including signal peptide:

1 MGWSWTFLL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
 51 YNMHWVKQNN GKTLIEWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
 101 ELRLTSEDS AVYYCARLG YDDIYDDWYFD VWGAGTTVTV SSAKTPPSV
 151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
 201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDDKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTPQ REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMITD FFPEDITVEW
 401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
 451 LHNHTEKSL SHSPGK (SEQ ID NO:187)

[0234] Nucleic acid sequence of the Ab-10 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAACCTG AACAGTCTGG ACCTGAAC TAATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCAGTAC
 151 TACAACATGC ACTGGGTGAA GCAGAACCAA GGAAAGACCC TAGAATGGAT
 201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA
 251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 351 ATTGGGCTAC GATGATATCT ACGACGACTG GTACTTCGAT GTCTGGGGCG
 401 CAGGGACCAC GGTACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA

551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
 601 TCTGACCTCT AACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCC CAAAGCCCCA
 801 GGATGTGCTC ACCATTACTC TGA CTCTCTAA GGTACAGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGGAATG GGCAGCCAGC GGAGAACTAC AAGAACA CTGAGCCATCAT
 1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCCTCTC CTGGTAAATG
 1401 A (SEQ ID NO:188)

Ab-11

[0235] The sequences of the Antibody 11 (also referred to herein as Ab-11) LC and HC are as follows:

Ab-11 Light Chain:

[0236] Amino acid sequence of the mature form (signal peptide removed) of the Ab-11 LC:

1 QIVLSQSPAF LSVSPGDKVT MTCRASSSIS YIHWFQOKPG SSPRSWIYAT
 51 SNLASGVPGR FSGSGSGTSY SLTISRVEAE DAATYYCQW SSDPLTFGAG
 101 TKLELKRA DA APTVSIFPPS SEQLTSGGAS VVCFLNMFYP KDINVKWKID
 151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
 201 TSPIVKSFNR NEC (SEQ ID NO:189)

[0237] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-11 LC:

1 CAAATTGTTTCTCTCCAGTC TCCAGCATTC CTGTCTGTAT CTCCAGGGGA
 51 TAAGGTCACA ATGACTTGCA GGGCCAGCTC AAGTATAAGT TACATACACT
 101 GGTTTCAGCA GAAGCCAGGA TCCTCCCCCA GATCCTGGAT TTATGCCACA
 151 TCCAACCTGG CTTCTGGAGT CCCTGGTCGC TTCAGTGGCA GTGGGTCTGG
 201 GACCTCTTAC TCTCTCACA TCAGCAGAGT GGAGGCTGAG GATGCTGCCA
 251 CTTATTACTG CCAGCAGTGG AGTAGTGACC CACTCACGTT CGGTGCTGGG
 301 ACCAAGCTGG AGCTGAAACG GGCTGATGCT GCACCAACTG TATCCATCTT
 351 CCCACCATCC AGTGAGCAGT TAACATCTGG AGGTGCCTCA GTCGTGTGCT
 401 TCTTGAACAA CTTCTACCCC AAAGACATCA ATGTCAAGTG GAAGATTGAT
 451 GGCAGTGAAC GACAAAATGG CGTCCTGAAC AGTTGGACTG ATCAGGACAG
 501 CAAAGACAGC ACCTACAGCA TGAGCAGCAC CCTCACGTTG ACCAAGGACG
 551 AGTATGAACG ACATAACAGC TATACCTGTG AGGCCACTCA CAAGACATCA
 601 ACTTCACCCA TTGTCAAGAG CTTCAACAGG AATGAGTGTT AG (SEQ ID
 NO:190)

[0238] Amino acid sequence of the Ab-11 LC including signal peptide:

1 MDFQVQIFSF LLISASVIMS RGQIVLSQSP AFLSVSPGDK VTMTCRASSS
 51 ISYIHWFQQK PGSSPRSWIY ATSNLASGVP GRFSGSGSGT SYSLTISRVE
 101 AEDAATYYCQ QWSSDPLTFG AGTKLELKRA DAAPTVSIFP PSSEQLTSGG
 151 ASVVCFLNMF YPKDINVKWK IDGSERQNGV LNSWTDQDSK DSTYSMSSTL
 201 TLTKDEYERH NSYTCEATHK TSTSPIVKSF NRNEC (SEQ ID NO:191)

[0239] Nucleic acid sequence of the Ab-11 LC including signal peptide encoding sequence:

1 ATGGATTTTC AAGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCTTCAGT
 51 CATAATGTCC AGAGGACAAA TTGTTCTCTC CCAGTCTCCA GCATTCCTGT
 101 CTGTATCTCC AGGGGATAAG GTCACAATGA CTTGCAGGGC CAGCTCAAGT
 151 ATAAGTTACA TACACTGGTT TCAGCAGAAG CCAGGATCCT CCCCCAGATC
 201 CTGGATTTAT GCCACATCCA ACCTGGCTTC TGGAGTCCCT GGTCGCTTCA
 251 GTGGCAGTGG GTCTGGGACC TCTTACTCTC TCACAATCAG CAGAGTGGAG
 301 GCTGAGGATG CTGCCACTTA TTA CTGCCAG CAGTGGAGTA GTGACCCACT
 351 CACGTTCCGT GCTGGGACCA AGCTGGAGCT GAAACGGGCT GATGCTGCAC
 401 CAACTGTATC CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
 451 GCCTCAGTCG TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT
 501 CAAGTGGAAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
 551 GGA CTGATCA GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCCTC
 601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
 651 CACTCACAAG ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG
 701 AGTGTTAG (SEQ ID NO:192)

Ab-11 Heavy Chain:

[0240] Amino acid sequence of the mature form (signal peptide removed) of the Ab-11 HC:

1 EVQLQSGAD LVQPGASVKV SCTASGFDIK DYYHWMKQR PDQGLEWIGR
 51 VDPDNGETEF APKFPGKATF TTDTSNTAY LQLRGLTSED TAIYYCGRED
 101 YDGTYTWFY WGQGLTVTS AAKTTPPSVY PLAPGSAAQT NSMVTLGCLV
 151 KGYFPEPVTV TWNSGSLSSG VHTFPAVLQS DLYTLSSSVT VPSSTWPSET
 201 VTCNVAHPAS STKVDKKIVP RDCGCKPCIC TVPEVSSVFI FPPKPKDVLV
 251 ITLTPKVTCV VVDISKDDPE VQFSWFVDDV EVHTAQTPR EEQFNSTFRS
 301 VSELPIMHQD WLNGKEFKCR VNSAAFPAPI EKTISKTKGR PKAPQVYTIP
 351 PPKEQMAKDK VSLTCMITDF FPEDITVEWQ WNGQPAENYK NTQPIMDTDG
 401 SYFIYSKLVN QKSNWEAGNT FTCSVLHEGL HNHHTEKSLS HSPGK (SEQ ID
 NO:193)

[0241] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-11 HC:

1 GAAGTTCAGC TGCAACAGTC TGGGGCAGAC CTTGTGCAGC CAGGGGCCTC
 51 AGTCAAGGTG TCCTGCACAG CTTCTGGCTT CGACATTAAG GACTACTATA
 101 TACACTGGAT GAAACAGAGG CCTGACCAGG GCCTGGAGTG GATTGGAAGG
 151 GTTGATCCTG ACAATGGTGA GACTGAATTT GCCCCGAAGT TCCCGGGCAA
 201 GGCCACTTTT ACAACAGACA CATCCTCCAA CACAGCCTAC CTACAACTCA
 251 GAGGCCTGAC ATCTGAGGAC ACTGCCATCT ATTACTGTGG GAGAGAAGAC
 301 TACGATGGTA CCTACACCTG GTTTCCTTAT TGGGGCCAAG GGA CTCTGGT
 351 CACTGTCTCT GCAGCCAAAA CGACACCCCT ATCTGTCTAT CCACTGGCCC
 401 CTGGATCTGC TGCCCAAACCT AACTCCATGG TGACCCTGGG ATGCCTGGTC
 451 AAGGGCTATT TCCCTGAGCC AGTGACAGTG ACCTGGAACCT CTGGATCCCT
 501 GTCCAGCGGT GTGCACACCT TCCAGCTGT CCTGCAGTCT GACCTCTACA
 551 CTCTGAGCAG CTCAGTGACT GTCCCTCCA GCACCTGGCC CAGCGAGACC

601 GTCACCTGCA ACGTTGCCCA CCCGGCCAGC AGCACCAAGG TGGACAAGAA
 651 AATTGTGCCC AGGGATTGTG GTTGTAAGCC TTGCATATGT ACAGTCCCAG
 701 AAGTATCATC TGTCTTCATC TTCCCCCAA AGCCCAAGGA TGTGCTCACC
 751 ATTACTCTGA CTCCTAAGGT CACGTGTGTT GTGGTAGACA TCAGCAAGGA
 801 TGATCCCGAG GTCCAGTTCA GCTGGTTTGT AGATGATGTG GAGGTGCACA
 851 CAGCTCAGAC GCAACCCCGG GAGGAGCAGT TCAACAGCAC TTTCCGCTCA
 901 GTCAGTGAAC TTCCCATCAT GCACCAGGAC TGGCTCAATG GCAAGGAGTT
 951 CAAATGCAGG GTCAACAGTG CAGCTTTCCC TGCCCCCATC GAGAAAACCA
 1001 TCTCCAAAAC CAAAGGCAGA CCGAAGGCTC CACAGGTGTA CACCATTCCA
 1051 CCTCCAAGG AGCAGATGGC CAAGGATAAA GTCAGTCTGA CCTGCATGAT
 1101 AACAGACTTC TTCCCTGAAG ACATTACTGT GGAGTGGCAG TGGAAATGGGC
 1151 AGCCAGCGGA GAACTACAAG AACACTCAGC CCATCATGGA CACAGATGGC
 1201 TCTTACTTCA TCTACAGCAA GCTCAATGTG CAGAAGAGCA ACTGGGAGGC
 1251 AGGAAATACT TTCACCTGCT CTGTGTTACA TGAGGGCCTG CACAACCACC
 1301 ATACTGAGAA GAGCCTCTCC CACTCTCCTG GTAAATGA (SEQ ID NO:194)

[0242] Amino acid sequence of the Ab-11 HC including signal peptide:

1 MKCSWVIFFL MAVVTGVNSE VQLQQSGADL VQPGASVKVS CTASGFDIKD
 51 YYIHWMKQRP DQGLEWIGRV DPDNGETEFK PKFPGKATFT TDTSSNTAYL
 101 QLRGLTSEDY AIYYCGREDY DGTYTWFYVW GQGTLVTVSA AKTTPPSVYP
 151 LAPGSAAQTN SMVTLGCLVK GYFPEPVTVT WNSGSLSSGV HTFPAVLQSD
 201 LYTLSSSVTV PSSTWPSETV TCNVAHPASS TKVDKKIVPR DCGCKPCICT
 251 VPEVSSVFIF PPKPKDVLTI TLTPKVTCTV VDISKDDPEV QFSWFVDDVE
 301 VHTAQTQPRE EQFNSTFRSV SELPIMHQDW LNGKEFKCRV NSAAFPAPIE
 351 KTISKTKGRP KAPQVYTIPP PKEQMAKDKV SLTCMITDFF PEDITVEWQW
 401 NGQPAENYKN TQPIMDTDGS YFIYSKLVNQ KSNWEAGNTF TCSVLHEGLH
 451 NHHTEKSLSH SPGK (SEQ ID NO:195)

[0243] Nucleic acid sequence of the Ab-11 HC including signal peptide encoding sequence:

1 ATGAAATGCA GCTGGGTCAT CTTCTTCCTG ATGGCAGTGG TTACAGGGGT
 51 CAATTCAGAA GTTCAGCTGC AACAGTCTGG GGCAGACCTT GTGCAGCCAG
 101 GGGCCTCAGT CAAGGTGTCC TGCACAGCTT CTGGCTTCGA CATTAAAGGAC
 5 151 TACTATATAC ACTGGATGAA ACAGAGGCCT GACCAGGGCC TGGAGTGGAT
 201 TGGGAAGGGTT GATCCTGACA ATGGTGAGAC TGAATTTGCC CCGAAGTTCC
 251 CGGGCAAGGC CACTTTTACA ACAGACACAT CCTCCAACAC AGCCTACCTA
 301 CAACTCAGAG GCCTGACATC TGAGGACACT GCCATCTATT ACTGTGGGAG
 10 351 AGAAGACTAC GATGGTACCT ACACCTGGTT TCCTTATTGG GGCCAAGGGA
 401 CTCTGGTCAC TGTCTCTGCA GCCAAAACGA CACCCCCATC TGTCTATCCA
 451 CTGGCCCCTG GATCTGCTGC CCAAATAAC TCCATGGTGA CCCTGGGATG
 501 CCTGGTCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAAGTCTG
 15 551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCCT GCAGTCTGAC
 601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCCTCCAGCA CCTGGCCCCAG
 651 CGAGACCGTC ACCTGCAACG TTGCCACCC GGCCAGCAGC ACCAAGGTGG
 701 ACAAGAAAAT TGTGCCCAGG GATTGTGGTT GTAAGCCTTG CATATGTACA
 751 GTCCCAAGAG TATCATCTGT CTTTCATCTC CCCCCAAGC CCAAGGATGT
 20 801 GCTCAACATT ACTCTGACTC CTAAGGTCAC GTGTGTTGTG GTAGACATCA
 851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTTTGTAGA TGATGTGGAG
 901 GTGCACACAG CTCAGACGCA ACCCCGGGAG GAGCAGTTCA ACAGCACTTT
 951 CCGCTCAGTC AGTGAACCTC CCATCATGCA CCAGGACTGG CTCAATGGCA
 25 1001 AGGAGTTCAA ATGCAGGGTC AACAGTGAG CTTTCCCTGC CCCCATCGAG

1051 AAAACCATCT CCAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
 1101 CATTCCACCT CCAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
 30 1151 GCATGATAAC AGACTTCTTC CCTGAAGACA TTACTGTGGA GTGGCAGTGG
 1201 AATGGGCAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
 1251 AGATGGCTCT TACTTCATCT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
 1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTTACATGA GGGCCTGCAC
 35 1351 AACCACCATA CTGAGAAGAG CCTCTCCAC TCTCCTGGTA AATGA (SEQ ID
 NO:196)

Ab-12

[0244] The sequences of the Antibody 12 (also referred to herein as Ab-12) LC and HC are as follows:

Ab-12 Light Chain:

[0245] Amino acid sequence of the mature form (signal peptide removed) of the Ab-12 LC:

1 DLQMTQTSS LSASLGDRVT ISCRASQDIS NYLNWYQQKP DGTVKLLIFY
 51 TSTLQSGVPS RFSGSGSGTN YSLTITNLEQ DDAATYFCQQ GDEPYTFGG
 101 GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVWKI
 50 151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:197)

[0246] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-12 LC:

1 GATCTCCAGA TGACACAGAC TACTTCCTCC CTGTCTGCCT CTCTGGGAGA
 51 CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC AATTATTTAA
 101 ACTGGTATCA GCAGAAACCA GATGGAAGTCA TTAAGCTCCT GATCTTCTAC
 5 151 ACATCAACAT TACAGTCAGG AGTCCCATCG AGGTTTCAGTG GCAGTGGGTC
 201 TGGAAACAAAT TATTCTCTCA CCATTACCAA CCTGGAGCAA GATGATGCTG
 251 CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC GTTCGGAGGG
 301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 10 351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
 15 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGAÇA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
 NO:198)

[0247] Amino acid sequence of the Ab-12 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGSRC DLQMTQTTSS LSASLGDRVT ISCRASQDIS
 51 NYLNWYQQKP DGTVKLLIFY TSTLQSGVPS RFSGSGSGTN YSLTITNLEQ
 101 DDAATYFCQQ GDTLPYTFGG GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA
 25 151 SVVCFLNNFY PKDINVWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:199)

[0248] Nucleic acid sequence of the Ab-12 LC including signal peptide encoding sequence:

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
 51 TTCCAGATGT GATCTCCAGA TGACACAGAC TACTTCCTCC CTGTCTGCCT
 101 CTCTGGGAGA CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC

151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAAGTCA TTAAGCTCCT
 201 GATCTTCTAC ACATCAACAT TACAGTCAGG AGTCCCATCG AGGTTTCAGTG
 251 GCAGTGGGTC TGGAAACAAAT TATTCTCTCA CCATTACCAA CCTGGAGCAA
 301 GATGATGCTG CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC
 351 GTTCGGAGGG GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 50 701 GTTAG (SEQ ID NO:200)

Ab-12 Heavy Chain:

[0249] Amino acid sequence of the mature form (signal peptide removed) of the Ab-12 HC:

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWMKQN QGKSLEWIGE
 51 INPNSGGSGY NQKFKGKATL TVDKSSSTAY MELRSLTSED SAVYYCARLG
 101 YYGNYEDWYF DVWGAGTTVT VSSAKTTPPS VYPLAPGSAA QTNSMVTLGC
 151 LVKGYFPEPV TWTWNSGSLG SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
 201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAFAPIEKTISKTK GRPKAPQVYT
 351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID
 NO:201)

[0250] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-12 HC:

1 GAGGTCCAGT TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA CACATTCACCT GACTACAACA
 101 TGCCTGGAT GAAGCAGAAC CAAGGAAAGA GCCTAGAGTG GATAGGAGAG
 151 ATTAATCCTA ACAGTGGTGG TTCTGGTTAC AACCAGAAAGT TCAAAGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAG CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACTATGGTA ACTACGAGGA CTGGTATTTC GATGTCTGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCCTCTG CCAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAAGTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCTTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
 601 GAGACCGTCA CCTGCAACGT TGCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
 701 TCCAGAAAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
 1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
 1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
 1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
 1151 ATGGGCAGCC AGCGGAGAAC TACAAGACA CTCAGCCCAT CATGGACACA
 1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
 1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
 1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID
 NO:202)

[0251] Amino acid sequence of the Ab-12 HC including signal peptide:

1 MGWSWTFLL LSGTSGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
 51 YNMHWMKQNN GKSLEWIGEI NPNSGGSGYN QKFKGKATLT VDKSSSTAYM
 101 ELRLTSEDS AVYYCARLGY YGNIEDWYFD VWGAGTTVTV SSAKTTPPSV
 5 151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
 201 SDLYTLSSSV TVPSSTWPSE TVTCNVHPA SSTKVDDKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQQTQ REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 10 351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMITD FFPEDITVEW
 401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
 451 LHNHHTKSL SHSPGK (SEQ ID NO:203)

[0252] Nucleic acid sequence of the Ab-12 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTTCGGGTGT
 51 CCTCTCTGAG GTCCAGTTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCAGTGAC
 20 151 TACAACATGC ACTGGATGAA GCAGAACCAA GGAAAGAGCC TAGAGTGGAT
 201 AGGAGAGATT AATCCTAACA GTGGTGGTTC TGGTTACAAC CAGAAGTTCA
 251 AAGGCAAGGC CACATTGACT GTAGACAAGT CCTCCAGCAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 25 351 ATTGGGCTAC TATGGTAACT ACGAGGACTG GTATTTCGAT GTCTGGGGCG
 401 CAGGGACCAC GGTACCGTC TCCTCTGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 30 551 ACTCTGGATC CTTGTCCAGC GGTGTGCACA CCTTCCAGC TGTCTGCAG
 601 TCTGACCTCT AACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
 35 801 GGATGTGCTC ACCATTACTC TGAATCCTAA GGTACAGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 40 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 45 1201 CAGTGGAAATG GGCAGCCAGC GGAGAACTAC AAGAACAATC AGCCCATCAT
 1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAATG
 50 1401 A (SEQ ID NO:204)

Ab-13

[0253] The sequences of the Antibody 13 (also referred to herein as Ab-13) LC and HC are as follows:

Ab-13 Light Chain:

[0254] Amino acid sequence of the mature form (signal peptide removed) of the Ab-13 LC:

1 QIVLTQSPAI MSASPGEKVT MTCRASSSVT SSYLNWYQQK PGSSPKLWIY
 51 STSNLASGVP ARFSGSGSGT SYSLTISSVE AEDAATYYCQ QYDFFPSTFG
 101 GGTKLEIKRA DAAPTYSIFP PSSEQLTSGG ASVVCFLNNF YPKDINVKWK
 151 IDGSERQNGV LNSWTDQDSK DSTYSMSSTL TLTKDEYERH NSYTCEATHK
 201 TSTSPIVKSF NRNEC (SEQ ID NO:205)

[0255] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-13 LC:

1 CAGATTGTTT TCACCCAGTC TCCAGCAATC ATGTCTGCAT CTCCAGGGGA
 51 GAAGGTCACC ATGACCTGCA GGGCCAGCTC AAGTGTAAC TCCAGTTACT
 101 TGAAGTGGTA CCAGCAGAAG CCAGGATCTT CCCCCAAACT CTGGATTTAT
 151 AGCACATCCA ACCTGGCTTC AGGAGTCCCA GCTCGCTTCA GTGGCAGTGG
 201 GTCTGGGACC TCTTACTCTC TACAATCAG CAGTGTGGAG GCTGAGGATG
 251 CTGCCACTTA TTAAGTCCAG CAGTATGATT TTTTCCCATC GACGTTCCGT
 301 GGAGGCACCA AGCTGGAAAT CAAGCGGGCT GATGCTGCAC CAACTGTATC
 351 CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT GCCTCAGTCG
 401 TGTGCTTCTT GAACAACCTC TACCCCAAAG ACATCAATGT CAAGTGGAAG
 451 ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT GGACTGATCA
 501 GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCTC ACGTTGACCA
 551 AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC CACTCACAAG
 601 ACATCAACTT CACCCATCGT CAAGAGCTTC AACAGGAATG AGTGT (SEQ ID
 NO:206)

[0256] Amino acid sequence of the Ab-13 LC including signal peptide:

1 MDSQVQIFS LLISALVKMS RGQIVLTQSP AIMSASPGEK VTMTCRASSS
 51 VTSSYLNWYQ QKPGSSPKLW IYSTSNLASG VPARFSGSGS GTSYSLTISS
 101 VEAEDAATYY CQYDFFPST FGGGTKLEIK RADAAPTYSI FPPSSEQLTS
 151 GGASVVCFLN NFYPKDINVK WKIDGSERQN GVLNSWTDQD SKDSTYSMS
 201 TLTLTKDEYE RHNSYTCEAT HKTSTSPIVK SFNRNEC (SEQ ID NO:207)

[0257] Nucleic acid sequence of the Ab-13 LC including signal peptide encoding sequence:

1 ATGGATTCTC AAGTGCAGAT TTTAGCTTC CTTCTAATCA GTGCCTTAGT
 51 CAAAATGTCC AGAGGACAGA TTGTTCTCAC CCAGTCTCCA GCAATCATGT
 101 CTGCATCTCC AGGGGAGAAG GTCACCATGA CCTGCAGGGC CAGCTCAAGT
 151 GTAACCTCCA GTTACTTGAA CTGGTACCAG CAGAAGCCAG GATCTTCCCC
 201 CAAACTCTGG ATTTATAGCA CATCCAACCT GGCTTCAGGA GTCCAGCTC
 251 GCTTCAGTGG CAGTGGGTCT GGGACCTCTT ACTCTCTCAC AATCAGCAGT
 301 GTGGAGGCTG AGGATGCTGC CACTTATTAC TGCCAGCAGT ATGATTTTTT
 351 CCCATCGACG TTCGGTGGAG GCACCAAGCT GGAAATCAAG CGGGCTGATG
 401 CTGCACCAAC TGTATCCATC TTCCACCAT CCAGTGAGCA GTTAACATCT
 451 GGAGGTGCCT CAGTCGTGTG CTTCTTGAAC AACTTCTACC CCAAAGACAT
 501 CAATGTCAAG TGGAAGATTG ATGGCAGTGA ACGACAAAAT GGCGTCCTGA

551 ACAGTTGGAC TGATCAGGAC AGCAAAGACA GCACCTACAG CATGAGCAGC
 601 ACCCTCACGT TGACCAAGGA CGAGTATGAA CGACATAACA GCTATACCTG
 651 TGAGGCCACT CACAAGACAT CAACTTCACC CATCGTCAAG AGCTTCAACA
 701 GGAATGAGTG T (SEQ ID NO:208)

Ab-13 Heavy Chain:

[0258] Amino acid sequence of the mature form (signal peptide removed) of the Ab-13 HC:

1 EVQLQQSGPE LVKPGASVKM SCKASGYTFT DYYMNWVKQS HGESLEWIGD
 51 INPYNDDTTY NHKFKGKATL TVDKSSNTAY MQLNSLTSED SAVYYCARET
 101 AVITTNAMDY WGQGTSVTVS SAKTTPPSVY PLAPGSAAQT NSMVTLGCLV
 151 KGYFPEPVTV TWNSGSLSSG VHTFPAVLQS DLYTLSSSVT VPSSTWPSET
 201 VTCNVAHPAS STKVDDKIVP RDCGCKPCIC TVPEVSSVFI FPPKPKDVLV
 251 ITLTPKVTCV VVDISKDDPE VQFSWFVDDV EVHTAQTPR EEQFNSTFRS
 301 VSELPIMHQD WLNGKEFKCR VNSAAFPAPI EKTISKTKGR PKAPQVYTIP
 351 PPKEQMAKDK VSLTCMITDF FPEDITVEWQ WNGQPAENYK NTQPIMDTDG
 401 SYFIYSKLVN QKSNWEAGNT FTCSVLHEGL HNHHTEKSLS HSPGK (SEQ ID
 NO:209)

[0259] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-13 HC:

1 GAGGTCCAGC TGCAACAATC TGGACCTGAG CTGGTGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGTAAGG CTTCTGGATA CACATTCAC TACTACTACA
 101 TGAAGTGGGT GAAGCAGAGC CATGGAGAGA GCCTTGAGTG GATTGGAGAT
 5 151 ATTAATCCTT ACAACGATGA TACTACCTAC AACCACAAGT TCAAGGGCAA
 201 GGCCACATTG ACTGTAGACA AATCCTCCAA CACAGCCTAC ATGCAGCTCA
 251 ACAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGAGAGACG
 301 GCCGTTATTA CTACGAATGC TATGGACTAC TGGGGTCAAG GAACCTCAGT
 10 351 CACCGTCTCC TCAGCCAAAA CGACACCCCC ATCTGTCTAT CCACTGGCCC
 401 CTGGATCTGC TGCCCAAAC TAACTCCATGG TGACCCTGGG ATGCCTGGTC
 451 AAGGGCTATT TCCCTGAGCC AGTGACAGTG ACCTGGAAC CTGGATCCCT
 501 GTCCAGCGGT GTGCAACCT TCCCAGCTGT CCTGCAGTCT GACCTCTACA
 551 CTCTGAGCAG CTCAGTGA CTGCCCCCTCCA GCACCTGGCC CAGCGAGACC
 15 601 GTCACCTGCA ACGTTGCCCA CCCGGCCAGC AGCACCAAGG TGGACAAGAA
 651 AATTGTGCC AGGGATTGTG GTTGTAAGCC TTGCATATGT ACAGTCCCAG
 701 AAGTATCATC TGTCTTCATC TTCCCCCAA AGCCCAAGGA TGTGCTCACC
 751 ATTACTCTGA CTCCTAAGGT CACGTGTGTT GTGGTAGACA TCAGCAAGGA
 20 801 TGATCCCGAG GTCCAGTTCA GCTGGTTTGT AGATGATGTG GAGGTGCACA
 851 CAGCTCAGAC GCAACCCCGG GAGGAGCAGT TCAACAGCAC TTCCGCTCA
 901 GTCAGTGAAC TTCCCATCAT GCACCAGGAC TGGCTCAATG GCAAGGAGTT
 951 CAAATGCAGG GTCAACAGTG CAGCTTTCCC TGCCCCCATC GAGAAAACCA
 25 1001 TCTCCAAAAC CAAAGGCAGA CCGAAGGCTC CACAGGTGTA CACCATTCCA
 1051 CCTCCCAAGG AGCAGATGGC CAAGGATAAA GTCAGTCTGA CCTGCATGAT
 1101 AACAGACTTC TTCCCTGAAG ACATTACTGT GGAGTGGCAG TGAATGGGC
 1151 AGCCAGCGGA GAACTACAAG AACACTCAGC CCATCATGGA CACAGATGGC
 30 1201 TCTTACTTCA TCTACAGCAA GCTCAATGTG CAGAAGAGCA ACTGGGAGGC
 1251 AGGAAATACT TTCACCTGCT CTGTGTTACA TGAGGGCCTG CACAACCACC
 1301 ATACTGAGAA GAGCCTCTCC CACTCTCCTG GTAAA (SEQ ID NO:210)

[0260] Amino acid sequence of the Ab-13 HC including signal peptide:

1 MGWNWIFLFL LSGTAGVYSE VQLQQSGPEL VKPGASVKMS CKASGYTFTD
 51 YYMNWVKQSH GESLEWIGDI NPYND DTTYN HKFKGKATLT VDKSSNTAYM
 101 QLNSLTSEDS AVYYCARETA VITTNAMDYW GQGTSTVTVSS AKTTPPSVYP
 40 151 LAPGSAAQTN SMVTLGCLVK GYFPEPVTVT WNSGSLSSGV HTFPAVLQSD
 201 LYTLSSSVTV PSSTWPSETV TCNVAHPASS TKVDKKIVPR DCGCKPCICT
 251 VPEVSSVFIF PPKPKDVLTI TLTPKVTCVV VDISKDDPEV QFSWFVDDVE
 301 VHTAQTQPRE EQFNSTFRSV SELPIMHQDW LNGKEFKCRV NSAAFPAPIE
 45 351 KTISKTKGRP KAPQVYTIPP PKEQMAKDKV SLTCMITDFF PEDITVEWQW
 401 NGQPAENYKN TQPIMDTDGS YFIYSKLVNQ KSNWEAGNTF TCSVLHEGLH
 451 NHHTEKSLSH SPGK (SEQ ID NO:211)

[0261] Nucleic acid sequence of the Ab-13 HC including signal peptide encoding sequence:

1 ATGGGATGGA ACTGGATCTT TCTCTTCCTC TTGTCAGGAA CTGCAGGTGT
 51 CTACTCTGAG GTCCAGCTGC AACAATCTGG ACCTGAGCTG GTGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGTAAGGCTT CTGGATACAC ATTCAGTGAC
 5 151 TACTACATGA ACTGGGTGAA GCAGAGCCAT GGAGAGAGCC TTGAGTGGAT
 201 TGGAGATATT AATCCTTACA ACGATGATAC TACCTACAAC CACAAGTTCA
 251 AGGGCAAGGC CACATTGACT GTAGACAAAT CCTCCAACAC AGCCTACATG
 301 CAGCTCAACA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 10 351 AGAGACGGCC GTTATTACTA CGAATGCTAT GGACTACTGG GGTCAAGGAA
 401 CCTCAGTCAC CGTCTCCTCA GCCAAAACGA CACCCCCATC TGTCTATCCA
 451 CTGGCCCCTG GATCTGCTGC CCAAATAAC TCCATGGTGA CCCTGGGATG
 501 CCTGGTCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAACTCTG
 15 551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCCT GCAGTCTGAC
 601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCCTCCAGCA CCTGGCCCAG
 651 CGAGACCGTC ACCTGCAACG TTGCCACCC GGCCAGCAGC ACCAAGGTGG
 701 ACAAGAAAAT TGTGCCCAGG GATTGTGGTT GTAAGCCTTG CATATGTACA
 751 GTCCCAGAAG TATCATCTGT CTTTCATCTC CCCCCAAAGC CCAAGGATGT
 20 801 GCTCACCATT ACTCTGACTC CTAAGGTCAC GTGTGTTGTG GTAGACATCA
 851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTTTGTAGA TGATGTGGAG
 901 GTGCACACAG CTCAGACGCA ACCCCGGGAG GAGCAGTTCA ACAGCACTTT
 951 CCGCTCAGTC AGTGAACCTC CCATCATGCA CCAGGACTGG CTCAATGGCA
 25 1001 AGGAGTTCAA ATGCAGGGTC AACAGTGCAG CTTTCCCTGC CCCCATCGAG
 1051 AAAACCATCT CCAAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
 1101 CATTCCACCT CCCAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
 1151 GCATGATAAC AGACTTCTTC CCTGAAGACA TTAAGTGTGA GTGGCAGTGG
 30 1201 AATGGGCAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
 1251 AGATGGCTCT TACTTCATCT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
 1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTTACATGA GGGCCTGCAC
 1351 AACCACCATA CTGAGAAGAG CCTCTCCAC TCTCCTGGTA AA (SEQ ID
 35 NO:212)

[0262] Ab-13 was humanized to generate Ab-14.

[0263] The sequences of the Antibody 14 (also referred to herein as Ab-14) LC and HC are as follows:

40 Ab-14 Light Chain:

[0264] Amino acid sequence of the mature form (signal peptide removed) of the Ab-14 LC:

1 DIQLTQSPSF LSASVGDRVIT ITCRASSSVT SSYLNWYQQK PGKAPKLLIY
 51 STSNLASGVP SRFSGSGSGT EFTLTISLQ PEDFATYYCQ QYDEFPSTFG
 101 GGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK
 151 VDNALQSGNS QESVTEQDSK DSTYLSSTL TLSKADYEKH KVVACEVTHQ
 50 201 GLSSPVTKSF NRGEC (SEQ ID NO:213)

[0265] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-14 LC:

1 GACATCCAGC TGACCCAGAG CCCCAGCTTC CTTTCCGCAT CCGTTGGTGA
 51 CCGAGTAACA ATCACATGCC GCGCCTCATC TTCAGTTACA TCTTCTTATC
 101 TTAATTGGTA TCAACAAAAA CCAGGAAAAG CACCTAAACT TCTTATATAC
 151 TCTACATCTA ATCTCGCATC AGGAGTTCCC TCTCGATTTT CAGGATCTGG
 201 ATCAGGCACA GAATTTACAC TTACTATATC ATCACTCCAA CCAGAAGACT
 251 TCGCCACTTA TTACTGCCAA CAATACGATT TTTTCCAAG CACATTCGGA
 301 GGAGGTACAA AAGTAGAAAT CAAGCGTACG GTGGCTGCAC CATCTGTCTT
 351 CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAACT GCCTCTGTTG
 401 TGTGCCTGCT GAATAACTTC TATCCCAGAG AGGCCAAAGT ACAGTGGAAG
 451 GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG TCACAGAGCA
 501 GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCTG ACGCTGAGCA
 551 AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT CACCCATCAG
 601 GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG AGTGT (SEQ ID
 NO:214)

[0266] Amino acid sequence of the Ab-14 LC including signal peptide:

1 MDMRVPAQLL GLLLLWLPGA RCDIQLTQSP SFLSASVGDR VTITCRASSS
 51 VTSSYLNWYQ QKPGKAPKLL IYSTSNLASG VPSRFSGSGS GTEFTLTSS
 101 LQPEDFATYY CQQYDFFPST FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS
 151 GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS
 201 TLTLKADYE KHKVYACEVT HQGLSPVTK SFNRGEC (SEQ ID NO:215)

[0267] Nucleic acid sequence of the Ab-14 LC including signal peptide encoding sequence:

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TACTCTGGCT
 51 CCCAGGTGCC AGATGTGACA TCCAGCTGAC CCAGAGCCCC AGCTTCCTTT
 101 CCGCATCCGT TGGTGACCGA GTAACAATCA CATGCCGCGC CTCATCTTCA
 151 GTTACATCTT CTTATCTTAA TTGGTATCAA CAAAAACCAG GAAAAGCACC
 201 TAAACTTCTT ATATACTCTA CATCTAATCT CGCATCAGGA GTTCCCTCTC
 251 GATTTTCAGG ATCTGGATCA GGCACAGAAT TTACACTTAC TATATCATCA
 301 CTCCAACCAG AAGACTTCGC CACTTATTAC TGCCAACAAT ACGATTTTTT
 351 TCCAAGCACA TTCGGAGGAG GTACAAAAGT AGAAATCAAG CGTACGGTGG
 401 CTGCACCATC TGTCTTCATC TTCCCGCCAT CTGATGAGCA GTTGAAATCT
 451 GGAAGTGCCT CTGTTGTGTG CCTGCTGAAT AACTTCTATC CCAGAGAGGC
 501 CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCCAGG
 551 AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC
 601 ACCCTGACGC TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG
 651 CGAAGTCACC CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA
 701 GGGGAGAGTG T (SEQ ID NO:216)

Ab-14 Heavy Chain:

[0268] Amino acid sequence of the mature form (signal peptide removed) of the Ab-14 HC:

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYYMNWVRQA PGQRLEWMGD
 51 INPYNDDTTY NHKEKGRVTI TRDTSASTAY MELSSLRSED TAVYYCARET
 101 AVITTNAMDY WGQGTTVTVS **SASTKGPSVF PLAPCSRSTS ESTAALGCLV**
 151 **KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ**
 201 **TYTCNVDHKP SNTKVDKTV E RKCCVECPPC PAPPVAGPSV FLFPPKPKDT**
 251 **LMISRTPEVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF**
 301 **RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT**
 351 **LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPMLDS**
 401 **DGSFFLYSKL TVDKSRWQQG NVFSCSV MHE ALHNHYTQKS LSLSPGK** (SEQ ID
 NO:217)

[0269] Amino acid sequence of the mature form (signal peptide removed) of the Ab-14 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYYMNWVRQA PGQRLEWMGD
 51 INPYNDDTTY ~~NHKEKGRVTI~~ TRDTSASTAY MELSSLRSED TAVYYCARET
 101 AVITTNAMDY WGQGTTVTVS **SASTKGPSVF PLAPCSRSTS ESTAALGCLV**
 151 **KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ**
 201 **TYTCNVDHKP SNTKVDKTV E RKCCVECPPC PAPPVAGPSV FLFPPKPKDT**
 251 **LMISRTPEVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF**
 301 **RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT**
 351 **LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPMLDS**
 401 **DGSFFLYSKL TVDKSRWQQG NVFSCSV MHE ALHNHYTQKS LSLSPG** (SEQ ID
 NO:393)

[0270] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-14 HC:

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTCAAGAAAC CTGGAGCAAG
 51 CGTAAAGGTT AGTTGCAAAG CATCTGGATA CACATTTACC GACTACTACA
 101 TGAATTGGGT ACGACAAGCC CCTGGACAAA GACTTGAATG GATGGGAGAC
 151 ATTAACCCTT ATAACGACGA CACTACATAC AATCATAAAT TTAAAGGAAG
 201 AGTTACAATT ACAAGAGATA CATCCGCATC AACCGCCTAT ATGGAACTTT
 251 CCTCATTGAG ATCTGAAGAC ACTGCTGTTT ATTACTGTGC AAGAGAAACT
 301 GCCGTTATTA CTACTAACGC TATGGATTAC TGGGGTCAAG GAACCACTGT
 351 TACCGTCTCT AGTGCCTCCA CCAAGGGCCC ATCGGTCTTC CCCCTGGCGC
 401 CCTGCTCCAG GAGCACCTCC GAGAGCACAG CGGCCCTGGG CTGCCTGGTC
 451 AAGGACTACT TCCCCGAACC GGTGACGGTG TCGTGGAAC T CAGGCGCTCT
 501 GACCAGCGGC GTGCACACCT TCCAGCTGT CCTACAGTCC TCAGGACTCT
 551 ACTCCCTCAG CAGCGTGGTG ACCGTGCCCT CCAGCAACTT CGGCACCCAG
 601 ACCTACACCT GCAACGTAGA TCACAAGCCC AGCAACACCA AGGTGGACAA
 651 GACAGTTGAG CGCAAATGTT GTGTCGAGTG CCCACCGTGC CCAGCACCAC
 701 CTGTGGCAGG ACCGTCAGTC TTCCTCTTCC CCCAAAACC CAAGGACACC
 751 CTCATGATCT CCCGGACCCC TGAGGTCACG TCGGTGGTGG TGGACGTGAG
 801 CCACGAAGAC CCCGAGGTCC AGTTCAACTG GTACGTGGAC GGCGTGGAGG
 851 TGCATAATGC CAAGACAAAG CCACGGGAGG AGCAGTTCAA CAGCACGTTC
 901 CGTGTGGTCA GCGTCTCAC CGTTGTGCAC CAGGACTGGC TGAACGGCAA
 951 GGAGTACAAG TGCAAGGTCT CCAACAAAGG CCTCCCAGCC CCCATCGAGA
 1001 AAACCATCTC CAAAACCAA GGGCAGCCCC GAGAACCACA GGTGTACACC

1051 CTGCCCCCAT CCCGGGAGGA GATGACCAAG AACCAGGTCA GCCTGACCTG
 1101 CCTGGTCAAA GGCTTCTACC CCAGCGACAT CGCCGTGGAG TGGGAGAGCA
 1151 ATGGGCAGCC GGAGAACAAC TACAAGACCA CACCTCCCAT GCTGGACTCC
 1201 GACGGCTCCT TCTTCCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG
 1251 GCAGCAGGGG AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA
 1301 ACCACTACAC GCAGAAGAGC CTCTCCCTGT CTCCGGGTAA A (SEQ ID
 NO:218)

[0271] Amino acid sequence of the Ab-14 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASGYTFTD
 51 YYMNWVRQAP GQRLEWMGDI NPYNDDTTYN HKFKGRVTIT RDTASTAYM
 101 ELSSLRSEDV AVYYCARETA VITTNAMDYW GQGTTVTVSS ASTKGPSVFP
 151 LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
 201 GLYSLSSVVT VPSSNFGTQT YTCNVDPKPS NTKVDKTVR KCCVECPPEP
 251 APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG
 301 VEVHNAKTKP REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNGKLPAP
 351 IEKTIKTKG QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDIAVEW
 401 ESNGQPENNY KTTTPMLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA
 451 LHNHYTQKSL SLSPGK (SEQ ID NO:219)

[0272] Nucleic acid sequence of the Ab-14 HC including signal peptide encoding sequence:

1 ATGGA CTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACTCCGAG GTGCAGCTGG TGCAGAGCGG CGCCGAGGTC AAGAAACCTG
 101 GAGCAAGCGT AAAGGTTAGT TGCAAAGCAT CTGGATACAC ATTTACCGAC
 151 TACTAATGA ATTGGGTACG ACAAGCCCCT GGACAAAGAC TTGAATGGAT
 201 GGGAGACATT AACCCCTATA ACGACGACAC TACATACAAT CATAAATTTA
 251 AAGGAAGAGT TACAATTACA AGAGATACAT CCGCATCAAC CGCCTATATG
 301 GAACTTTCCT CATTGAGATC TGAAGACACT GCTGTTTATT ACTGTGCAAG
 351 AGAAACTGCC GTTATTACTA CTAACGCTAT GGATTACTGG GGTCAAGGAA
 401 CCACTGTTAC CGTCTCTAGT GCCTCCACCA AGGGCCCATC GGTCTTCCCC
 451 CTGGCGCCCT GCTCCAGGAG CACCTCCGAG AGCACAGCGG CCCTGGGCTG
 501 CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG TGAAGTCAAG
 551 GCGCTCTGAC CAGCGGCGTG CACACCTTCC CAGCTGTCCT ACAGTCCTCA
 601 GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG
 651 CACCCAGACC TACACCTGCA ACGTAGATCA CAAGCCCAGC AACACCAAGG
 701 TGGACAAGAC AGTTGAGCGC AAATGTTGTG TCGAGTGCCC ACCGTGCCCCA
 751 GCACCACCTG TGGCAGGACC GTCAGTCTTC CTCTTCCCCC CAAAACCCAA
 801 GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACGTGC GTGGTGGTGG
 851 ACGTGAGCCA CGAAGACCCC GAGGTCCAGT TCAACTGGTA CGTGGACGGC
 901 GTGGAGGTGC ATAATGCCAA GACAAAGCCA CGGGAGGAGC AGTTCAACAG
 951 CACGTTCCGT GTGGTCAGCG TCCTCACCGT TGTGCACCAG GACTGGCTGA
 1001 ACGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAGGCCT CCCAGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGG CAGCCCCGAG AACCACAGGT
 1101 GTACACCCTG CCCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTCAGCC
 1151 TGACCTGCCT GGTCAAAGGC TTCTACCCCA GCGACATCGC CGTGGAGTGG
 1201 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACAC CTCCCATGCT
 1251 GGA CTCCGAC GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA
 1301 GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT
 1351 CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAA

(SEQ ID NO:220)

[0273] The CDR sequences in the variable region of the heavy chain of Ab-14 are:

CDR-H1: DYYMN (SEQ ID NO:296)
 CDR-H2: DINPYNDTTYNHKFKG (SEQ ID NO:297)
 CDR-H3: ETA VITINAMD (SEQ ID NO:298)

[0274] The light chain variable region CDR sequences of Ab-14 are:

CDR-L1: RASSVTSSYLN (SEQ ID NO:284)
 CDR-L2: STSNLAS (SEQ ID NO:285)
 CDR-L3: QQYDFFPST (SEQ ID NO:286)

Ab-14 Variable domains:

[0275] Ab-14 light chain variable domain amino acid sequence (without signal sequence):

1 DIQLTQSPSF LSASVGDRVT ITCRASSSVT SSYLEN~~WYQ~~QK PGKAPKLLIY
 51 STSNLASGVP SRFSGSGSGT EFTLTISLQ PEDFATYYCQ QYDFFPSTFG
 101 GGTKVEIK (SEQ ID NO:380)

[0276] Ab-14 light chain variable domain DNA sequence (without signal sequence):

1 GACATCCAGC TGACCCAGAG CCCAGCTTC CTTTCCGCAT CCGTTGGTGA
 51 CCGAGTAACA ATCACATGCC GCGCCTCATC TTCAGTTACA TCTTCTTATC
 101 TTAATTGGTA TCAACAAAAA CCAGGAAAAG CACCTAAACT TCTTATATAC
 151 TCTACATCTA ATCTCGCATC AGGAGTTCCC TCTCGATTTT CAGGATCTGG
 201 ATCAGGCACA GAATTTACAC TTACTATATC ATCACTCCAA CCAGAAGACT
 251 TCGCCACTTA TTACTGCCAA CAATACGATT TTTTCCAAG CACATTCGGA
 301 GGAGGTACAA AAGTAGAAAT CAAG (SEQ ID NO:381)

[0277] Ab-14 heavy chain variable domain amino acid sequence (without signal sequence):

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DY~~YMN~~WVRQA PGQRLEWMGD
 51 INPYNDDTTY NHKFKGRVTI TRDTSASTAY MELSSLRSED TAVYYCARET
 101 AVITTNAMDY WGQGTTVTVS S (SEQ ID NO:382)

[0278] Ab-14 heavy chain variable domain DNA sequence (without signal sequence):

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTCAAGAAAC CTGGAGCAAG
 51 CGTAAAGGTT AGTTGCAAAG CATCTGGATA CACATTTACC GACTACTACA
 101 TGAATTGGGT ACGACAAGCC CCTGGACAAA GACTTGAATG GATGGGAGAC
 151 ATTAACCCTT ATAACGACGA CACTACATAC AATCATAAAT TTAAAGGAAG
 201 AGTTACAATT ACAAGAGATA CATCCGCATC AACCGCCTAT ATGGAACCTT
 251 CCTCATTGAG ATCTGAAGAC ACTGCTGTTT ATTACTGTGC AAGAGAAACT

 301 GCCGTTATTA CTACTAACGC TATGGATTAC TGGGGTCAAG GAACCACTGT
 351 TACCGTCTCT AGT (SEQ ID NO:383)

[0279] Ab-3 was humanized to generate Ab-15.

Ab-15

[0280] The sequences of the Antibody 15 (also referred to herein as Ab-15) LC and HC are as follows:

Ab-15 Light Chain:

[0281] Amino acid sequence of the mature form (signal peptide removed) of the Ab-15 LC:

1 DIQMTQSPSS LSASVGDRVT ITC~~SV~~SSTIS SNHLHW~~FQ~~QK PGKAPKSLIY
 51 GTSN~~LA~~SGVP SRFSGSGSGT DFTLTISLQ PEDFATYYCQ QWSSYPLTFG
 101 GGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK
 151 VDNALQSGNS QESVTEQDSK DSTYLSSTL TLSKADYEKH KVYACEVTHQ
 201 GLSSPVTKSF NRGEC (SEQ ID NO:221)

[0282] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-15 LC:

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCAGCAT CCGTAGGCGA
 5 51 TAGAGTTACA ATAACATGCA GCGTATCATC AACTATATCA TCAAATCATC
 101 TTCATTGGTT CCAACAGAAA CCCGGCAAAG CACCTAAATC ACTTATATAC
 151 GGCACATCAA ATCTCGCATC AGGCGTTCCT TCAAGATTTT CAGGCTCTGG
 201 CTCAGGCACC GACTTTACTC TTACAATATC CTCCCTCCAA CCCGAAGACT
 251 TCGCAACCTA TTA CTGTCAA CAATGGTCCT CATATCCACT CACATTGTC
 10 301 GCGGCGACAA AAGTAGAAAT TAAACGTACG GTGGCTGCAC CATCTGTCTT
 351 CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAAGT GCCTCTGTTG
 401 TGTGCCTGCT GAATAACTTC TATCCAGAG AGGCCAAAGT ACAGTGGAAG
 451 GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG TCACAGAGCA
 15 501 GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCCTG ACGCTGAGCA
 551 AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT CACCCATCAG
 601 GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG AGTGT (SEQ ID
 NO:222)

[0283] Amino acid sequence of the Ab-15 LC including signal peptide:

1 MDMRVPAQLL GLLLLWL RGA RCDIQMTQSP SLSASVGDR VTITCSVSST
 25 51 ISSNHLHW FQ QKPGKAPKSL IYGTSNLASG VPSRFSGSGS GTDFTLTSS
 101 LPEDFATYY CQWSSYPLT FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS
 151 GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS
 201 TLTLKADYE KHKVYACEVT HQGLSPVTK SFNRGEC (SEQ ID NO:223)

[0284] Nucleic acid sequence of the Ab-15 LC including signal peptide encoding sequence:

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TACTCTGGCT
 35 51 CCGAGGTGCC AGATGTGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTCT

101 CAGCATCCGT AGGCGATAGA GTTACAATAA CATGCAGCGT ATCATCAACT
 151 ATATCATCAA ATCATCTTCA TTGGTTCCAA CAGAAACCCG GCAAAGCACC
 40 201 TAAATCACTT ATATACGGCA CATCAAATCT CGCATCAGGC GTTCCTTCAA
 251 GATTTTCAGG CTCTGGCTCA GGCACCGACT TTA CTCTTAC AATATCCTCC
 301 CTCCAACCCG AAGACTTCGC AACCTATTAC TGTCAACAAT GGTCCTCATA
 351 TCCACTCACA TTTGGCGGCG GCACAAAAGT AGAAATTAAG CGTACGGTGG
 40 401 CTGCACCATC TGTCTTCATC TTCCCGCCAT CTGATGAGCA GTTGAAATCT
 451 GGAAGTGCCT CTGTTGTGTG CCTGCTGAAT AACTTCTATC CCAGAGAGGC
 501 CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCAGG
 551 AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC
 601 ACCCTGACGC TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG
 50 651 CGAAGTCACC CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA
 701 GGGGAGAGTG T (SEQ ID NO:224)

A-15 Heavy Chain

[0285] Amino acid sequence of the mature form (signal peptide removed) of Ab-15 HC.

1 EVQLVQSGAE VKKPGASVKV SCKASDFNIK ~~DFYLHWVRQA~~ PGQGLEWIGR
 51 IDPENGDTLY DPKFQDKVTM TTDSTSTAY MELRSLRSDD TAVYYCAREA
 101 DYFHDGTSYW YFDVWGRGTL VTVSSASTKG PSVFPLAPCS RSTSESTAAL
 151 GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSN
 201 FGTQTYTCNV DHKPSNTKVD KTVRKCCVE CPPCPAPPVA GPSVFLFPPK
 251 PKDTLMISRT PEVTCVVVDV SHEDPEVQFN WYVDGVEVHN AKTKPREEQF
 301 NSTFRVSVL TVVHQDWLNG KEYKCKVSNK GLPAPIEKTI SKTKGQPREP
 351 QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD LAVEWESNGQ PENNYKTPP
 401 MLDSGDSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG
 451 K (SEQ ID NO:225)

[0286] Amino acid sequence of the mature form (signal peptide removed) of Ab-15 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGASVKV SCKASDFNIK ~~DFYLHWVRQA~~ PGQGLEWIGR
 51 IDPENGDTLY DPKFQDKVTM TTDSTSTAY MELRSLRSDD TAVYYCAREA
 101 DYFHDGTSYW YFDVWGRGTL VTVSSASTKG PSVFPLAPCS RSTSESTAAL
 151 GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSN
 201 FGTQTYTCNV DHKPSNTKVD KTVRKCCVE CPPCPAPPVA GPSVFLFPPK
 251 PKDTLMISRT PEVTCVVVDV SHEDPEVQFN WYVDGVEVHN AKTKPREEQF
 301 NSTFRVSVL TVVHQDWLNG KEYKCKVSNK GLPAPIEKTI SKTKGQPREP
 351 QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD LAVEWESNGQ PENNYKTPP
 401 MLDSGDSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG
 451 (SEQ ID NO:394)

[0287] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-15 HC:

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC

51 AGTGAAGGTC TCCTGCAAGG CTTCTGACTT CAACATTA AAA GACTTCTATC
 101 TACACTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATTGGAAGG
 151 ATTGATCCTG AGAATGGTGA TACTTTATAT GACCCGAAGT TCCAGGACAA
 201 GGTCAACATG ACCACAGACA CGTCCACCAG CACAGCCTAC ATGGAGCTGA
 251 GGAGCCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAGGCG
 301 GATTATTTCC ACGATGGTAC CTCCTACTGG TACTTCGATG TCTGGGGCCG
 351 TGGCACCTG GTCACCGTCT CTAGTGCCTC CACCAAGGGC CCATCGGTCT
 401 TCCCCCTGGC GCCCTGCTCC AGGAGCACCT CCGAGAGCAC AGCGGCCCTG
 451 GGCTGCCTGG TCAAGGACTA CTTCCCCGAA CCGGTGACGG TGTCGTGGAA
 501 CTCAGGCGCT CTGACCAGCG GCGTGACAC CTTCCAGCT GTCCTACAGT
 551 CCTCAGGACT CTACTCCCTC AGCAGCGTGG TGACCGTGCC CTCCAGCAAC
 601 TTCGGCACCC AGACCTACAC CTGCAACGTA GATCACAAGC CCAGCAACAC
 651 CAAGGTGGAC AAGACAGTTG AGCGCAAATG TTGTGTCGAG TGCCACCGT
 701 GCCCAGCACC ACCTGTGGCA GGACCGTCAG TCTTCCTCTT CCCCCAAAA
 751 CCCAAGGACA CCCTCATGAT CTCCCGGACC CCGTGAAGTCA CGTGCGTGGT
 801 GGTGGACGTG AGCCACGAAG ACCCCGAGGT CCAGTTCAAC TGGTACGTGG
 851 ACGGCGTGGA GGTGCATAAT GCCAAGACAA AGCCACGGGA GGAGCAGTTC
 901 AACAGCACGT TCCGTGTGGT CAGCGTCCTC ACCGTTGTGC ACCAGGACTG
 951 GCTGAACGGC AAGGAGTACA AGTGCAAGGT CTCCAACAAA GGCCTCCCAG
 1001 CCCCATCGA GAAAACCATC TCCAAAACCA AAGGGCAGCC CCGAGAACCA
 1051 CAGGTGTACA CCCTGCCCCC ATCCCGGGAG GAGATGACCA AGAACCAGGT
 1101 CAGCCTGACC TGCCTGGTCA AAGGCTTCTA CCCAGCGAC ATCGCCGTGG
 1151 AGTGGGAGAG CAATGGGCAG CCGGAGAACA ACTACAAGAC CACACCTCCC
 1201 ATGCTGGACT CCGACGGCTC CTTCTTCTC TACAGCAAGC TCACCGTGGA
 1251 CAAGAGCAGG TGGCAGCAGG GGAACGTCTT CTCATGCTCC GTGATGCATG
 1301 AGGCTCTGCA CAACCACTAC ACGCAGAAGA GCCTCTCCCT GTCTCCGGGT
 1351 AAA (SEQ ID NO:226)

[0288] Amino acid sequence of the Ab-15 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASDFNIKD
 51 FYLHWVRQAP GQGLEWIGRI DPENGDTLYD PKFQDKVTMT TDTSTSTAYM
 101 ELRSLRSDDT AVYYCAREAD YFHDGTSYWY FDVWGRGTLV TVSSASTKGP
 151 SVFPLAPCSR STSESTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV
 201 LQSSGLYSLS SVVTVPSNF GTQTYTCNVD HKPSNTKVDK TVERKCCVEC
 251 PPCPAPPVAG PSVFLFPPKP KDTLMISRTPEVTCVVVDVS HEDPEVQFNW
 301 YVDGVEVHNA KTKPREEQFN STFRVSVLT VVHQDWLNGK EYKCKVSNKG
 351 LPAPIEKTIS KTKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI
 401 AVEWESNGQP ENNYKTTTPM LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV
 451 MHEALHNHYT QKSLSLSPGK (SEQ ID NO:227)

[0289] Nucleic acid sequence of the Ab-15 HC including signal peptide encoding sequence:

1 ATGGA CTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACTCCGAG GTGCAGCTGG TGCAGTCTGG GGCTGAGGTG AAGAAGCCTG
 101 GGGCCTCAGT GAAGGTCTCC TGCAAGGCTT CTGACTTCAA CATTAAGAC
 151 TTCTATCTAC ACTGGGTGCG ACAGGCCCTT GGACAAGGGC TTGAGTGGAT
 201 TGGAAGGATT GATCCTGAGA ATGGTGATAC TTTATATGAC CCGAAGTTCC
 251 AGGACAAGGT CACCATGACC ACAGACACGT CCACCAGCAC AGCCTACATG
 301 GAGCTGAGGA GCCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG

351 AGAGGCGGAT TA¹TTTCCACG ATGGTACCTC C²ACTGGTAC TTCGATGTCT
 401 GGGGCCGTGG CACCTTGGTC ACCGTCTCTA GTGCCTCCAC CAAGGGCCCA
 451 TCGGTCTTCC CCCTGGCGCC CTGCTCCAGG AGCACCTCCG AGAGCACAGC
 501 GGCCCTGGGC TGCCTGGTCA AGGACTACTT CCCCGAACCG GTGACGGTGT
 551 CGTGGA³ACTC AGGCGCTCTG ACCAGCGGCG TGCACACCTT CCCAGCTGTC
 601 CTACAGTCCT CAGGACTCTA CTCCCTCAGC AGCGTGGTGA CCGTGCCCTC
 651 CAGCAACTTC GGCACCCAGA CCTACACCTG CAACGTAGAT CACAAGCCCA
 701 GCAACACCAA GGTGGACAAG ACAGTTGAGC GCAAATGTTG TGTCGAGTGC
 751 CCACCGTGCC CAGCACCACC TGTGGCAGGA CCGTCAGTCT TCCTCTTCCC
 801 CCCAAAACCC AAGGACACCC TCATGATCTC CCGGACCCCT GAGGTCA⁴CGT
 851 GCGTGGTGGT GGACGTGAGC CACGAAGACC CCGAGGTCCA GTTCAACTGG
 901 TACGTGGACG GCGTGGAGGT GCATAATGCC AAGACAAAGC CACGGGAGGA
 951 GCAGTTCAAC AGCACGTTCC GTGTGGTCAG CGTCCTCACC GTTGTGCACC
 1001 AGGACTGGCT GAACGGCAAG GAGTACAAGT GCAAGGTCTC CAACAAAGGC
 1051 CTCCCAGCCC CCATCGAGAA AACCATCTCC AAAACCAAAG GGCAGCCCCG
 1101 AGAACCACAG GTGTACACCC TGCCCCCATC CCGGGAGGAG ATGACCAAGA
 1151 ACCAGGTCAG CCTGACCTGC CTGGTCAAAG GCTTCTACCC CAGCGACATC
 1201 GCCGTGGAGT GGGAGAGCAA TGGGCAGCCG GAGAACA⁵ACT ACAAGACCAC
 1251 ACCTCCCATG CTGGACTCCG ACGGCTCCTT CTTCTCTAC AGCAAGCTCA
 1301 CCGTGGACAA GAGCAGGTGG CAGCAGGGGA ACGTCTTCTC ATGCTCCGTG
 1351 ATGCATGAGG CTCTGCACAA CCACTACACG CAGAAGAGCC TCTCCCTGTC
 1401 TCCGGGTAAA (SEQ ID NO:228)

[0290] The CDR sequences in the variable region of the heavy chain of Ab-15 are:

CDR-H1: DFYLH (SEQ ID NO:290)
 CDR-H2: RIDPENGDTLYDPKFQD (SEQ ID NO:291)
 CDR-H3: EADYFHDGTSYWYFDV (SEQ ID NO:292)

[0291] The light chain variable region CDR sequences of Ab-15 are:

CDR-L1: SVSSTTSSNHLH (SEQ ID NO:278)
 CDR-L2: GTSNLAS (SEQ ID NO:279)
 CDR-L3: QQWSSYPLT (SEQ ID NO:280)

Ab-15 Variable domains:

[0292] Ab-15 light chain variable domain amino acid sequence (without signal sequence):

1 DIQMTQSPSS LSASVGDRVIT ITCSVSSTIS SNHEHWFOQK PGKAPKSLIY
 51 GTSNLAGSVP SRFSGSGSGT DFTLTSSLQ PEDFATYYCQ QWSSYPLTFG
 101 GTKVEIK (SEQ ID NO:384)

[0293] Ab-15 light chain variable domain DNA sequence (without signal sequence):

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCAGCAT CCGTAGGCGA
 51 TAGAGTTACA ATAACATGCA GCGTATCATC AACTATATCA TCAAATCATC

101 TTCATTGGTT CCAACAGAAA CCCGGCAAAG CACCTAAATC ACTTATATAC
 151 GGCACATCAA ATCTCGCATC AGGCGTTCCT TCAAGATTTT CAGGCTCTGG
 201 CTCAGGCACC GACTTTACTC TTACAATATC CTCCCTCCAA CCCGAAGACT
 251 TCGCAACCTA TTA CTGTCAA CAATGGTCTT CATATCCACT CACATTTGGC
 301 GCGGCACAA AAGTAGAAAT TAAA (SEQ ID NO:385)

[0294] Ab-15 heavy chain variable domain amino acid sequence (without signal sequence):

1 EVQLVQSGAE VKKPGASVKV SCKASDFNIK DFYLHWVRQA PGQGLEWIGR
 51 DPENGDITLY DPKFQDKVTM TTDSTSTAY MELRSLRSDT TAVYYCAREA
 101 DYFHDGTSYW YFDVWGRGTL VTVSS (SEQ ID NO:386)

[0295] Ab-15 heavy chain variable domain DNA sequence (without signal sequence):

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC
 51 AGTGAAGGTC TCCTGCAAGG CTTCTGACTT CAACATTAAA GACTTCTATC
 101 TACACTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATTGGAAGG
 151 ATTGATCCTG AGAATGGTGA TACTTTATAT GACCCGAAGT TCCAGGACAA
 201 GGTCACCATG ACCACAGACA CGTCCACCAG CACAGCCTAC ATGGAGCTGA
 251 GGAGCCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAGGCG
 301 GATTATTTCC ACGATGGTAC CTCCTACTGG TACTTCGATG TCTGGGGCCG
 351 TGGCACCTG GTCACCGTCT CTAGT (SEQ ID NO:387)

[0296] Ab-11 was humanized to generate Ab-16.

Ab-16

[0297] The sequences of the Antibody 16 (also referred to herein as Ab-16) LC and HC are as follows:

Ab-16 Light Chain:

[0298] Amino acid sequence of the mature form (signal peptide removed) of the Ab-16 LC:

1 DIQLTQSPSF LSASVGDRVIT ITCRASSIS YHWYQKPG KAPKLLIYAT
 51 SNLAGVPSR FSGSGSGTEF TLTISSLQPE DFATYYCQQWSSDELTFGGG
 101 TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNFFYP REAKVQWKVD
 151 NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
 201 SSPVTKSFNR GEC (SEQ ID NO:229)

[0299] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-16 LC:

1 GACATCCAGT TGACCCAGTC TCCATCCTTC CTGTCTGCAT CTGTAGGAGA
 51 CAGAGTCACC ATCACTTGCA GGGCCAGCTC AAGTATAAGT TACATACT
 101 GGTATCAGCA AAAACCAGGG AAAGCCCCTA AGCTCCTGAT CTATGCCACA
 151 TCCAACCTGG CTTCTGGGGT CCCATCAAGG TTCAGCGGCA GTGGATCTGG
 201 GACAGAATTC ACTCTCACA TCAGCAGCCT GCAGCCTGAA GATTTTGCAA
 251 CTTATTACTG TCAGCAGTGG AGTAGTGACC CACTCACGTT CGGCGGAGGG
 301 ACCAAGGTGG AGATCAAACG TACGGTGGCT GCACCATCTG TCTTCATCTT
 351 CCCGCCATCT GATGAGCAGT TGAAATCTGG AACTGCCTCT GTTGTGTGCC

 401 TGCTGAATAA CTTCTATCCC AGAGAGGCCA AAGTACAGTG GAAGGTGGAT
 451 AACGCCCTCC AATCGGGTAA CTCCCAGGAG AGTGTCACAG AGCAGGACAG
 501 CAAGGACAGC ACCTACAGCC TCAGCAGCAC CCTGACGCTG AGCAAAGCAG
 551 ACTACGAGAA ACACAAAGTC TACGCCTGCG AAGTCACCCA TCAGGGCCTG
 601 AGCTCGCCCG TCACAAAGAG CTTCAACAGG GGAGAGTGT (SEQ ID NO:230)

[0300] Amino acid sequence of the Ab-16 LC including signal peptide:

1 MDMRVPALL GLLLLWLPGA RCDIQLTQSP SFLSASVGDR VTITCRASSS
 51 ISYIHWYQQK PGKAPKLLIY ATSNLASGVP SRFSGSGSGT EFTLTSSLQ
 101 PEDFATYYCQ QWSSDPLTFG GGTKVEIKRT VAAPSVFIFP PSDEQLKSGT
 151 ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSTL
 201 TLSKADYEKH KVIACEVTHQ GLSSPVTKSF NRGEC (SEQ ID NO:231)

[0301] Nucleic acid sequence of the Ab-16 LC including signal peptide encoding sequence:

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TGCTCTGGCT
 51 CCCAGGTGCC AGATGTGACA TCCAGTTGAC CCAGTCTCCA TCCTTCCTGT
 101 CTGCATCTGT AGGAGACAGA GTCACCATCA CTTGCAGGGC CAGCTCAAGT
 151 ATAAGTTACA TAACTGGTA TCAGCAAAAA CCAGGGAAAG CCCCTAAGCT
 201 CCTGATCTAT GCCACATCCA ACCTGGCTTC TGGGGTCCCA TCAAGGTTCA
 251 GCGGCAGTGG ATCTGGGACA GAATTCATC TCACAATCAG CAGCCTGCAG
 301 CCTGAAGATT TTGCAACTTA TACTGTGTCAG CAGTGGAGTA GTGACCCACT
 351 CACGTTTCGC GGAGGGACCA AGGTGGAGAT CAAACGTACG GTGGCTGCAC
 401 CATCTGTCTT CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAAT
 451 GCCTCTGTTG TGTGCCTGCT GAATAACTTC TATCCAGAG AGGCCAAAGT
 501 ACAGTGGAAG GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG
 551 TCACAGAGCA GACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCTG
 601 ACGCTGAGCA AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT
 651 CACCCATCAG GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG
 701 AGTGT (SEQ ID NO:232)

Ab-16 Heavy Chain:

[0302] Amino acid sequence of the mature form (signal peptide removed) of the Ab-16 HC:

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDY~~YIH~~WVRQA PGQGLEWIGR
 51 VDPDNGETEF APKFPGKVTM TTDTSISTAY MELSRLRSDD TAVYYCARED
 101 YDGT~~YTW~~FPY WGQGT~~LV~~TVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV
 5 151 KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ
 201 TYTCNV~~DH~~KP SNTKVDK~~TV~~E RKCCVEC~~PP~~C PAPPVAGPSV FLFPPKPKDT
 251 LMISRTPEVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF
 301 RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT
 10 351 LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPMLDS

401 DGSFFLYSKL TVDKSRWQQG NVFSCSV~~MHE~~ ALHNHYTQKS LSLSPGK (SEQ ID
 NO:233)

[0303] Amino acid sequence of the mature form (signal peptide removed) of the Ab-16 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDY~~YIH~~WVRQA PGQGLEWIGR
 51 VDPDNGETEF APKFPGKVTM TTDTSISTAY MELSRLRSDD TAVYYCARED
 101 YDGT~~YTW~~FPY WGQGT~~LV~~TVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV
 151 KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ
 201 TYTCNV~~DH~~KP SNTKVDK~~TV~~E RKCCVEC~~PP~~C PAPPVAGPSV FLFPPKPKDT
 251 LMISRTPEVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF
 301 RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT
 351 LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPMLDS
 401 DGSFFLYSKL TVDKSRWQQG NVFSCSV~~MHE~~ ALHNHYTQKS LSLSPG (SEQ ID
 NO:395)

[0304] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-16 HC:

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC
 51 AGTGAAGGTC TCCTGCAAGG CTTCTGGATT CGACATTAAG GACTACTATA
 101 TACACTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATCGGAAGG
 151 GTTGATCCTG ACAATGGTGA GACTGAATTT GCCCCGAAGT TCCCGGGCAA
 201 GGTACCATG ACCACAGACA CGTCCATCAG CACAGCCTAC ATGGAGCTGA
 251 GCAGGCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAAGAC
 301 TACGATGGTA CCTACACCTG GTTTCCTTAT TGGGGCCAAG GGACTCTGGT
 351 CACCGTCTCT AGTGCCTCCA CCAAGGGCCC ATCGGTCTTC CCCCTGGCGC
 401 CCTGCTCCAG GAGCACCTCC GAGAGCACAG CGGCCCTGGG CTGCCTGGTC
 451 AAGGACTACT TCCCCGAACC GGTGACGGTG TCGTGGAAct CAGGCGCTCT
 501 GACCAGCGGC GTGCACACCT TCCAGCTGT CCTACAGTCC TCAGGACTCT
 551 ACTCCCTCAG CAGCGTGGTG ACCGTGCCCT CCAGCAACTT CGGCACCCAG
 601 ACCTACACCT GCAACGTAGA TCACAAGCCC AGCAACACCA AGGTGGACAA
 651 GACAGTTGAG CGCAAATGTT GTGTGAGTG CCCACCGTGC CCAGCACCAC
 701 CTGTGGCAGG ACCGTCAGTC TTCCTCTTCC CCCCAAAACC CAAGGACACC
 751 CTCATGATCT CCCGGACCCC TGAGGTCACG TCGGTGGTGG TGGACGTGAG
 801 CCACGAAGAC CCCGAGGTCC AGTTCAACTG GTACGTGGAC GGCCTGGAGG
 851 TGCATAATGC CAAGACAAAG CCACGGGAGG AGCAGTTCAA CAGCACGTTC
 901 CGTGTGGTCA GCGTCCTCAC CGTTGTGCAC CAGGACTGGC TGAACGGCAA
 951 GGAGTACAAG TGCAAGGTCT CCAACAAAGG CCTCCAGCC CCCATCGAGA
 1001 AAACATCTC CAAAACCAA GGCAGCCCC GAGAACCACA GGTGTACACC
 1051 CTGCCCCCAT CCCGGGAGGA GATGACCAAG AACCAGGTCA GCCTGACCTG
 1101 CCTGGTCAAA GGCTTCTACC CCAGCGACAT CGCCGTGGAG TGGGAGAGCA
 1151 ATGGGCAGCC GGAGAACAAC TACAAGACCA CACCTCCCAT GCTGGACTCC
 1201 GACGGCTCCT TCTTCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG
 1251 GCAGCAGGGG AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA
 1301 ACCACTACAC GCAGAAGAGC CTCTCCCTGT CTCCGGGTAA A (SEQ ID
 NO:234)

[0305] Amino acid sequence of the Ab-16 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPASVKVS CKASGFDIKD
 51 YYIHWVRQAP GQGLEWIGRV DPDNGETEF A PKFPGKVTMT TDTSISTAYM
 101 ELSRLRSDDT AVYYCAREDY DGTYTWFPYW GQGLVTVSS ASTKGPSVFP
 151 LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
 201 GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPCP
 251 APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG
 301 VEVHNAKTKP REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNGKLPAP
 351 IEKTISKTKG QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDIAVEW
 401 ESNGQPENNY KTTTPMLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA
 451 LHNHYTQKSL SLSPGK (SEQ ID NO:235)

[0306] Nucleic acid sequence of the Ab-16 HC including signal peptide encoding sequence:

1 ATGGACTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACTCCGAG GTGCAGCTGG TGCAGTCTGG GGCTGAGGTG AAGAAGCCTG
 101 GGGCCTCAGT GAAGGTCTCC TGCAAGGCTT CTGGATTCGA CATTAAGGAC
 5 151 TACTATATAC ACTGGGTGCG ACAGGCCCTT GGACAAGGGC TTGAGTGGAT
 201 CGGAAGGGTT GATCCTGACA ATGGTGAGAC TGAATTTGCC CCGAAGTTCC
 251 CGGGCAAGGT CACCATGACC ACAGACACGT CCATCAGCAC AGCCTACATG
 301 GAGCTGAGCA GGCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG
 10 351 AGAAGACTAC GATGGTACCT ACACCTGGTT TCCTTATTGG GGCCAAGGGA
 401 CTCTGGTCAC CGTCTCTAGT GCCTCCACCA AGGGCCCATC GGTCTTCCCC
 451 CTGGCGCCCT GCTCCAGGAG CACCTCCGAG AGCACAGCGG CCCTGGGCTG
 501 CCTGGTCAAG GACTACTTCC CCGAACCAGT GACGGTGTCT TGGAAGTCTG
 15 551 GCGCTCTGAC CAGCGGCGTG CACACCTTCC CAGCTGTCCT ACAGTCCTCA
 601 GGAAGTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG
 651 CACCCAGACC TACACCTGCA ACGTAGATCA CAAGCCCAGC AACACCAAGG
 701 TGGACAAGAC AGTTGAGCGC AAATGTTGTG TCGAGTGCCC ACCGTGCCCA
 751 GCACCACCTG TGGCAGGACC GTCAGTCTTC CTCTTCCCCC CAAAACCCAA
 20 801 GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACGTGC GTGGTGGTGG
 851 ACGTGAGCCA CGAAGACCCC GAGGTCCAGT TCAACTGGTA CGTGGACGGC
 901 GTGGAGGTGC ATAATGCCAA GACAAAGCCA CGGGAGGAGC AGTTCAACAG
 951 CACGTTCCGT GTGGTCAAGC TCCTCACCCT TGTGCACCAG GACTGGCTGA
 25 1001 ACGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAGGCCCT CCCAGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGG CAGCCCCGAG AACACAGGT
 1101 GTACACCCTG CCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTCAGCC
 1151 TGACCTGCCT GGTCAAAGGC TTCTACCCCA GCGACATCGC CGTGGAGTGG
 30 1201 GAGAGCAATG GGCAGCCGGA GAACAACCTAC AAGACCACAC CTCCCATGCT
 1251 GGAAGTCCGAC GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA
 1301 GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT
 1351 CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAA (SEQ
 ID NO:236)

[0307] The CDR sequences in the variable region of the heavy chain of Ab-16 are:

CDR-H1 : DYYIH (SEQ ID NO:293)
 CDR-H2 : RVDPDNGETEFAPKFPG (SEQ ID NO:294)
 CDR-H3 : EDYDGYTWFPY (SEQ ID NO:295)

[0308] The light chain variable region CDR sequences of Ab-16 are:

CDR-L1: RASSSISYIH (SEQ ID NO:281)
 CDR-L2: ATSNLAS (SEQ ID NO:282)
 CDR-L3: QQWSSDPLT (SEQ ID NO:283)

Ab-16 Variable domains:

[0309] Ab-16 light chain variable domain amino acid sequence (without signal sequence):

1 DIQLTQSPSF LSASVGDRVIT ITCRASSSIS YIHWHYQQKPG KAPKLLIYAT
 51 SNLASGVPSR FSGSGSGTEF TLTISSLQPE DFATYYCQQW SSDPLTFGGG
 101 TKVEIK (SEQ ID NO:388)

[0310] Ab-16 light chain variable domain DNA sequence (without signal sequence):

1 GACATCCAGT TGACCCAGTC TCCATCCTTC CTGTCTGCAT CTGTAGGAGA
 5 51 CAGAGTCACC ATCACTTGCA GGGCCAGCTC AAGTATAAGT TACATACACT
 101 GGTATCAGCA AAAACCAGGG AAAGCCCCTA AGCTCCTGAT CTATGCCACA
 151 TCCAACCTGG CTTCTGGGGT CCCATCAAGG TTCAGCGGCA GTGGATCTGG
 201 GACAGAATTC ACTCTCACA TCAGCAGCCT GCAGCCTGAA GATTTTGCAA
 10 251 CTTATTACTG TCAGCAGTGG AGTAGTGACC CACTCACGTT CGGCGGAGGG
 301 ACCAAGGTGG AGATCAAA (SEQ ID NO:389)

[0311] Ab-16 heavy chain variable domain amino acid sequence (without signal sequence):

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDY^YHWVRQA PGQGLEWIGR
 15 51 VDPDNGETEF APKFP^KGKVTM TTDTSISTAY MELSR^LLRSDD TAVYYCARE^D
 101 YDGT^YYTWEPY WGQGT^LLVTVS S (SEQ ID NO:390)

[0312] Ab-16 heavy chain variable domain DNA sequence (without signal sequence):

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC
 25 51 AGTGAAGGTC TCCTGCAAGG CTTCTGGATT CGACATTAAG GACTACTATA
 101 TACTACTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATCGGAAGG
 151 GTTGATCCTG ACAATGGTGA GACTGAATTT GCCCCGAAGT TCCCGGGCAA
 201 GGTCACCATG ACCACAGACA CGTCCATCAG CACAGCCTAC ATGGAGCTGA
 30 251 GCAGGCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAAGAC
 301 TACGATGGTA CCTACACCTG GTTTCCTTAT TGGGGCCAAG GGACTCTGGT
 351 CACCGTCTCT AGT (SEQ ID NO:391)

[0313] Additional antibodies are referred to herein as Antibodies 17-22 (also referred to herein as Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, and Ab-22). The Kappa Constant region for all VK regions of Ab-17, Ab-19, and Ab-21 is as follows:

TDAAPT^VSIFPPSSEQLTSGGASVVCFLNNFYPKDINV^KWKIDG^SERQNGVLNSWTDQD
 40 SKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVK^SFN^RNEC (SEQ ID NO:323)

[0314] The Heavy Constant Region for all VH regions of antibodies 17, 19 and 21 is as follows:

AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQS
 45 DLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIF
 PPKPKDVLTTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRS
 VSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKD
 KVS^LTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSK^LNVQKSNWEA
 50 GNTFTCSVLHEGLHNHHT^EKSLSHSPGK (SEQ ID NO:324)

[0315] In the following antibody amino acid sequences, the boxed-shaded amino acids represent complement-determining regions (CDRs) and the underlined amino acids represent signal peptide.

Ab-17

[0316] Amino acid sequence of the Ab-17 LC including signal peptide:

MDFQVOIFSFMLISVTVLSSGEIVLTQSPALMAASPGEKVTITCSVSSSISSSNLHWSQOK
SGTSPKLWYTGTSNLASGVFVRFSGSGSGTSYSLTISSMEAEDAATYYCQQWTTTYTFG
 SGTKLELKR (SEQ ID NO:299)

[0317] Nucleic acid sequence of the Ab-17 LC including signal peptide:

ATGGATTTTCAGGTGCAGATTTTCAGCTTCATGCTAATCAGTGTCACAGTCATATTG
 TCCAGTGGAGAAATTGTGCTACCCAGTCTCCAGCACTCATGGCTGCATCTCCAGGG
 GAGAAGGTCACCATCACCTGCAGTGTGAGCTCGAGTATAAGTTCCAGCAACTTACA
 CTGGTCCCAGCAGAAAGTCAGGAACCTCCCCAAACTCTGGATTATGGCACATCCA
 ACCTTGCTTCTGGAGTCCCTGTTTCGCTTCAGTGGCAGTGGATCTGGGACCTCTTATTC
 TCTACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATTACTGTCAACAGT
 GGACTACTACGTATACGTTTCGGATCGGGGACCAAGCTGGAGCTGAAACGT (SEQ ID
 NO:300)

[0318] Amino acid sequence of the Ab-17 HC including signal peptide:

MGWNWIIFFLMAVVTGVNSEVOLRQSGADLVKPGASVKLSCTASGFNIKDYIHWVK
 QRPEQGLEWIGRIDPDNGESTYVPKFQGGKATITADTSSNTAYLQLRSLTSEDTAIYYCGR
 EGLDYGDYYAVDYGQTSVTVSS (SEQ ID NO:301)

[0319] Nucleic acid sequence of the Ab-17 HC including signal peptide:

ATGGGATGGAACTGGATCATCTTCTTCTGATGGCAGTGGTTACAGGGGTCAATTCA
 GAGGTGCAGTTGCGGCAGTCTGGGGCAGACCTTGTGAAGCCAGGGGCCTCAGTCAA
 GTTGTCTGTCACAGCTTCTGGCTTCAACATTAAGACTACTATATACTGGGTGAA
 GCAGAGGCCTGAACAGGGCCTGGAGTGGATTGGAAGGATTGATCCTGATAATGGTG
 AAAGTACATATGTCCCGAAGTTCAGGGCAAGGCCACTATAACAGCAGACACATCA
 TCCAACACAGCCTACCTACAACTCAGAAAGCCTGACATCTGAGGACACTGCCATCTA

TTATTGTGGGAGAGAGGGGCTCGACTATGGTGACTACTATGCTGTGGACTACTGGG
 GTCAAGGAACCTCGGTCACAGTCTCGAGC (SEQ ID NO:302)

[0320] Ab-17 was humanized to generate Ab-18.

Ab-18

[0321] Amino acid sequence of the Ab-18 LC including signal peptide:

MDMRVPAQLLGLLLWLPGARCDIQLTQSPSFLSASVGDRVTITCSVSSSISSSNLHWYQ
QKPGKAPKLLIYGTSNLASGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQWTTTYTF
 GQGTKLEIKR (SEQ ID NO:303)

[0322] Nucleic acid sequence of the Ab-18 LC including signal peptide:

ATGGATATGCGCGTGCCGGCGCAGCTGCTGGGCCTGCTGCTGCTGTGGCTGCCGGG
 CGCGCGCTGCGATATTCAGCTGACCCAGAGCCCGAGCTTTCTGAGCGCGAGCGTGG
 GCGATCGCGTGACCATTAACCTGCAGCGTGAGCAGCAGCATTAGCAGCAGCAACCTG
 5 CATTGGTATCAGCAGAAACCGGGCAAAGCGCCGAACTGCTGATTTATGGCACCAG
 CAACCTGGCGAGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGCAGCGGCACCGAAT
 TTACCCTGACCATTAGCAGCCTGCAGCCGGAAGATTTTGCACCTATTATTGCCAGC
 10 AGTGGACCACCACTATACTTTGGCCAGGGCACCAAACTGGAAATTAAACGT (SEQ
 ID NO:304)

[0323] Amino acid sequence of the Ab-18 HC including signal peptide:

MDWTWSILFLVAAPTGAHSEVQLVQSGAEVKKPGASVKVSCKASGFNIDYIHWVR
 QAPGQGLEWMGRIDPDNGESTYYPKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYY
 CAREGLDYGDYYAVDYWGQGLVTVSS (SEQ ID NO:305)

[0324] Nucleic acid sequence of the Ab-18 HC including signal peptide:

ATGGATTGGACCTGGAGCATTCTGTTTCTGGTGGCGGCGCCGACCGGCGCGCATAG
 CGAAGTGAGCTGGTGAGAGCGGCGCGGAAGTGAAAAACCGGGCGCGAGCGTG
 25 AAAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATTTCATTGGGT
 GCGCCAGGCGCCGGGCCAGGGCCTGGAATGGATGGGCGCATTGATCCGGATAACG
 GCGAAAGCACCTATGTGCCGAAATTTAGGGCCGCGTGACCATGACCACCGATACC
 AGCACCAGCACCGCGTATATGGAAGTGCAGCAGCTGCGCAGCGATGATACCGCGGT
 30 GTATTATTGCGCGCGCGAAGGCCTGGATTATGGCGATTATTATGCGGTGGATTATTG
 GGGCCAGGGCACCTTGGTGACCGTCTCGAGC (SEQ ID NO:306)

[0325] Ab-18 light chain variable domain amino acid sequence (without signal sequence):

DIQLTQSPSFLSASVGDRTTTCVSSSSISNLHWYQQKPGKAPKLLIYGTSNLSGVPS
 RFSGSGSGTEFTLTISSLQPEDFATYYCQQWTTTYTFGQGTKLEIKR (SEQ ID NO:368)

[0326] Ab-18 light chain variable domain DNA sequence (without signal sequence):

GATATTCAGCTGACCCAGAGCCCGAGCTTTCTGAGCGCGAGCGTGGGCGATCGCGT
 GACCATTACCTGCAGCGTGAGCAGCAGCATTAGCAGCAGCAACCTGCATTGGTATC
 AGCAGAAACCGGGCAAAGCGCCGAACTGCTGATTTATGGCACCAGCAACCTGGCG
 45 AGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGCAGCGGCACCGAATTTACCCTGAC
 CATTAGCAGCCTGCAGCCGGAAGATTTTGCACCTATTATTGCCAGCAGTGGACCA
 CCACCTATACCTTTGGCCAGGGCACCAAACTGGAAATTAAACGT (SEQ ID NO:369)

[0327] Ab-18 heavy chain variable domain amino acid sequence (without signal sequence):

EVQLVQSGAEVKKPGASVKVSCKASGFNIDYIHWVRQAPGQGLEWMGRIDPDNGE
 STYVPKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAREGLDYGDYYAVDYWG
 55 QGTLVTVSS (SEQ ID NO:370)

[0328] Ab-18 heavy chain variable domain DNA sequence (without signal sequence):

GAAGTGCAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTGA
 AAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATTCATTGGGTG
 CGCCAGGCGCCGGGCGCAGGGCCTGGAATGGATGGGCGCATTGATCCGGATAACGG
 5 CGAAAGCACCTATGTGCCGAAATTTAGGGCCGCGTGACCATGACCACCGATACCA
 GCACCAGCACCGCGTATATGGAAGTGCAGCCTGCGCAGCGATGATACCGCGGTG
 TATTATTGCGCGCGCGAAGGCCTGGATTATGGCGATTATTATGCGGTGGATTATTGG
 GGCCAGGGCACCCCTGGTGACCGTCTCGAGC (SEQ ID NO:371)

Ab-19

[0329] Amino acid sequence of the Ab-19 LC including signal peptide:

MMSSAQFLGLLLLCFQGRCDIQMTQTSSLSASLGDRVNISCRA~~SODISSYLNWYQQK~~
 PDGTVKLLIY~~TSRLNSGVPSRFS~~SGSGTDYSLTISNLAQEDIATYFCQ~~QDIKHP~~TFGGG
 TKLELKR (SEQ ID NO:307)

[0330] Nucleic acid sequence of the Ab-19 LC including signal peptide:

ATGATGTCCTCTGCTCAGTTCCTTGGTCTCCTGTTGCTCTGTTTCAAGGTACCAGAT
 GTGATATCCAGATGACACAGACTACATCCTCCCTGTCTGCCTCTCTGGGAGACAGAG
 25 TCAACATCAGCTGCAGGGCAAGTCAGGACATTAGCAGTTATTTAAACTGGTATCAG
 CAGAAACCAGATGGAAGTGTAAACTCCTGATCTACTCCACATCAAGATTAAACTC
 AGGAGTCCCATCAAGGTTCAGTGGCAGTGGGTCTGGGACAGATTATTCTCTCACTAT
 TAGCAACCTGGCACAAGAAGATATTGCCACTTACTTTTGCCAACAGGATATTAAGC
 30 ATCCGACGTTTCGGTGGAGGCACCAAGTTGGAGCTGAAACGT (SEQ ID NO:308)

[0331] Amino acid sequence of the Ab-19 HC including signal peptide:

MEWIWIFLFLLSGTAGVHSEVQLQQSGPELVKPGASVKMSCKASGFTFT~~TDYIMHWVKQ~~
 KPGQGLEWIGYINPYNDDTEYNEKFKGKATLTSKSSSTAYMDLSSLTSEGS~~AVYYCA~~
 RSIYYDAPFAYWGQGT~~LVTVSS~~ (SEQ ID NO:309)

[0332] Nucleic acid sequence of the Ab-19 HC including signal peptide:

ATGGAATGGATCTGGATATTTCTCTTCCTCCTGTCAGGAACTGCAGGTGTCCACTCT
 GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCAGTGAA
 45 GATGTCTTGCAAGGCTTCTGGGTTACATTCACTGACTACATTATGCACTGGGTGAA
 GCAGAAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATTAATCCTTACAATGATG
 AACTGAATACAATGAGAAGTTCAAAGGCAAGGCCACACTGACTTCAGACAAATCC
 TCCAGCACAGCCTACATGGATCTCAGCAGTCTGACCTCTGAGGGCTCTGCGGTCTAT
 50 TACTGTGCAAGATCGATTTATTACTACGATGCCCCGTTTGCTTACTGGGGCCAAGGG
 ACTCTGGTCACAGTCTCGAGC (SEQ ID NO:310)

[0333] Ab-19 was humanized to generate Antibody 20 (also referred to herein as Ab-20) and Antibody 23 (also referred to herein as Ab-23).

Ab-20

IgG4 version

5 [0334] Amino acid sequence of the Ab-20 LC including signal peptide:

MMSSAQLGLLLLCFQGRCDIQMTQSPSSLSASVGDRVTTTCRASQDISSYLNWYQQK
 PGKAPKLLIYSTRLNSGVPSRFSGSGSDFTLTISLQPEDFATYYCCQQDIKHPTFGQG
 10 TKVEIKR (SEQ ID NO:311)

[0335] Nucleic acid sequence of the Ab-20 LC including signal peptide:

ATGATGTCCTCTGCTCAGTTCCTTGGTCTCCTGTTGCTCTGTTTTCAAGGTACCAGAT
 15 GTGATATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGTGACCGTG
 TCAACATCACTTGCCGCGCAAGTCAGGATATTAGCAGCTATTAAATTGGTATCAGC
 AGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATTCTACTTCCCGTTTGAATAGTG
 20 GGGTCCCATCACGCTTCAGTGGCAGTGGCTCTGGGACAGATTTCACTCTCACCATCA
 GCAGTCTGCAACCTGAAGATTTTGAACCTACTACTGTCAACAGGATATTAAACACC
 CTACGTTTCGGTCAAGGCACCAAGGTGGAGATCAAACGT (SEQ ID NO:312)

25 [0336] Amino acid sequence of the Ab-20 HC including signal peptide:

MEWIWIFLFLLSGTAGVHSEVQLVQSGAEVKKPGSSVKVSCKASGFTFTDYIMHWVRQ
 APGQGLEWMGYINPYNDDEYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCA
 30 RSIYYFDAPFAYWGQGLTVTVSS (SEQ ID NO:313)

[0337] Nucleic acid sequence of the Ab-20 HC including signal peptide:

ATGGAATGGATCTGGATATTTCTCTTCCTCCTGTCAGGAACTGCAGGTGTCCACTCT
 35
 GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAA
 GGTCTCCTGCAAGGCTTCTGGTTTTACCTTCACCGACTATATTATGCACTGGGTGCG
 40 TCAGGCCCTGGTCAAGGGCTTGAGTGGATGGGCTATATCAACCCTTATAATGATG
 ACACCGAATAACAACGAGAAGTTCAAGGGCCGTGTCACGATTACCGCGGACAAATCC
 ACGAGCACAGCCTACATGGAGCTGAGCAGCCTGCGCTCTGAGGACACGGCCGTGTA
 TTACTGTGCGCGTTCGATTATTACTACGATGCCCCGTTTGCTTACTGGGGCCAAGG
 45 GACTCTGGTCACAGTCTCGAGC (SEQ ID NO:349)

Ab-23

IgG2 version

50

Light Chain:

[0338] Amino acid sequence of the mature form (signal peptide removed) of the Ab-23 LC:

55

1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYS
 51 TSRLNSGVPS RFSGSGSGTD FTLTISSLOP EDFATYYCQQ DIKHPTFGQG
 101 TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD
 151 NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
 201 SSPVTKSFNR GEC (SEQ ID NO:341)

[0339] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-23 LC:

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGTGA
 51 CCGTGTCAACC ATCACTTGCC GCGCAAGTCA GGATATTAGC AGCTATTTAA
 101 ATTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTATTCT
 151 ACTTCCCGTT TGAATAGTGG GGTCCCATCA CGCTTCAGTG GCAGTGGCTC
 201 TGGGACAGAT TCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG
 251 CAACTTACTA CTGTCAACAG GATATTAAAC ACCCTACGTT CGGTCAAGGC
 301 ACCAAGGTGG AGATCAAACG TACGGTGGCT GCACCATCTG TCTTCATCTT
 351 CCCGCCATCT GATGAGCAGT TGAAATCTGG AACTGCCTCT GTTGTGTGCC
 401 TGCTGAATAA CTTCTATCCC AGAGAGGCCA AAGTACAGTG GAAGGTGGAT
 451 AACGCCCTCC AATCGGGTAA CTCCAGGAG AGTGTCACAG AGCAGGACAG
 501 CAAGGACAGC ACCTACAGCC TCAGCAGCAC CCTGACGCTG AGCAAAGCAG
 551 ACTACGAGAA ACACAAAGTC TACGCCTGCG AAGTCACCCA TCAGGGCCTG
 601 AGCTCGCCCC TCACAAAGAG CTCAACAGG GGAGAGTGT (SEQ ID NO:342)

[0340] Amino acid sequence of the Ab-23 LC including signal peptide:

1 MDMRVPAQLL GLLLLWLRGA RCDIQMTQSP SLSASVGDR VTITCRASQD
 51 ISSYLNWYQQ KPGKAPKLLI YSTSRLNSGV PSRFSGSGSG TDFTLTISSL
 101 QPEDFATYYC QQDIKHPTFG QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT
 151 ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYLSSTL
 201 TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC (SEQ ID NO:343)

[0341] Nucleic acid sequence of the Ab-23 LC including signal peptide encoding sequence:

1 ATGGACATGA GGGTGCCCGC TCAGCTCCTG GGGCTCCTGC TGCTGTGGCT
 51 GAGAGGTGCC AGATGTGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTGT
 101 CTGCATCTGT AGGTGACCGT GTCACCATCA CTTGCCGCGC AAGTCAGGAT
 151 ATTAGCAGCT ATTTAAATTG GTATCAGCAG AAACCAGGGA AAGCCCCTAA
 201 GCTCCTGATC TATTCTACTT CCCGTTTGAA TAGTGGGGTC CCATCACGCT
 251 TCAGTGGCAG TGGCTCTGGG ACAGATTTC A CTCTACCAT CAGCAGTCTG
 301 CAACCTGAAG ATTTTGCAAC T TACTACTGT CAACAGGATA TTAAACACCC
 351 TACGTTCCGGT CAAGGCACCA AGGTGGAGAT CAAACGTACG GTGGCTGCAC
 401 CATCTGTCTT CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAAC
 451 GCCTCTGTTG TGTGCCTGCT GAATAACTTC TATCCAGAG AGGCCAAAGT
 501 ACAGTGGAAG GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG
 551 TCACAGAGCA GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCTG
 601 ACGCTGAGCA AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT
 651 CACCCATCAG GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG
 701 AGTGT (SEQ ID NO:344)

Heavy Chain:

[0342] Amino acid sequence of the mature form (signal peptide removed) of the Ab-23 HC:

5
1 EVQLVQSGAE VKKPGSSVKV SCKASGFTFT DYIMHWVRQA PGQGLEWMGY
51 INPYNDDEY NEKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARSI
101 YYYDAPFAYW GQGTLVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK
151 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT
201 YTCNVDPHKPS NTKVDKTVR KCCVECPPCP APPVAGPSVF LFPPKPKDTL
251 MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR
301 VVSVLTVVHQ DWLNGKEYKC KVSNGKLPAP IEKTISKTKG QPREPQVYTL
351 PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPMLDSD
15 401 GSFFLYSKLT VDKSRWQQGN VFSCSVMEHA LHNHYTQKSL SLSPGK (SEQ ID
NO:345)

[0343] Amino acid sequence of the mature form (signal peptide removed) of the Ab-23 HC without carboxy-terminal lysine:

25
1 EVQLVQSGAE VKKPGSSVKV SCKASGFTFT DYIMHWVRQA PGQGLEWMGY
51 INPYNDDEY NEKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARSI
101 YYYDAPFAYW GQGTLVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK
151 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT
201 YTCNVDPHKPS NTKVDKTVR KCCVECPPCP APPVAGPSVF LFPPKPKDTL
251 MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR
301 VVSVLTVVHQ DWLNGKEYKC KVSNGKLPAP IEKTISKTKG QPREPQVYTL
351 PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPMLDSD
401 GSFFLYSKLT VDKSRWQQGN VFSCSVMEHA LHNHYTQKSL SLSPG (SEQ ID
NO:396)

[0344] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-23 HC:

40
1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGTCCTC
51 GGTGAAGGTC TCCTGCAAGG CTTCTGGTTT TACCTTCACC GACTATATTA
101 TGCACTGGGT GCGTCAGGCC CCTGGTCAAG GGCTTGAGTG GATGGGCTAT
151 ATCAACCCTT ATAATGATGA CACCGAATAC AACGAGAAGT TCAAGGGCCG

201 TGTCACGATT ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGA
 251 GCAGCCTGCG CTCTGAGGAC ACGGCCGTGT ATTACTGTGC GCGTTCGATT
 301 TATTACTACG ATGCCCCGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC
 351 CGTCTCTAGT GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCGCCCT
 401 GCTCCAGGAG CACCTCCGAG AGCACAGCGG CCCTGGGCTG CCTGGTCAAG
 451 GACTACTTCC CCGAACCGGT GACGGTGTCG TGGAACCTAG GCGCTCTGAC
 501 CAGCGGCGTG CACACCTTCC CAGCTGTCTT ACAGTCCTCA GGACTCTACT
 551 CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG CACCCAGACC
 601 TACACCTGCA ACGTAGATCA CAAGCCCAGC AACACCAAGG TGGACAAGAC
 651 AGTTGAGCGC AAATGTTGTG TCGAGTGCCC ACCGTGCCCC GCACCACCTG
 701 TGGCAGGACC GTCAGTCTTC CTCTTCCCCC CAAAACCCAA GGACACCCTC
 751 ATGATCTCCC GGACCCCTGA GGTCACGTGC GTGGTGGTGG ACGTGAGCCA
 801 CGAAGACCCC GAGGTCCAGT TCAACTGGTA CGTGGACGGC GTGGAGGTGC
 851 ATAATGCCAA GACAAAGCCA CGGGAGGAGC AGTTCAACAG CACGTTCCGT
 901 GTGGTCAGCG TCCTCACCGT TGTGCACCA GACTGGCTGA ACGGCAAGGA
 951 GTACAAAGTG AAGGTCTCCA ACAAAGGCCT CCCAGCCCCC ATCGAGAAAA
 1001 CCATCTCCAA AACCAAAGGG CAGCCCCGAG AACCACAGGT GTACACCCTG
 1051 CCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTCAGCC TGACCTGCCT
 1101 GGTCAAAGGC TTCTACCCCA GCGACATCGC CGTGGAGTGG GAGAGCAATG
 1151 GGCAGCCGGA GAACAACTAC AAGACCACAC CTCCCATGCT GGACTCCGAC
 1201 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA
 1251 GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC
 1301 ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAA (SEQ ID NO:346)

[0345] Amino acid sequence of the Ab-23 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPSSSVKVS CKASGFTFTD
 51 YIMHWVRQAP GQGLEWMGYI NPYNDDETEYN EKFKGRVTIT ADKSTSTAYM
 101 ELSSLRSEDV AVYYCARSIY YYDAPFAYWG QGTLVTVSSA STKGPSVFPL
 151 APCSRSTSES TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPVAVLQSSG
 201 LYSLSVSVTV PSSNFGTQTY TCNVDHKPSN TKVDKTVKCK CCVECPPCPA
 251 PPVAGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV
 301 EVHNAKTKPR EEQFNSTFRV VSVLTIVVHQD WLNGKEYKCK VSNKGLPAPI
 351 EKTISKTKGQ PREPQVYTL PPSREEMTKNQ VSLTCLVKGF YPSDIAVEWE
 401 SNGQPENNYK TTPPMLESDG SFFLYSKLT VDKSRWQQGNV FSCSVMEAL
 451 HNHYTQKSLS LSPGK (SEQ ID NO:347)

[0346] Nucleic acid sequence of the Ab-23 HC including signal peptide encoding sequence:

1 ATGGA CTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACTCCGAG GTGCAGCTGG TGCAGTCTGG GGCTGAGGTG AAGAAGCCTG
 101 GGTCC TCGGT GAAGGTCTCC TGCAAGGCTT CTGGTTTTAC CTTCACCGAC
 151 TATATTATGC ACTGGGTGCG TCAGGCCCCCT GGTCAAGGGC TTGAGTGGAT
 201 GGGCTATATC AACCTTATA ATGATGACAC CGAATACAAC GAGAAGTTCA
 251 AGGGCCGTGT CACGATTACC GCGGACAAAT CCACGAGCAC AGCCTACATG
 301 GAGCTGAGCA GCCTGCGCTC TGAGGACACG GCCGTGTATT ACTGTGCGCG
 351 TTCGATTTAT TACTACGATG CCCC GTTTG T TACTGGGGC CAAGGGACTC
 401 TGGTCACCGT CTCTAGTGCC TCCACCAAGG GCCCATCGGT CTTCCCCCTG
 451 GCGCCCTGCT CCAGGAGCAC CTCCGAGAGC ACAGCGGCCC TGGGCTGCCT
 501 GGTCAAGGAC TACTTCCCCG AACCGGTGAC GGTGTCGTGG AACTCAGGCG
 551 CTCTGACCAG CGGCGTGCA C ACCTTCCCAG CTGTCCTACA GTCCTCAGGA

601 CTCTACTCCC TCAGCAGCGT GGTGACCGTG CCCTCCAGCA ACTTCGGCAC
 651 CCAGACCTAC ACCTGCAACG TAGATCACAA GCCCAGCAAC ACCAAGGTGG
 701 ACAAGACAGT TGAGCGCAAA TGTTGTGTCG AGTGCCCACC GTGCCCAGCA
 751 CCACCTGTGG CAGGACCGTC AGTCTTCTC TTCCCCCAA AACCCAAGGA
 801 CACCCTCATG ATCTCCCGGA CCCCTGAGGT CACGTGCGTG GTGGTGGACG
 851 TGAGCCACGA AGACCCCGAG GTCCAGTTCA ACTGGTACGT GGACGGCGTG
 901 GAGGTGCATA ATGCCAAGAC AAAGCCACGG GAGGAGCAGT TCAACAGCAC
 951 GTTCCGTGTG GTCAGCGTCC TCACCGTTGT GCACCAGGAC TGGCTGAACG
 1001 GCAAGGAGTA CAAGTGCAAG GTCTCAAAC AAGGCCTCCC AGCCCCATC
 1051 GAGAAAACCA TCTCCAAAAC CAAAGGGCAG CCCCAGAAAC CACAGGTGTA
 1101 CACCCTGCCC CCATCCCGGG AGGAGATGAC CAAGAACCAG GTCAGCCTGA
 1151 CCTGCCTGGT CAAAGGCTTC TACCCAGCG ACATCGCCGT GGAGTGGGAG
 1201 AGCAATGGGC AGCCGGAGAA CAACTACAAG ACCACACCTC CCATGCTGGA
 1251 CTCCGACGGC TCCTTCTTCC TCTACAGCAA GCTCACCGTG GACAAGAGCA
 1301 GGTGGCAGCA GGGGAACGTC TTCTCATGCT CCGTGATGCA TGAGGCTCTG
 1351 CACAACCACT ACACGCAGAA GAGCCTCTCC CTGTCTCCGG GTAAA (SEQ ID
 NO:348)

[0347] The CDR (complementarity determining region) sequences in the variable region of the heavy chain of Ab-23 are as follows:

CDR-H1: DYIMH (SEQ ID NO:269)
 CDR-H2: YINPYNDTEYNEKFKG (SEQ ID NO:270)
 CDR-H3: SIYYDAPFAY (SEQ ID NO:271)

[0348] The light chain variable region CDR sequences of Ab-23 are:

CDR-L1: RASQDISSYLN (SEQ ID NO:239)
 CDR-L2: STSRLNS (SEQ ID NO:240)
 CDR-L3: QQDIKHPT (SEQ ID NO:241)

Ab-23 Variable domains:

[0349] Ab-23 light chain variable domain amino acid sequence (without signal sequence):

DIQMTQSPSS LSASVGDRVIT ITCRASQDIS SYLNWYQQKP GKAPKLLIYS
 TSRLNSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ DIKHPTFGQG
 TKVEIK (SEQ ID NO:364)

[0350] Ab-23 light chain variable domain DNA sequence (without signal sequence):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGTGACCGTGTC
 ACC ATCACTTGCC GCGCAAGTCA GGATATTAGC AGCTATTAAATTGGTATCA
 GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTATTCTACTTCCCGTT
 TGAATAGTGG GGTCCCATCA CGCTTCAGTG GCAGTGGCTCTGGGACAGAT
 TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTGCAACTTACTA
 CTGTCAACAG GATATTAAAC ACCCTACGTT CCGTCAAGGCACCAAGGTGG
 AGATCAAA (SEQ ID NO:365)

[0351] Ab-23 heavy chain variable domain amino acid sequence (without signal sequence):

EVQLVQSGAE VKKPGSSVKV SCKASGFTFT DYIMHWVRQA
 PGQGLEWMGYINPYNDDEY NEKFKGRVTI TADKSTSTAY MELSSLRSED
 TAVYYCARSIYYDAPFAYW GQGTLLTVSS (SEQ ID NO:366)

[0352] Ab-23 heavy chain variable domain DNA sequence (without signal sequence):

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAA
 GGTC TCCTGCAAGG CTTCTGGTTT TACCTTCACC GACTATATTATGCACTGGGT
 GCGTCAGGCC CCTGGTCAAG GGCTTGAGTG GATGGGCTATATCAACCCTT
 ATAATGATGA CACCGAATAC AACGAGAAGT TCAAGGGCCGTGTCACGATT
 ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGAGCAGCCTGCG
 CTCTGAGGAC ACGGCCGTGT ATTACTGTGC GCGTTCGATTTATTACTACG
 ATGCCCCGTT TGCTTACTGG GGCCAAGGGACTCTGGTCACCGTCTCTAGT (SEQ ID
 NO:367)

Ab-21

[0353] Amino acid sequence of the Ab-21 LC including signal peptide:

MKSQTQVFVYMLLWLSGVEGDIVMTQSHKFMSTSVGDRVITITCKASQDVFTAVAWYQ
QKPGQSPKLLIYWASTRTGTVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPLT
FGAGTKLELKR (SEQ ID NO:315)

[0354] Nucleic acid sequence of the Ab-21 LC including signal peptide:

ATGAAGTCACAGACCCAGGTCTTTGTATACATGTTGCTGTGGTTGTCTGGTGTGAA
 GGAGACATTGTGATGACCCAGTCTCACAATTCATGTCCACGTCAGTAGGAGACAG
 GGTCACCATCACCTGCAAGGCCAGTCAGGATGTCTTTACTGCTGTAGCCTGGTATCA
 ACAGAAACCAGGACAATCTCCTAAACTACTGATTTACTGGGCATCCACCCGGCACA
 CTGGAGTCCCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
 TTAGCAATGTGCAGTCTGAAGACTTGGCAGATTATTTCTGTCAACAATATAGCAGCT
 ATCCTCTCACGTTCCGGTGCTGGGACCAAGTTGGAGCTGAAACGT (SEQ ID NO:316)

[0355] Amino acid sequence of the Ab-21 HC including signal peptide:

MGWNWIIFFLMAVVTGVNSEVQLQOSGAEIVRPGALVKLSCKASGFNIKDYMHVW
KORPEQGLEWIGRIDPENGDIIYDPKFOGKASITTDTSNTAYLQLSSLTSEDVAVYYCA
YDAGDPAWFETYWGQGLVTVSS (SEQ ID NO:317)

[0356] Nucleic acid sequence of the Ab-21 HC including signal peptide:

ATGGGATGGAACCTGGATCATCTTCTTCTGATGGCAGTGGTTACAGGGGTCAATTCA
GAGGTTGAGCTGCAGCAGTCTGGGGCTGAGCTTGTGAGGCCAGGGGCCTTAGTCAA
GTTGTCCTGCAAAGCTTCTGGCTTCAATATTAAAGACTACTATATGCACTGGGTGAA
GCAGAGGCCTGAACAGGGCCTGGAGTGGATTGGAAGGATTGATCCTGAGAATGGTG
ATATTATATATGACCCGAAGTTCCAGGGCAAGGCCAGTATAACAACAGACACATCC
TCCAACACAGCCTACCTGCAGCTCAGCAGCCTGACGTCTGAGGACACTGCCGTCTAT
TACTGTGCTTACGATGCTGGTGACCCCGCCTGGTTTACTTACTGGGGCCAAGGGACT
CTGGTCACCGTCTCGAGC (SEQ ID NO:318)

[0357] Ab-21 was humanized to yield Ab-22.

Ab-22

[0358] Amino acid sequence of the Ab-22 LC including signal peptide:

MDMRVPAQLLGLLLLWLRGARCIDIQMTQSPSSLSASVGDRTTICKASQDVFTAVAW
YQKPKGAPKLLIYWASTRHTGVPSRFSGSGSGTDFLTISLQPEDFATYYCQQYSSYP
LTFGGGTKVEIKR (SEQ ID NO:319)

[0359] Nucleic acid sequence of the Ab-22 LC including signal peptide:

ATGGATATGCGCGTGCCGGCGCAGCTGCTGGGCCTGCTGCTGCTGTGGCTGCGCGG
CGCGCGCTGCGATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCGAGCGTGG
GCGATCGCGTGACCATTACCTGCAAAGCGAGCCAGGATGTGTTTACCGCGGTGGCG
TGGTATCAGCAGAAACCGGGCAAAGCGCCGAAACTGCTGATTTATTGGGCGAGCAC
CCGCCATACCGGCGTGCCGAGTCGCTTTAGCGGCAGCGGCAGCGGCACCGATTTTA
CCCTGACCATTAGCAGCCTGCAGCCGGAAGATTTTGCAGCCTATTATTGCCAGCAGT
ATAGCAGCTATCCGCTGACCTTTGGCGGCGGCACCAAAGTGGAATTAACGT (SEQ
ID NO:320)

[0360] Amino acid sequence of the Ab-22 HC including signal peptide:

MDWTWSILFLVAAPTGAHSEVQLVQSGAEVKKPGASVKVSCKASGFNIKDYMHVW
RQAPGQGLEWIGRIDPENGDIIYDPKFOGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC
AYDAGDPAWFETYWGQGLVTVSS (SEQ ID NO:321)

[0361] Nucleic acid sequence of the Ab-22 HC including signal peptide:

ATGGATTGGACCTGGAGCATTCTGTTTCTGGTGGCGGGCGCCGACCGGCGCGCATAG
 CGAAGTGAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTG
 AAAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATGCATTGGGT
 5 GCGCCAGGCGCCGGGCCAGGGCCTGGAATGGATCGGCCGCATTGATCCGGAAAAC
 GCGGATATTATTTATGATCCGAAATTTACAGGGCCGCGTGACCATGACCACCGATAACC
 AGCACCAGCACCGCGTATATGGAAGTGCAGCAGCTGCGCAGCGATGATACCGCGGT
 GTATTATTGCGCGTATGATGCGGGCGATCCGGCGTGTTTACCTATTGGGGCCAGGG
 10 CACCCTGGTGACCGTCTCGAGC (SEQ ID NO:322)

[0362] Ab-22 light chain variable domain amino acid sequence (without signal sequence):

DIQMTQSPSS LSASVGDRVT ITCKASQDVF TAVAWYQQKP GKAPKLLIYW
 ASTRHTGVPS RFGSGSGTD FTLTISSLQP EDFATYYCQQ YSSYPLTFGG
 GTKVEIKR (SEQ ID NO:336)

[0363] Ab-22 light chain variable domain DNA sequence (without signal sequence):

GATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCGAGCGTGCGGTGGGCGATCGCGT
 GACCATACCTGCAAAGCGAGCCAGGATGTGTTTACCGCGGTGGCGTGGTATCAGC

AGAAACCGGGCAAAGCGCCGAAACTGCTGATTTATTGGGCGAGCACCCGCCATACC
 GGCGTGCCGAGTCGCTTTAGCGGCAGCGGCAGCGGCACCGATTTTACCCTGACCAT
 TAGCAGCCTGCAGCCGGAAGATTTTGCAGCCTATTATTGCCAGCAGTATAGCAGCT
 30 ATCCGCTGACCTTTGGCGGCGGCACCAAAGTGGAATTAACGT (SEQ ID NO:337)

[0364] Ab-22 heavy chain variable domain amino acid sequence (without signal sequence):

EVQLVQSGAE VKKPGASVKV SCKASGFNIK DYMHWVRQA
 PGQGLEWIGRIDPENGDIIY DPKFQGRVTM TTDSTSTAY MELRSLRSDD
 TAVYYCAYDAGDPAWFTYWG QGTLTVSS (SEQ ID NO:338)

[0365] Ab-22 heavy chain variable domain DNA sequence (without signal sequence):

GAAAGTGAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTGA
 AAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATGCATTGGGTG
 45 CGCCAGGCGCCGGGCCAGGGCCTGGAATGGATCGGCCGCATTGATCCGGAAAACG
 GCGATATTATTTATGATCCGAAATTTACAGGGCCGCGTGACCATGACCACCGATACCA
 GCACCAGCACCGCGTATATGGAAGTGCAGCAGCTGCGCAGCGATGATACCGCGGTG
 TATTATTGCGCGTATGATGCGGGCGATCCGGCGTGTTTACCTATTGGGGCCAGGGC
 50 ACCCTGGTGACCGTCTCGAGC (SEQ ID NO:339).

[0366] For Ab-18, Ab-20, and Ab-22, the light chain human kappa constant region is as follows:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
 SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:325)

and the heavy chain human gamma-4 constant region is as follows:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV
FLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSR
WQEGNVFSCSVMEALHNHYTQKSLSLGLK* (SEQ ID NO:326)

[0367] The hinge region contains the Ser-241-Pro mutation to improve hinge stability (Angal S et al, (1993), Mol Immunol, 30(1), 105-108).

Ab-24

[0368] The sequences of Antibody 24 (also referred to herein as Ab-24) LC and HC are as follows:

Light Chain:

[0369] Amino acid sequence of the mature form (signal peptide removed) of the Ab-24 LC:

1 DIVLTQSPAS LAVSLGQRAT IACKASQSD YDGTSYMNWY QOKPGQPPKL
51 LIYAASNLES EIPARFSGTG SGTDFTLNIH PVEEEDITTY YCQQSNEPFI

101 TFGGGTKLEI KRADAAPTVS IFPPSSEQLT SGGASVVCFL NNFYPKDINV
151 KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS STLTLTKDEY ERHNSYTCEA
201 THKTSTSPIV KSFNRNEC (SEQ ID NO:350)

[0370] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-24 LC:

1 GACATTGTGT TGACCCAGTC TCCAGCTTCT TTGGCTGTGT CTCTAGGGCA
51 GAGGGCCACC ATCGCCTGCA AGGCCAGCCA AAGTGTGAT TATGATGGTA
101 CTAGTTATAT GAATTGGTAC CAACAGAAAC CAGGACAGCC ACCCAAATC
151 CTCATCTATG CTGCATCCAA TCTAGAATCT GAGATCCCAG CCAGGTTTAG
201 TGGCACTGGG TCTGGGACAG ACTTCACCCT CAACATCCAT CCTGTGGAGG
251 AGGAGGATAT CACAACCTAT TACTGTCAGC AAAGTAATGA GGATCCGTTT
301 ACGTTCGGAG GGGGGACCAA GTTGGAATA AAACGGGCTG ATGCTGCACC
351 AACTGTATCC ATCTTCCCAC CATCCAATGA GCAGTTAACA TCTGGAGGTG
401 CCTCAGTCGT GTGCTTCTTG AACAATCTT ACCCAAAGA CATCAATGTC
451 AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC TGAACAGTTG
501 GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC AGCACCTCA
551 CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC CTGTGAGGCC
601 ACTCAAGA CATCAACTT ACCCATGTC AAGAGCTTCA ACAGGAATGA
651 GTGTTAG (SEQ ID NO:354)

[0371] Amino acid sequence of the Ab-24 LC including signal peptide:

1 METDTILLWV LLLWVPGSTG DIVLTQSPAS LAVSLGQRAT IACKASQSVD
 51 YDGTSYMNWY QQKPGQPPKL LIYAASNLES EIPARFSGTG SGTDFTLNIH
 101 PVEEEDITTY YCQQSNEDPF TFGGGTKLEI KRADAAPTVS IFPPSSEQLT
 151 SGGASVVCFL NNFYPKDINV KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS
 201 STLTLTKDEY ERHNSYTCEA THKTSTSPIV KSFNRNEC (SEQ ID NO:355)

[0372] Nucleic acid sequence of the Ab-24 LC including signal peptide encoding sequence:

1 ATGGAGACAG ACACAATCCT GCTATGGGTG CTGCTGCTCT GGGTTCCAGG
 51 CTCCACTGGT GACATTGTGT TGACCCAGTC TCCAGCTTCT TTGGCTGTGT
 101 CTCTAGGGCA GAGGGCCACC ATCGCCTGCA AGGCCAGCCA AAGTGTTGAT
 151 TATGATGGTA CTAGTTATAT GAATTGGTAC CAACAGAAAC CAGGACAGCC
 201 ACCCAAETC CTCATCTATG CTGCATCCAA TCTAGAATCT GAGATCCCAG
 251 CCAGGTTTAG TGGCACTGGG TCTGGGACAG ACTTCACCCT CAACATCCAT
 301 CCTGTGGAGG AGGAGGATAT CACAACCTAT TACTGTCAGC AAAGTAATGA
 351 GGATCCGTTT ACGTTCGGAG GGGGGACCAA GTTGGAAATA AAACGGGCTG
 401 ATGCTGCACC AACTGTATCC ATCTTCCCAC CATCCAGTGA GCAGTTAACA
 451 TCTGGAGGTG CCTCAGTCGT GTGCTTCTTG AACAACTTCT ACCCCAAAGA
 501 CATCAATGTC AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC
 551 TGAACAGTTG GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC
 601 AGCACCTCA CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC
 651 CTGTGAGGCC ACTCACAAGA CATCAACTTC ACCCATTGTC AAGAGCTTCA
 701 ACAGGAATGA GTGTTAG (SEQ ID NO:356)

Ab-24 Heavy Chain:

[0373] Amino acid sequence of the mature form (signal peptide removed) of the Ab-24 HC:

1 QVQLQQPGTE LVRPGTSVKL SCKASGYIFT TYWMN~~WVKQR~~ PGQGLEWIGM
 51 ~~I~~HPSASEIRL ~~DQKFKDK~~ATL TLDKSSSTAY MHL~~SGPTSVD~~ SAVYYCARS~~G~~
 101 ~~EWGSMDYWGQ~~ GTSVTVSSAK ~~TPPSVYPLA~~ ~~PGSAAQTNSM~~ ~~VTLGCLVKGY~~
 151 ~~FPEPVTVTWN~~ ~~SGSLSSGVHT~~ ~~FPAVLQSDLY~~ ~~TLSSSVTVPS~~ ~~STWPSETVTC~~
 201 ~~NVAHPASSTK~~ ~~VDKKIVPRDC~~ ~~GCKPCICTVP~~ ~~EVSSVFIFPP~~ ~~KPKDVLITL~~
 251 ~~TPKVTCVVVD~~ ~~ISKDDPEVQF~~ ~~SWFVDDVEVH~~ ~~TAQTQPREEQ~~ ~~FNSTFRSVSE~~
 301 ~~LPIMHQDWLN~~ ~~GKEFKCRVNS~~ ~~AAFPAPIEKT~~ ~~IS~~TK~~GRP~~KA~~~~ ~~PQVYTIPPPK~~
 351 ~~EQMAKDKVSL~~ ~~TCMITDFFPE~~ ~~DITVEWQWNG~~ ~~QPAENYKNTQ~~ ~~PIMDTDGSYF~~
 401 ~~IYSKLVN~~~~VQKS~~ ~~NWEAGNTFTC~~ ~~SVLHEGLHNH~~ ~~HTEKSLSHSP~~ GK (SEQ ID NO:357)

[0374] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-24 HC:

1 CAGGTCCAAC TACAGCAGCC TGGGACTGAG CTGGTGAGGC CTGGAACCTC
 51 AGTGAAGTTG TCCTGTAAGG CTTCTGGCTA CATCTTCACC ACCTACTGGA
 101 TGAAGTGGGT GAAACAGAGG CCTGGACAAG GCCTTGAGTG GATTGGCATG
 5 151 ATTCATCCTT CCGCAAGTGA AATTAGGTTG GATCAGAAAT TCAAGGACAA
 201 GGCCACATTG ACTCTTGACA AATCCTCCAG CACAGCCTAT ATGCACCTCA
 251 GCGGCCCCGAC ATCTGTGGAT TCTGCGGTCT ATTACTGTGC AAGATCAGGG
 301 GAATGGGGGT CTATGGACTA CTGGGGTCAA GGAACCTCAG TCACCGTCTC
 10 351 CTCAGCCAAA ACGACACCCC CATCTGTCTA TCCACTGGCC CCTGGATCTG
 401 CTGCCCAAAC TAACTCCATG GTGACCTGG GATGCCTGGT CAAGGGCTAT
 451 TTCCCTGAGC CAGTGACAGT GACCTGGAAC TCTGGATCCC TGTCCAGCGG
 501 TGTGCACACC TTCCCAGCTG TCCTGCAGTC TGACCTCTAC ACTCTGAGCA
 551 GCTCAGTGAC TGTCCCCTCC AGCACCTGGC CCAGCGAGAC CGTCACCTGC
 15 601 AACGTTGCCC ACCCGGCCAG CAGCACCAAG GTGGACAAGA AAATTGTGCC
 651 CAGGGATTGT GGTGTAAGC CTTGCATATG TACAGTCCCA GAAGTATCAT
 701 CTGTCTTCAT CTTCCCCCA AAGCCCAAGG ATGTGCTCAC CATTACTCTG
 751 ACTCCTAAGG TCACGTGTGT TGTGGTAGAC ATCAGCAAGG ATGATCCCGA
 20 801 GGTCCAGTTC AGCTGGTTTG TAGATGATGT GGAGGTGCAC ACAGCTCAGA
 851 CGCAACCCCG GGAGGAGCAG TTCAACAGCA CTTCCGCTC AGTCAGTGAA
 901 CTTCCCATCA TGCACCAGGA CTGGCTCAAT GGCAAGGAGT TCAAATGCAG
 951 GGTCAACAGT GCAGCTTTC CTGCCCCCAT CGAGAAAACC ATCTCCAAAA
 25 1001 CCAAAGGCAG ACCGAAGGCT CCACAGGTGT ACACCATTC ACCTCCCAAG
 1051 GAGCAGATGG CCAAGGATAA AGTCAGTCTG ACCTGCATGA TAACAGACTT
 1101 CTTCCCTGAA GACATTACTG TGGAGTGGCA GTGGAATGGG CAGCCAGCGG
 1151 AGAACTACAA GAACACTCAG CCCATCATGG ACACAGATGG CTCTTACTTC
 30 1201 ATCTACAGCA AGCTCAATGT GCAGAAGAGC AACTGGGAGG CAGGAAATAC
 1251 TTTCACCTGC TCTGTGTTAC ATGAGGGCCT GCACAACCAC CATACTGAGA
 1301 AGAGCCTCTC CCACTCTCCT GTAAATGA (SEQ ID NO:361)

[0375] Amino acid sequence of the Ab-24 HC including signal peptide:

1 MGWSSILFL VATATGVHSQ VQLQQPGTEL VRPGTSVKLS CKASGYIFTT
 51 YWMNWVKQRP GQGLEWIGMI HPSASEIRLD QKFKDKATLT LDKSSSTAYM
 101 HLSGPTSVDV AVYYCARSGE WGSMDYWGQG TSVTVSSAKT TPPSVYPLAP
 40
 151 GSAAQTNSMV TLGCLVKGYF PEPVTVTWNS GSLSSGVHTF PAVLQSDLYT
 201 LSSSVTVPSS TWPSETVTCN VAHPASSTKV DKKIVPRDCG CKPCICTVPE
 251 VSSVFIFPPK PKDVLITLT PKVTCVVVDI SKDDPEVQFS WFDVDDVEVHT
 301 AQTQPREEQF NSTFRSVSEL PIMHQDWLNG KEFKCRVNSA AFPAPIEKTI
 351 SKTKGRPKAP QVYTIPPPKE QMAKDKVSLT CMITDFFPED ITVEWQWNGQ
 401 PAENYKNTQP IMDTDGSYFI YSKLNVQKSN WEAGNTFTCS VLHEGLHNHH
 451 TEKSLSHSPG K (SEQ ID NO:362)

[0376] Nucleic acid sequence of the Ab-24 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTCTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT
 51 CCACTCCAG GTCCAACACTAC AGCAGCCTGG GACTGAGCTG GTGAGGCCTG
 101 GAACTTCAGT GAAAGTTGTCC TGTAAAGGCTT CTGGCTACAT CTTCACCACC
 151 TACTGGATGA ACTGGGTGAA ACAGAGGCCT GGACAAGGCC TTGAGTGGAT
 201 TGGCATGATT CATCCTTCCG CAAGTGAAAT TAGGTTGGAT CAGAAATTCA
 251 AGGACAAGGC CACATTGACT CTTGACAAAT CCTCCAGCAC AGCCTATATG
 301 CACCTCAGCG GCCCGAATC TGTGGATTCT GCGGTCTATT ACTGTGCAAG
 351 ATCAGGGGAA TGGGGGTCTA TGGACTACTG GGGTCAAGGA ACCTCAGTCA
 401 CCGTCTCCTC AGCCAAAACG ACACCCCAT CTGTCTATCC ACTGGCCCCT
 451 GGATCTGCTG CCCAACTAA CTCCATGGTG ACCCTGGGAT GCCTGGTCAA
 501 GGGCTATTTT CCTGAGCCAG TGACAGTGAC CTGGAAGTCT GGATCCCTGT
 551 CCAGCGGTGT GCACACCTTC CCAGCTGTCC TGCAGTCTGA CCTCTACACT
 601 CTGAGCAGCT CAGTGACTGT CCCCTCCAGC ACCTGGCCCA GCGAGACCGT
 651 CACCTGCAAC GTTGCCACC CGGCCAGCAG CACCAAGGTG GACAAGAAAA
 701 TTGTGCCAG GGATTGTGGT TGTAAAGCCTT GCATATGTAC AGTCCAGAA
 751 GTATCATCTG TCTTCATCTT CCCCCAAAG CCCAAGGATG TGCTACCAT
 801 TACTCTGACT CTAAGGTCA CGTGTGTTGT GGTAGACATC AGCAAGGATG
 851 ATCCCGAGGT CCAGTTCAGC TGGTTTGTAG ATGATGTGGA GGTGCACACA
 901 GCTCAGACGC AACCCCGGGA GGAGCAGTTC AACAGCACTT TCCGCTCAGT
 951 CAGTGAAGTT CCCATCATGC ACCAGGACTG GCTCAATGGC AAGGAGTTCA
 1001 AATGCAGGGT CAACAGTGCA GCTTTCCTG CCCCATCGA GAAAACCATC
 1051 TCCAAAACCA AAGGCAGAC GAAGGCTCCA CAGGTGTACA CCATTCCACC
 1101 TCCAAGGAG CAGATGGCCA AGGATAAAGT CAGTCTGACC TGCATGATAA
 1151 CAGACTTCTT CCCTGAAGAC ATTACTGTGG AGTGGCAGTG GAATGGGCAG
 1201 CCAGCGGAGA ACTACAAGAA CACTCAGCCC ATCATGGACA CAGATGGCTC
 1251 TTAATTCATC TACAGCAAGC TCAATGTGCA GAAGAGCAAC TGGGAGGCAG
 1301 GAAATACTTT CACCTGCTCT GTGTTACATG AGGGCCTGCA CAACCACCAT
 1351 ACTGAGAAGA GCCTCTCCA CTCTCCTGGT AAATGA (SEQ ID NO:363)

[0377] The CDR sequences in the variable region of the light chain of Ab-24 are as follows:

CDR-L1: KASQSVYDGTSYNIN (SEQ ID NO:351)

CDR-L2: AASNLES (SEQ ID NO:352)

CDR-L3: QQSNEPFT (SEQ ID NO:353)

[0378] The CDR sequences in the variable region of the heavy chain of Ab-24 are as follows:

CDR-H1: TYWMN (SEQ ID NO:358)

CDR-H2: MIHPSASEIRLDQKFKD (SEQ ID NO:359)

CDR-H3: SGEWGSMDY (SEQ ID NO:360)

[0379] Table 1 below provides the SEQ ID NOs and amino acid sequences of the CDR's of Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24. L1, L2, and L3 refer to light chain CDR's 1,2, and 3, and H1, H2, and H3 refer to heavy chain CDR's 1,2, and 3 according to the Kabat numbering system (Kabat *et al.*, 1987 in *Sequences of Proteins of Immunological Interest*, U.S. Department of Health and Human Services, NIH, USA).

Table 1		
SEQ ID NO	DESCRIPTION	AMINO ACID SEQUENCE
54	Ab-A and Ab-1 CDR-L1	QSSQSVYDNNWLA

EP 2 251 351 B1

(continued)

Table 1		
SEQ ID NO	DESCRIPTION	AMINO ACID SEQUENCE
55	Ab-A and Ab-1 CDR L2	DASDLAS
56	Ab-A and Ab-1 CDR-L3	QGAYNDVIYA
51	Ab-A and Ab-1 CDR-H1	SYWMN
52	Ab-A and Ab-1 CDR-H2	TIDSGGRTDYASWAKG
53	Ab-A and Ab-1 CDR-H3	NWNL
60	Ab-B CDR-L1	SASSSVSFVD
61	Ab-B CDR-L2	RTSNLGF
62	Ab-BCDR-L3	QQRSTYPPT
57	Ab-B CDR-H1	TSGMGVG
58	Ab-B CDR-H2	HIWWDDVKRYNPVLKS
59	Ab-B CDR-H3	EDFDYDEEYYAMDY
48	Ab-C CDR-L1	KASQSVDYDCDSYMN
49	Ab-C CDR-L2	AASNLES
50	Ab-C CDR-L3	QQSNEDPWT
45	Ab-C CDR-H1	DCYMN
46	Ab-CCDR-H2	DINPFNGGTTYNQKFKG
47	Ab-C CDR-H3	SHYYFDGRVPWDAMDY
42	Ab-DCDR-L1	QASQGTSINLN
43	Ab-D CDR-L2	GSSNLED
44	Ab-D CDR-L3	LQHSYLPYT
39	Ab-D CDR-H1	DHYMS
40	Ab-D CDR-H2	DINPYSGETTYNQKFKG
41	Ab-D CDR-H3	DDYDASPFAY
275	Ab-2 CDR-L1	RASSSVYYMH
276	Ab-2 CDR-L2	ATSNLAS
277	Ab-2 CDR-L3	QQWSSDPLT
287	Ab-2 CDR-H1	DYFIH
288	Ab-2 CDR-H2	RLDPEDGESDYAPKFQD
289	Ab-2CDR-H3	EDYPGTYTFFPY
278	Ab-3 and Ab-15CDR-L1	SVSSTISSNHLH
279	Ab-3 and Ab-15 CDR-L2	GTSNLAS
280	Ab-3 and Ab-15 CDR-L3	QQWSSYPLT
290	Ab-3 and Ab-15 CDR-H1	DFYLH
291	Ab-3 and Ab-15 CDR-H2	RIDPENGDTLYPPKFQD
292	Ab-3 and Ab-15 CDR-H3	EADYFHDGTSYWYFDV
78	Ab-4 and Ab-5 CDR-L1	RASQDISNYLN
79	Ab-4 and Ab-5 CDR-L2	YTSRLLS

EP 2 251 351 B1

(continued)

Table 1		
SEQ ID NO	DESCRIPTION	AMINO ACID SEQUENCE
80	Ab-4 and Ab-5 CDR-L3	QQGDTLPYT
245	Ab-4 and Ab-5 CDR-H1	DYIMH
246	Ab-4 and Ab-5 CDR-H2	EINPIVSGGAQYNQKFKG
247	Ab-4 and Ab-5 CDR-H3	LGYDDIYDI7WYFDV
81	Ab-6 CDR-L1	RASQDISNYLN
99	Ab-6 CDR-L2	YTSRLHS
100	Ab-6CDR-L3	QQGDTLPYT
248	Ab-6 CDR-H1	DYNMH
249	Ab-6 CDR-H2	EINPNSGGSGYNQKFKG
250	Ab-6 CDR-H3	LVYDGSYEDWYFDV
101	Ab-7 CDR-L1	RASQVITNYLY
102	Ab-7 CDR-L2	YTSRLHS
103	Ab-7 CDR-L3	QQGDTLPYT
251	Ab-7 CDR-H1	DYNMH
252	Ab-7 CDR-H2 Ab-7 CDR-H2	EINPNSGGAGYNQQFKG
253	Ab-7 CDR-H3	LGYVGNVEDWYFDV
104	Ab-8 CDR-L1	RASQDISNYLN
105	Ab-8 CDR-L2	YTSRLLS
106	Ab-8 CDR-L3	QQGDTLPYT
254	Ab-8 CDR-H1	DYIMH
255	Ab-8 CDR-H2	EINPNSGGAGYNQKFKG
256	Ab-8 CDR-H3	LGYDDIYDDWYFDV
107	Ab-9 CPR-L1	RASQDISNYLN
108	Ab-9 CDR-L2	YTSRLFS
109	Ab-9 CDR-L3	QQGDTLPYT
257	Ab-9 CDR-H1	DYNMH
258	Ab-9 CDR-H2	EINPNSGGAGYNQKFKG
259	Ab-9 CDR-H3	LOYDDIYPDWYTDV
110	Ab-10 CDR-L1	RASQDISNYLN
111	Ab-10 CDR-L2	YTSRLLS
112	Ab-10 CDR-L3	QQGDTLPYT
260	Ab-10 CDR-H1	DYIMH
261	Ab-10 CDR-H2	EINPNSGGAGYNQKFKG
262	Ab-10 CDR-H3	LGYDDIYDDWYFDV
281	Ab-11 and Ab-16 CDR-L1	RASSSISYIH
282	Ab-11 and Ab-16 CDR-L2	ATSNLAS
283	Ab-11 and Ab-16 CDR-L3	QQWSSDPLT

EP 2 251 351 B1

(continued)

Table 1		
SEQ ID NO	DESCRIPTION	AMINO ACID SEQUENCE
293	Ab-11 and Ab-16 CDR-H1	DYYIH
294	Ab-11 and Ab-16 CDR-H2	RVDPDNGETEFAPKFPG
295	Ab-11 and Ab-16 CDR-H3	EDYDGTYTWFY
113	Ab-12 CDR-L1	RASQDISNYLN
114	Ab-12 CDR-L2	YTSTLQS
115	Ab-12 CDR-L3	QQGDTLPYT
263	Ab-12 CDR-H1	DYNMH
264	Ab-12 CDR-H2	EDNPNSGGSGYNQKFKG
265	Ab-12 CDR-H3	LGYYGNVEDWYFDV
284	Ab-13 and Ab-14 CDR-L1	RASSSVTSSYLN
285	Ab-13 and Ab-14 CDR-L2	STSNLAS
286	Ab-13 and Ab-14 CDR-L3	QQYDFFPST
296	Ab-13 and Ab-14 CDR-H1	DYYMN
297	Ab-13 and Ab-14 CDR-H2	DINPYNDDTTYNHKFKG
298	Ab-13 and Ab-14 CDR-H3	ETAVITTNAMD
116	Ab-17 and Ab-18 CDR-L1	SVSSSISSSNLH
237	Ab-17 and Ab-18 CDR-L2	GTSNLAS
238	Ab-17 and Ab-18 CDR-L3	QQWTTTYT
266	Ab-17 and Ab-18 CDR-H1	DYYIH
267	Ab-17 and Ab-18 CDR-H2	RIDPDNGESTYVPKFQG
268	Ab-17 and Ab-18 CDR-H3	EGLDYGDYYAVDY
239	Ab-19, Ab-20 and Ab-23 CDR-L1	RASQDISSYLN
240	Ab-19, Ab-20 and Ab-23 CDR-L2	STSRINS
241	Ab-19, Ab-20 and Ab-23 CDR-L3	QQDIKHPT
269	Ab-19, Ab-20 and Ab-23 CDR-H1	DYIMH
270	Ab-19, Ab-20 and Ab-23 CDR-H2	YINPYNDDTEYNEKFKG
271	Ab-19, Ab-20 and Ab-23 CDR-H3	SIYYDAPFAY
242	Ab-21 and Ab-22 CDR-L1	KASQDVFTAVA
243	Ab-21 and Ab-22 CDR-L2	WASTRHT
244	Ab-21 and Ab-22 CDR-L3	QQYSSYPLT
272	Ab-21 and Ab-22 CDR-H1	DYYMH
273	Ab-21 and Ab-22 CDR-H2	RIDPENGDIIDPKFQG
274	Ab-21 and Ab-22 CDR-H3	DAGDPAWFTY
351	Ab-24 CDR-L1	KASQSVDDYDGTSMN
352	Ab-24 CDR-L2	AASNLES
353	Ab-24 CDR-L3	QQSNEDPFT
358	Ab-24 CDR-H1	TYWMN

(continued)

Table 1		
SEQ ID NO	DESCRIPTION	AMINO ACID SEQUENCE
359	Ab-24 CDR-H2	MIHPSASEIRLDQKFKD
360	Ab-24 CDR-H3	SGEWGSMDY

[0380] An oligopeptide or polypeptide is within the scope of the disclosure if it has an amino acid sequence that is at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to least one of the CDR's of Table 1 above; and/or to a CDR of a sclerostin binding agent that cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 to sclerostin, and/or is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24; and/or to a CDR of a sclerostin binding agent wherein the binding agent can block the inhibitory effect of sclerostin in a cell based mineralization assay (*i.e.* a sclerostin neutralizing binding agent); and/or to a CDR of a sclerostin binding agent that binds to a Loop 2 epitope; and/or to a CDR of a sclerostin binding agent that binds to a T20.6 epitope; and/or to a CDR of a sclerostin binding agent that binds to a "T20.6 derivative (cystine-knot + 4 arms)" epitope.

[0381] Sclerostin binding antibodies are within the scope of the disclosure if they have amino acid sequences that are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a variable region of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24, and cross-block the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 to sclerostin, and/or are cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24; and/or can block the inhibitory effect of sclerostin in a cell based mineralization assay (*i.e.* a sclerostin neutralizing binding agent); and/or bind to a Loop 2 epitope; and/or bind to a T20.6 epitope; and/or bind to a "T20.6 derivative (cystine-knot + 4 arms)" epitope.

[0382] Polynucleotides encoding sclerostin binding agents are within the scope of the disclosure if they have polynucleotide sequences that are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polynucleotide encoding a variable region of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24, and wherein the encoded sclerostin binding agents cross-block the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 to sclerostin, and/or are cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24; and/or can block the inhibitory effect of sclerostin in a cell based mineralization assay (*i.e.* a sclerostin neutralizing binding agent); and/or bind to a Loop 2 epitope; and/or bind to a T20.6 epitope; and/or bind to a "T20.6 derivative (cystine-knot + 4 arms)" epitope.

[0383] Antibodies according to the invention may have a binding affinity for human sclerostin of less than or equal to $1 \times 10^{-10}M$, less than or equal to $1 \times 10^{-11}M$, or less than or equal to $1 \times 10^{-12}M$.

[0384] The affinity of an antibody, as well as the extent to which inhibits binding, can be determined by one of ordinary skill in the art using conventional techniques, for example those described by Scatchard et al. (Ann. N.Y. Acad. Sci. 51:660-672 (1949)) or by surface plasmon resonance (SPR; BIAcore, Biosensor, Piscataway, NJ). For surface plasmon resonance, target molecules are immobilized on a solid phase and exposed to ligands in a mobile phase running along a flow cell. If ligand binding to the immobilized target occurs, the local refractive index changes, leading to a change in SPR angle, which can be monitored in real time by detecting changes in the intensity of the reflected light. The rates of change of the SPR signal can be analyzed to yield apparent rate constants for the association and dissociation phases of the binding reaction. The ratio of these values gives the apparent equilibrium constant (affinity) (*see, e.g.,* Wolff et al., Cancer Res. 53:2560-65 (1993)).

[0385] An antibody according to the present invention may belong to any immunoglobulin class, for example IgG, IgE, IgM, IgD, or IgA. It may be obtained from or derived from an animal, for example, fowl (*e.g.,* chicken) and mammals, which includes but is not limited to a mouse, rat, hamster, rabbit, or other rodent, cow, horse, sheep, goat, camel, human,

or other primate. The antibody may be an internalizing antibody. Production of antibodies is disclosed generally in U.S. Patent Publication No. 2004/0146888 A1.

Characterization Assays

[0386] In the methods described above to generate antibodies, including the manipulation of the specific Ab-A, Ab-B, Ab-C, Ab-D, and Antibody 1-24 (Ab-1 to Ab-24) CDRs into new frameworks and/or constant regions, appropriate assays are available to select the desired antibodies (*i.e.* assays for determining binding affinity to sclerostin; cross-blocking assays; Biacore-based "human sclerostin peptide epitope competition binding assay;" MC3T3-E1 cell based assay; *in vivo* assays).

Epitope Binding Assays

[0387] Mature form human sclerostin is a 190 amino acid glycoprotein with a cystine-knot structure (Figures 8 and 9). In addition to the cystine-knot structure, the protein is characterized as having three loops designated as Loop 1, Loop 2 and Loop 3. Human sclerostin was subjected to proteolytic digestion to produce fragments. Briefly, using different proteases, including trypsin, aspN, and lysC, fragments with various cleavage sites and sizes were generated. The sequences and mass for various human sclerostin peptides were determined. Antibody protection was evaluated to determine the effect on accessibility for proteolysis, including clipped site masking and peptide shifting. Finally, a Biacore-based "human sclerostin peptide epitope competition assay" was performed.

[0388] Exposure of sclerostin to trypsin cleavage resulted in a pattern of peptide fragments as summarized in Figure 13. The fragments are referred to as T19.2, T20, T20.6, and T21-22. As shown schematically in Figure 19B, the T20.6 epitope is a complex of four separate peptide sequences which are joined by the three disulfide bonds of the cystine-knot region. Two of the peptides are joined by two disulfide bonds. The other two peptides are linked by one disulfide bond that, schematically, bisects the first two polypeptides.

[0389] The T20.6 epitope that was generated by trypsin digestion retains the cystine-knot structure of the native polypeptide and is recognized by antibodies Ab-C and Ab-D. A derivative of epitope T20.6 consists of the cystine-knot region and amino acids 58-64, 73-81, 112-117 and 138-141 in sequence position with reference to SEQ ID NO:1. This derivative epitope is shown in Figure 21. An epitope comprising the cystine-knot region may have one or more amino acids that is present in the T20.6 epitope (Figure 19B) but not present in the T20.6 derivative epitope (Figure 21).

[0390] Another epitope-containing region was identified in the Loop 2 region of human sclerostin (Figure 19A) and is recognized by antibodies Ab-A and Ab-B. A Loop 2 epitope comprises amino acids 86-111 of SEQ ID NO:1 (C4GPARLLPNAIGRGKWWRPSGPDFRC5, SEQ ID NO:6). Sterically, with reference to full-length sclerostin of SEQ ID NO: 1, the Loop 2-containing structure is defined at one end by a disulfide bond between cysteine at position 86 (C4) and cysteine at position 144 (C8), and at the other end by a disulfide bond between cysteine at position 111 (C5) and cysteine at position 57 (C1).

[0391] The peptides generated by aspN cleavage of human sclerostin are shown in Figure 12. In the Figure, these peptides are designated as AspN14.6, AspN18.6, and AspN22.7-23.5, and are also referred to herein as N14.6, N18.6, and N22.7-23.5, respectively.

[0392] One group of antibodies exhibits a specific pattern of binding to certain epitopes as evidenced by a Biacore-based "human sclerostin peptide epitope competition binding assay." Briefly, the antibody is preincubated with the epitope to be tested, at concentrations that will saturate the epitope-binding sites on the antibody. The antibody is then exposed to sclerostin bound to a chip surface. After the appropriate incubation and washing procedures, a pattern of competitive binding is established. As shown in Figure 18, exemplary antibody Ab-D bound to sclerostin molecules attached to the surface of the chip. Preincubation of antibody Ab-D with sclerostin decreased the binding of the antibody to the sclerostin on the chip to close to zero. Preincubation with a peptide consisting of epitope T19.2 showed that T19.2 did not compete with sclerostin for antibody binding. However, preincubation with any one of the epitopes designated T20, T20.6, T21-22, or N22.7-23.5 abolished a large proportion of the binding of antibody to sclerostin on the chip. In contrast, preincubation of the antibody with any one of the epitopes designated T19.2, N14.6 or N18.6 did not abolish the ability of the antibody to bind to sclerostin. A second exemplary antibody with this binding profile (Fig. 17) is Ab-C.

[0393] Antibody Ab-D therefore is exemplary and representative of a group of antibodies that bind to the epitopes T20, T20.6, T21-22, and N22.7-23.5, and have minimal detectable binding to epitopes T19.2, N14.6 and N18.6, as measured by the ability to block antibody binding to sclerostin. Antibodies having this characteristic binding pattern may or may not share amino acid sequence in one or more regions of the antibody molecule. Antibody similarity is determined functionally such as by the ability to bind to sclerostin following preincubation with each of the epitopes described above. Antibodies that exhibit a binding pattern similar or identical to that of antibody Ab-D are included in the invention. By "similar to" is meant, for example, the antibody will exhibit binding to each of the polypeptides T20, T20.6, T21-22 and N22.7-23.5 whereby this binding will specifically compete out at least 50% of the antibody's binding to sclerostin that

would otherwise occur in the absence of preincubation with sclerostin or a sclerostin peptide. The antibody will also exhibit little or no detectable binding to polypeptides T19.2, N14.6 and N18.6, resulting in a reduction of 30% or less of the binding that would occur in the absence of preincubation with sclerostin or a sclerostin peptide.

[0394] For example, without being bound by a particular mechanism, the antibody binding pattern of Figure 18 suggests that the epitope space to which antibody Ab-D and other antibodies having the epitope binding pattern of Ab-D bind consists of a polypeptide comprising the cystine-knot region of sclerostin.

[0395] Thus, as disclosed herein and with reference to Figure 19B, an exemplary T20.6 epitope comprises four peptide chains attached via three separate disulfide bonds. Peptide chain SAKPVTELVC3SCQC4GPAR (SEQ ID NO:3) is attached to peptide chain LVASC7KC8KRLTR (SEQ ID NO:5) by disulfide bonds from C3 to C7, and from C4 to C8. Peptide chain DVSEYSC1RELHFTR (SEQ ID NO:2) is attached to peptide chain WWRPSGPDFRC5IPDRYR (SEQ ID NO:4) by a disulfide bond from C1 to C5. The polypeptides of SEQ ID NOs:3 and 5 remain associated with the polypeptides of SEQ ID NOs:2 and 4 through a steric construct whereby the C1-C5 bond crosses the plane of the C4-C8 and C3-C7 bonds and is located between them, as illustrated in Figure 19B.

[0396] As disclosed herein and with reference to Figure 21, an exemplary derivative epitope of T20.6 comprises four peptide chains attached via three separate disulfide bonds. Peptide chain SAKPVTELVC3SGQC4 (SEQ ID NO:70) is attached to peptide chain LVASC7KC8 (SEQ ID NO:71) by disulfide bonds from C3 to C7, and from C4 to C8. Peptide chain C1RELHFTR (SEQ ID NO:72) is attached to peptide chain C5IPDRYR (SEQ ID NO:73) by a disulfide bond from C1 to C5. The polypeptides of SEQ ID NOs:70 and 71 remain associated with the polypeptides of SEQ ID NOs:72 and 73 through a steric construct whereby the C1-C5 bond crosses the plane of the C4-C8 and C3-C7 bonds and is located between them, as illustrated in Figure 21.

[0397] Antibody Ab-A is exemplary and representative of a second group of antibodies that have a characteristic binding pattern to human sclerostin peptides that is distinct from that obtained for antibodies Ab-C and Ab-D. Ab-A and the group of antibodies it represents bind to the N22.7-23.5 epitope and have minimal detectable binding to epitopes T19.2, T20, T20.6, T21-22, N14.6 or N18.6, as measured by the ability to block antibody binding to sclerostin (Fig 15).

A second exemplary antibody with this binding profile (Fig. 16) is Ab-B. Antibodies having this characteristic binding pattern may or may not share amino acid sequence in one or more regions of the antibody molecule. Antibody similarity is determined functionally such as by the ability to bind to sclerostin following preincubation with each of the epitopes described above. Antibodies that exhibit a binding pattern similar or identical to that of antibody Ab-A are included in the invention. By "similar to" is meant, for example, the antibody will exhibit binding to the N22.7-23.5 polypeptide whereby this binding will specifically compete out at least 50% of the antibody's binding to sclerostin that would otherwise occur in the absence of preincubation with sclerostin or a sclerostin peptide. The antibody will also exhibit little or no detectable binding to polypeptides T19.2, T20, T20.6, T21-22, N14.6 and N18.6, resulting in a reduction of 30% or less of the binding that would occur in the absence of preincubation with sclerostin or a sclerostin peptide.

[0398] For example, without being bound by a particular mechanism, the antibody binding pattern of Figure 15 suggests that the epitope space to which antibody Ab-A and other antibodies having the epitope binding pattern of Ab-A bind consists of a polypeptide comprising the Loop 2 region of sclerostin. Thus, as disclosed herein and with reference to Figure 19A, the Loop 2 region can be described as a linear peptide, but it acquires a tertiary structure when it is present in native sclerostin or a cystine-knot-containing portion of sclerostin in which the native disulfide bond structure is maintained. The linear or tertiary structure of the Loop 2 epitope can affect antibody binding thereto, as discussed in the Examples. A Loop 2 region can comprise the following amino acid sequence: C4GPARLLPNAIGRGKWWRPSGPDFRC5 (SEQ ID NO:6). "C4" refers to a cysteine residue located at position 86 with reference to SEQ ID NO:1. "C5" refers to a cysteine residue located at position 111 with reference to SEQ ID NO:1. In native sclerostin protein, C4 is linked to a cysteine at position 144 (C8) by a disulfide bond, and C5 is linked to a cysteine at position 57 (C1) by a disulfide bond. Epitopes derived from the Loop 2 region include CGPARLLPNAIGRGKWWRPS (SEQ ID NO:63);

GPARLLPNAIGRGKWWRPSG (SEQ ID NO:64); PARLLPNAIGRGKWWRPSGP (SEQ ID NO:65); ARLLPNAIGRGKWWRPSGPD (SEQ ID NO:66); RLLPNAIGRGKWWRPSGPDF (SEQ ID NO:67); LLPNAIGRGKWWRPSGPDFR (SEQ ID NO:68); and LPNAIGRGKWWRPSGPDFRC (SEQ ID NO:69)

CROSS-BLOCKING ASSAYS

[0399] The terms "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or other binding agent to interfere with the binding of other antibodies or binding agents to sclerostin.

[0400] The extent to which an antibody or other binding agent is able to interfere with the binding of another to sclerostin, and therefore whether it can be said to cross-block according to the invention, can be determined using competition binding assays. One particularly suitable quantitative assay uses a Biacore machine which can measure the extent of interactions using surface plasmon resonance technology. Another suitable quantitative cross-blocking assay uses an ELISA-based approach to measure competition between antibodies or other binding agents in terms of their binding to

sclerostin.

BIACORE CROSS-BLOCKING ASSAY

[0401] The following generally describes a suitable Biacore assay for determining whether an antibody or other binding agent cross-blocks or is capable of cross-blocking according to the invention. For convenience reference is made to two antibodies, but it will be appreciated that the assay can be used with any of the sclerostin binding agents described herein. The Biacore machine (for example the Biacore 3000) is operated in line with the manufacturer's recommendations.

[0402] Thus in one cross-blocking assay, sclerostin is coupled to a CM5 Biacore chip using standard amine coupling chemistry to generate a sclerostin-coated surface. Typically 200-800 resonance units of sclerostin would be coupled to the chip (an amount that gives easily measurable levels of binding but that is readily saturable by the concentrations of test reagent being used).

[0403] The two antibodies (termed A* and B*) to be assessed for their ability to cross-block each other are mixed at a one to one molar ratio of binding sites in a suitable buffer to create the test mixture. When calculating the concentrations on a binding site basis the molecular weight of an antibody is assumed to be the total molecular weight of the antibody divided by the number of sclerostin binding sites on that antibody.

[0404] The concentration of each antibody in the test mix should be high enough to readily saturate the binding sites for that antibody on the sclerostin molecules captured on the Biacore chip. The antibodies in the mixture are at the same molar concentration (on a binding basis) and that concentration would typically be between 1.00 and 1.5 micromolar (on a binding site basis).

[0405] Separate solutions containing antibody A* alone and antibody B* alone are also prepared. Antibody A* and antibody B* in these solutions should be in the same buffer and at the same concentration as in the test mix.

[0406] The test mixture is passed over the sclerostin-coated Biacore chip and the total amount of binding recorded. The chip is then treated in such a way as to remove the bound antibodies without damaging the chip-bound sclerostin.

Typically this is done by treating the chip with 30 mM HCl for 60 seconds.

[0407] The solution of antibody A* alone is then passed over the sclerostin-coated surface and the amount of binding recorded. The chip is again treated to remove all of the bound antibody without damaging the chip-bound sclerostin.

[0408] The solution of antibody B* alone is then passed over the sclerostin-coated surface and the amount of binding recorded.

[0409] The maximum theoretical binding of the mixture of antibody A* and antibody B* is next calculated, and is the sum of the binding of each antibody when passed over the sclerostin surface alone. If the actual recorded binding of the mixture is less than this theoretical maximum then the two antibodies are cross-blocking each other.

[0410] Thus, in general, a cross-blocking antibody or other binding agent according to the invention is one which will bind to sclerostin in the above Biacore cross-blocking assay such that during the assay and in the presence of a second antibody or other binding agent of the invention the recorded binding is between 80% and 0.1% (e.g. 80% to 4%) of the maximum theoretical binding, specifically between 75% and 0.1% (e.g. 75% to 4%) of the maximum theoretical binding, and more specifically between 70% and 0.1% (e.g. 70% to 4%) of maximum theoretical binding (as just defined above) of the two antibodies or binding agents in combination.

[0411] The Biacore assay described above is a primary assay used to determine if antibodies or other binding agents cross-block each other according to the invention. On rare occasions particular antibodies or other binding agents may not bind to sclerostin coupled via amine chemistry to a CM5 Biacore chip (this usually occurs when the relevant binding site on sclerostin is masked or destroyed by the coupling to the chip). In such cases cross-blocking can be determined using a tagged version of Sclerostin, for example N-terminal His-tagged Sclerostin, (R & D Systems, Minneapolis, MN, USA; 2005 cat# 1406-ST-025). In this particular format, an anti-His antibody would be coupled to the Biacore chip and then the His-tagged Sclerostin would be passed over the surface of the chip and captured by the anti-His antibody. The cross blocking analysis would be carried out essentially as described above, except that after each chip regeneration cycle, new His-tagged sclerostin would be loaded back onto the anti-His antibody coated surface. In addition to the example given using N-terminal His-tagged Sclerostin, C-terminal His-tagged sclerostin could alternatively be used. Furthermore, various other tags and tag binding protein combinations that are known in the art could be used for such a cross-blocking analysis (e.g. HA tag with anti-HA antibodies; FLAG tag with anti-FLAG antibodies; biotin tag with streptavidin).

ELISA-BASED CROSS-BLOCKING ASSAY

[0412] The following generally describes an ELISA assay for determining whether an anti-sclerostin antibody or other sclerostin binding agent cross-blocks or is capable of cross-blocking according to the invention. For convenience, reference is made to two antibodies (Ab-X and Ab-Y), but it will be appreciated that the assay can be used with any of the sclerostin binding agents described herein.

[0413] The general principal of the assay is to have an anti-sclerostin antibody coated onto the wells of an ELISA plate. An excess amount of a second, potentially cross-blocking, anti-sclerostin antibody is added in solution (*i.e.* not bound to the ELISA plate). A limited amount of sclerostin is then added to the wells. The coated antibody and the antibody in solution compete for binding of the limited number of sclerostin molecules. The plate is washed to remove sclerostin that has not been bound by the coated antibody and to also remove the second, solution phase antibody as well as any complexes formed between the second, solution phase antibody and sclerostin. The amount of bound sclerostin is then measured using an appropriate sclerostin detection reagent. An antibody in solution that is able to cross-block the coated antibody will be able to cause a decrease in the number of sclerostin molecules that the coated antibody can bind relative to the number of sclerostin molecules that the coated antibody can bind in the absence of the second, solution phase, antibody.

[0414] This assay is described in more detail further below for Ab-X and Ab-Y. In the instance where Ab-X is chosen to be the immobilized antibody, it is coated onto the wells of the ELISA plate, after which the plates are blocked with a suitable blocking solution to minimize non-specific binding of reagents that are subsequently added. An excess amount of Ab-Y is then added to the ELISA plate such that the moles of Ab-Y sclerostin binding sites per well are at least 10 fold higher than the moles of Ab-X sclerostin binding sites that were used, per well, during the coating of the ELISA plate. Sclerostin is then added such that the moles of sclerostin added per well are at least 25-fold lower than the moles of Ab-X sclerostin binding sites that were used for coating each well. Following a suitable incubation period the ELISA plate is washed and a sclerostin detection reagent is added to measure the amount of sclerostin specifically bound by the coated anti-sclerostin antibody (in this case Ab-X). The background signal for the assay is defined as the signal obtained in wells with the coated antibody (in this case Ab-X), second solution phase antibody (in this case Ab-Y), sclerostin buffer only (*i.e.* no sclerostin) and sclerostin detection reagents. The positive control signal for the assay is defined as the signal obtained in wells with the coated antibody (in this case Ab-X), second solution phase antibody buffer only (*i.e.* no second solution phase antibody), sclerostin and sclerostin detection reagents. The ELISA assay needs to be run in such a manner so as to have the positive control signal be at least 6 times the background signal.

[0415] To avoid any artifacts (*e.g.* significantly different affinities between Ab-X and Ab-Y for sclerostin) resulting from the choice of which antibody to use as the coating antibody and which to use as the second (competitor) antibody, the cross-blocking assay needs to be run in two formats:

1) format 1 is where Ab-X is the antibody that is coated onto the ELISA plate and Ab-Y is the competitor antibody that is in solution and

2) format 2 is where Ab-Y is the antibody that is coated onto the ELISA plate and Ab-X is the competitor antibody that is in solution.

[0416] Ab-X and Ab-Y are defined as cross-blocking if, either in format 1 or in format 2, the solution phase anti-sclerostin antibody is able to cause a reduction of between 60% and 100%, specifically between 70% and 100%, and more specifically between 80% and 100%, of the sclerostin detection signal (*i.e.* the amount of sclerostin bound by the coated antibody) as compared to the sclerostin detection signal obtained in the absence of the solution phase anti-sclerostin antibody (*i.e.* the positive control wells).

[0417] An example of such an ELISA-based cross blocking assay can be found in Example 7 ("ELISA-based cross-blocking assay").

CELLBASED NEUTRALIZATION ASSAY

[0418] Mineralization by osteoblast-lineage cells in culture, either primary cells or cell lines, is used as an *in vitro* model of bone formation. Mineralization takes from about one to six weeks to occur beginning with the induction of osteoblast-lineage cell differentiation by one or more differentiation agents. The overall sequence of events involves cell proliferation, differentiation, extracellular matrix production, matrix maturation and finally deposition of mineral, which refers to crystallization and/or deposition of calcium phosphate. This sequence of events starting with cell proliferation and differentiation, and ending with deposition of mineral is referred to herein as mineralization. Measurement of calcium (mineral) is the output of the assay.

[0419] MC3T3-E1 cells (Sudo H, Kodama H-A, Amagai Y, Yamamoto S, Kasai S. 1983. In vitro differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvaria. J. Cell Biol. 96:191-198) and subclones of the original cell line can form mineral in culture upon growth in the presence of differentiating agents. Such subclones include MC3T3-E1-BF (Smith E, Redman R, Logg C, Coetzee G, Kasahara N, Frenkel B. 2000. Glucocorticoids inhibit developmental stage-specific osteoblast cell cycle. J. Biol. Chem. 275:19992-20001). For both the MC3T3-E1-BF subclone as well as the original MC3T3-E1 cells, sclerostin can inhibit one or more of the sequence of events leading

up to and including mineral deposition (*i.e.* sclerostin inhibits mineralization). Anti-sclerostin antibodies that are able to neutralize sclerostin's inhibitory activity allow for mineralization of the culture in the presence of sclerostin such that there is a statistically significant increase in deposition of calcium phosphate (measured as calcium) as compared to the amount of calcium measured in the sclerostin-only (*i.e.* no antibody) treatment group. The antibodies used in the cell based mineralization assay experiments shown in Figures 22, 23 and 24 have molecular weights of about 145 Kd and have 2 sclerostin binding sites per antibody molecule.

[0420] When running the assay with the goal of determining whether a particular anti-sclerostin antibody or anti-sclerostin binding agent can neutralize sclerostin (*i.e.*, is a sclerostin neutralizing antibody or derivative thereof, or is a sclerostin neutralizing binding agent), the amount of sclerostin used in the assay needs to be the minimum amount of sclerostin that causes at least a 70%, statistically significant, reduction in deposition of calcium phosphate (measured as calcium) in the sclerostin-only group, as compared to the amount of calcium measured in the no sclerostin group. An anti-sclerostin neutralizing antibody or an anti-sclerostin neutralizing binding agent is defined as one that causes a statistically significant increase in deposition of calcium phosphate (measured as calcium) as compared to the amount of calcium measured in the sclerostin-only (*i.e.* no antibody, no binding agent) treatment group. To determine whether an anti-sclerostin antibody or an anti-sclerostin binding agent is neutralizing or not, the amount of anti-sclerostin antibody or anti-sclerostin binding agent used in the assay needs to be such that there is an excess of moles of sclerostin binding sites per well as compared to the number of moles of sclerostin per well. Depending on the potency of the antibody, the fold excess that may be required can be 24, 18, 12, 6, 3, or 1.5, and one of skill is familiar with the routine practice of testing more than one concentration of binding agent. For example, a very potent anti-sclerostin neutralizing antibody or anti-sclerostin neutralizing binding agent will be able to neutralize sclerostin even when there is less than a 6-fold excess of moles of sclerostin binding sites per well as compared to the number of moles of sclerostin per well. A less potent anti-sclerostin neutralizing antibody or anti-sclerostin neutralizing binding agent will be able to neutralize sclerostin only at a 12, 18 or 24 fold excess. Sclerostin binding agents within this full range of potencies are suitable as neutralizing sclerostin binding agents. Exemplary cell based mineralization assays are described in detail in Example 8.

[0421] Anti-sclerostin antibodies and derivatives thereof that can neutralize human sclerostin, and sclerostin binding agents that can neutralize human sclerostin may be of use in the treatment of human conditions/disorders that are caused by, associated with, or result in at least one of low bone formation, low bone mineral density, low bone mineral content, low bone mass, low bone quality and low bone strength.

IN VIVO NEUTRALIZATION ASSAY

[0422] Increases in various parameters associated with, or that result from, the stimulation of new bone formation can be measured as an output from *in vivo* testing of sclerostin binding agents in order to identify those binding agents that are able to neutralize sclerostin and thus able to cause stimulation of new bone formation. Such parameters include various serum anabolic markers [*e.g.* osteocalcin, P1NP (n-terminal propeptide of type 1 procollagen)], histomorphometric markers of bone formation (*e.g.* osteoblast surface/bone surface; bone formation rate/bone surface; trabecular thickness), bone mineral density, bone mineral content, bone mass, bone quality and bone strength. A sclerostin neutralizing binding agent is defined as one capable of causing a statistically significant increase, as compared to vehicle treated animals, in any parameter associated with, or that results from, the stimulation of new bone formation. Such *in vivo* testing can be performed in any suitable mammal (*e.g.* mouse, rat, monkey). An example of such *in vivo* testing can be found in Example 5 ("*In vivo* testing of anti-sclerostin monoclonal antibodies").

[0423] Although the amino acid sequence of sclerostin is not 100% identical across mammalian species (*e.g.* mouse sclerostin is not 100% identical to human sclerostin), it will be appreciated by one skilled in the art that a sclerostin binding agent that can neutralize, *in vivo*, the sclerostin of a certain species (*e.g.* mouse) and that also can bind human sclerostin *in vitro* is very likely to be able to neutralize human sclerostin *in vivo*. Thus, such a human sclerostin binding agent (*e.g.* anti-human sclerostin antibody) may be of use in the treatment of human conditions/disorders that are caused by, associated with, or result in at least one of low bone formation, low bone mineral density, low bone mineral content, low bone mass, low bone quality and low bone strength. Mice in which homologous recombination had been used to delete the mouse sclerostin gene and insert the human sclerostin gene in its place (*i.e.* human sclerostin gene knock-in mice or human SOST knock-in mice) would be an example of an additional *in vivo* system.

[0424] Pharmaceutical compositions are provided, comprising one of the above-described binding agents such as at least one of antibody Ab-A, Ab-B, Ab-C, Ab-D and Ab-1 to Ab-24 to human sclerostin, along with a pharmaceutically or physiologically acceptable carrier, excipient, or diluent. Pharmaceutical compositions and methods of treatment are disclosed in copending Application Serial No. 10/868,497, filed June 16, 2004, which claims priority to Serial No. 60/478,977.

[0425] The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, subcutaneous, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for

general purposes of illustration.

[0426] In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

[0427] In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein subcutaneously, parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U.S. Patent No. 5,543,158; U.S. Patent No. 5,641,515 and U.S. Patent No. 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropyl-cellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

[0428] Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U.S. Patent No. 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0429] In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, Remington's Pharmaceutical Sciences, 15th ed., pp. 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

[0430] In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

[0431] The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

[0432] In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

[0433] The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example, Lasic, Trends Biotechnol. 16(7):307-21, 1998; Takakura, Nippon Rinsho 56(3):691-95, 1998; Chandran et al., Indian J. Exp. Biol. 35(8):801-09, 1997; Margalit, Crit. Rev. Ther. Drug Carrier Syst. 12(2-3):233-61, 1995; U.S. Patent No. 5,567,434; U.S. Patent No. 5,552,157; U.S. Patent No. 5,565,213; U.S. Patent

No. 5,738,868 and U.S. Patent No. 5,795,587). The use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery. In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)).

[0434] Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero et al., *Drug Dev. Ind. Pharm.* 24(12):1113-28, 1998). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for example, by Couvreur et al., *Crit. Rev. Ther. Drug Carrier Syst.* 5(1):1-20, 1988; zur Muhlen et al., *Eur. J. Pharm. Biopharm.* 45(2):149-55, 1998; Zambaux et al., *J. Controlled Release* 50(1-3):31-40, 1998; and U.S. Patent No. 5,145,684.

[0435] In addition, pharmaceutical compositions of the present invention may be placed within containers, along with packaging material that provides instructions regarding the use of such pharmaceutical compositions. Generally, such instructions will include a tangible expression describing the reagent concentration, as well as within certain embodiments, relative amounts of excipient ingredients or diluents (e.g., water, saline or PBS) that may be necessary to reconstitute the pharmaceutical composition.

[0436] The dose administered may range from 0.01 mg/kg to 100 mg/kg of body weight. As will be evident to one of skill in the art, the amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth. Typically, the compositions may be administered by a variety of techniques, as noted above.

[0437] Increases in bone mineral content and/or bone mineral density may be determined directly through the use of X-rays (e.g., Dual Energy X-ray Absorptometry or "DEXA"), or by inference through the measurement of 1) markers of bone formation and/or osteoblast activity, such as, but not limited to, osteoblast specific alkaline phosphatase, osteocalcin, type 1 procollagen C' propeptide (PICP), total alkaline phosphatase (see Comier, *Curr. Opin. in Rheu.* 7:243(1995)) and serum procollagen 1 N-terminal propeptide (P1NP) and/or 2) markers of bone resorption and/or osteoclast activity including, but not limited to, pyridinoline, deoxypyridinoline, N-telopeptide, urinary hydroxyproline, plasma tartrate-resistant acid phosphatases, and galactosyl hydroxylysine; (see Comier, *id*), serum TRAP 5b (tartrate-resistant acid phosphatase isoform 5b) and serum cross-linked C-telopeptide (sCTXI). The amount of bone mass may also be calculated from body weights or by using other methods (see Guinness-Hey, *Metab. Bone Dis. Relat. Res.* 5:177-181, 1984).

Animals and particular animal models are used in the art for testing the effect of the compositions and methods of the invention on, for example, parameters of bone loss, bone resorption, bone formation, bone strength or bone mineralization that mimic conditions of human disease such as osteoporosis and osteopenias. Examples of such models include the ovariectomized rat model (Kalu, D.N., *The ovariectomized rat model of postmenopausal bone loss. Bone and Mineral* 15:175-192 (1991); Frost, H.M. and Jee, W.S.S. *On the rat model of human osteopenias and osteoporosis. Bone and Mineral* 18:227-236 (1992); and Jee, W.S.S. and Yao, W., *Overview: animal models of osteopenia and osteoporosis. J. Musculoskel. Neuron. Interact.* 1:193-207 (2001)).

[0438] Particular conditions which may be treated by the compositions of the present invention include dysplasias, wherein growth or development of bone is abnormal and a wide variety of causes of osteopenia, osteoporosis and bone loss. Representative examples of such conditions include achondroplasia, cleidocranial dysostosis, enchondromatosis, fibrous dysplasia, Gaucher's Disease, hypophosphatemic rickets, Marfan's syndrome, multiple hereditary exostoses, neurofibromatosis, osteogenesis imperfecta, osteopetrosis, osteopoikilosis, sclerotic lesions, pseudoarthrosis, and pyogenic osteomyelitis, periodontal disease, anti-epileptic drug induced bone loss, primary and secondary hyperparathyroidism, familial hyperparathyroidism syndromes, weightlessness induced bone loss, osteoporosis in men, postmenopausal bone loss, osteoarthritis, renal osteodystrophy, infiltrative disorders of bone, oral bone loss, osteonecrosis of the jaw, juvenile Paget's disease, melorheostosis, metabolic bone diseases, mastocytosis, sickle cell anemia/disease, organ transplant related bone loss, kidney transplant related bone loss, systemic lupus erythematosus, ankylosing spondylitis, epilepsy, juvenile arthritides, thalassemia, mucopolysaccharidoses, fabry disease, turner syndrome, Down Syndrome, Klinefelter Syndrome, leprosy, Perthes' Disease, adolescent idiopathic scoliosis, infantile onset multi-system inflammatory disease, Winchester Syndrome, Menkes Disease, Wilson's Disease, ischemic bone disease (such as Legg-Calve-Perthes disease, regional migratory osteoporosis), anemic states, conditions caused by steroids, glucocorticoid-induced bone loss, heparin-induced bone loss, bone marrow disorders, scurvy, malnutrition, calcium deficiency, idiopathic osteopenia or osteoporosis, congenital osteopenia or osteoporosis, alcoholism, chronic liver disease, postmenopausal state, chronic inflammatory conditions, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, inflammatory colitis, Crohn's disease, oligomenorrhea, amenorrhea, pregnancy, diabetes mellitus, hyperthyroidism, thyroid disorders, parathyroid disorders, Cushing's disease, acromegaly, hypogonadism, immobilization or disuse, reflex sympathetic dystrophy syndrome, regional osteoporosis, osteomalacia, bone loss associated with joint replacement, HIV associated bone loss, bone loss associated with loss of growth hormone, bone loss associated with cystic fibrosis, fibrous dysplasia, chemotherapy associated bone loss, tumor induced bone loss, cancer-related bone loss, hormone ablative bone loss,

multiple myeloma, drug-induced bone loss, anorexia nervosa, disease associated facial bone loss, disease associated cranial bone loss, disease associated bone loss of the jaw, disease associated bone loss of the skull, and bone loss associated with space travel. Further conditions relate to bone loss associated with aging, including facial bone loss associated with aging, cranial bone loss associated with aging, jaw bone loss associated with aging, and skull bone loss associated with aging.

[0439] Compositions of the present invention may also be useful for improving outcomes in orthopedic procedures, dental procedures, implant surgery, joint replacement, bone grafting, bone cosmetic surgery and bone repair such as fracture healing, nonunion healing, delayed union healing and facial reconstruction. One or more compositions may be administered before, during and/or after the procedure, replacement, graft, surgery or repair.

[0440] The disclosure also provides a diagnostic kit comprising at least one anti-sclerostin binding agent according to the present invention. In addition, such a kit may optionally comprise one or more of the following:

(1) instructions for using the one or more binding agent(s) for screening, diagnosis, prognosis, therapeutic monitoring or any combination of these applications;

(2) a labeled binding partner to the anti-sclerostin binding agent(s);

(3) a solid phase (such as a reagent strip) upon which the anti-sclerostin binding agent(s) is immobilized; and

(4) a label or insert indicating regulatory approval for screening, diagnostic, prognostic or therapeutic use or any combination thereof.

If no labeled binding partner to the binding agent(s) is provided, the binding agent(s) itself can be labeled with one or more of a detectable marker(s), e.g. a chemiluminescent, enzymatic, fluorescent, or radioactive moiety.

[0441] The following examples are offered by way of illustration, and not by way of limitation.

EXAMPLES

EXAMPLE 1

Recombinant Expression of Sclerostin

[0442] Recombinant human sclerostin/SOST is commercially available from R&D Systems (Minneapolis, MN, USA; 2006 cat# 1406-ST-025). Additionally, recombinant mouse sclerostin/SOST is commercially available from R&D Systems (Minneapolis, MN, USA; 2006 cat# 1589-ST-025).

[0443] Alternatively, the different species of sclerostin can be expressed transiently in serum-free suspension adapted 293T or 293EBNA cells. Transfections can be performed as 500 mL or 1L cultures. The following reagents and materials are available from Gibco BRL (now Invitrogen, Carlsbad, CA). Catalog numbers are listed in parentheses: serum-free DMEM (21068-028); DMEM/F12 (3:1) (21068/11765); 1X Insulin-Transferrin-Selenium Supplement (51500-056); 1X Pen Strep Glut (10378-016); 2mM L-Glutamine (25030-081); 20 mM HEPES (15630-080); 0.01% Pluronic F68 (24040-032). Briefly, the cell inoculum ($5.0\text{--}10.0 \times 10^5$ cells/mL X culture volume) is centrifuged at 2,500 RPM for 10 minutes at 4°C to remove the conditioned medium.

[0444] The cells are resuspended in serum-free DMEM and centrifuged again at 2,500 RPM for 10 minutes at 4°C. After aspirating the wash solution, the cells are resuspended in growth medium [DMEM/F12 (3:1) + 1X Insulin-Transferrin-Selenium Supplement + 1X Pen Strep Glut + 2mM L-Glutamine + 20 mM HEPES + 0.01% Pluronic F68] in a 1L or 3L spinner flask culture. The spinner flask culture is maintained on magnetic stir plate at 125 RPM which is placed in a humidified incubator maintained at 37°C and 5% CO₂. The mammalian expression plasmid DNA (e.g. pcDNA3.1, pCEP4, Invitrogen Life Technologies, Carlsbad, CA), containing the complete coding region (and stop codon) of sclerostin with a Kozak consensus sequence (e.g., CCACC) directly 5' of the start site ATG, is complexed to the transfection reagent in a 50 mL conical tube.

[0445] The DNA-transfection reagent complex can be prepared in 5-10% of the final culture volume in serum-free DMEM or OPTI-MEM. The transfection reagents that can be used for this purpose include X-tremeGene RO-1539 (Roche Applied Science, Indianapolis, IN), FuGene6 (Roche Applied Science, Indianapolis, IN), Lipofectamine 2000 (Invitrogen, Carlsbad, CA) and 293fectin (Invitrogen, Carlsbad, CA). 1-5 µg plasmid DNA/mL culture is first added to serum-free DMEM, followed by 1-5 µl transfection reagent/mL culture. The complexes can be incubated at room temperature for approximately 10-30 minutes and then added to the cells in the spinner flask. The transfection/expression can be performed for 4-7 days, after which the conditioned medium (CM) is harvested by centrifugation at 4,000 RPM for 60 minutes at 44°C.

EXAMPLE 2

PURIFICATION OF RECOMBINANT SCLEROSTIN

[0446] Recombinant sclerostin was purified from mammalian host cells as follows. All purification processes were carried out at room temperature. One purification scheme was used to purify various species of sclerostin, including murine and human sclerostin. The purification scheme used affinity chromatography followed by cation exchange chromatography.

Heparin Chromatograph

[0447] The mammalian host cell conditioned medium (CM) was centrifuged in a Beckman J6-M1 centrifuge at 4000 rpm for 1 hour at 4°C to remove cell debris. The CM supernatant was then filtered through a sterile 0.2 µm filter. (At this point the sterile filtered CM may be optionally stored frozen until purification.) If the CM was frozen, it was thawed at the following temperatures, or combination thereof: 4°C, room temperature or warm water. Following thawing the CM was filtered through a sterile 0.2 µm filter and optionally concentrated by tangential flow ultrafiltration (TFF) using a 10 kD molecular weight cut-off membrane. The CM concentrate was filtered through a sterile 0.2 µm filter and then loaded onto a Heparin High Performance (Heparin HP) column (GE Healthcare, formerly Amersham Biosciences) equilibrated in PBS. Alternatively, the filtered CM supernatant may be loaded directly onto the Heparin HP column equilibrated in PBS.

[0448] After loading, the Heparin HP column was washed with PBS until the absorbance at 280 nm of the flow-through returned to baseline (*i.e.*, absorbance measured before loading CM supernatant). The sclerostin was then eluted from the column using a linear gradient from 150 mM to 2M sodium chloride in PBS. The absorbance at 280 nm of the eluate was monitored and fractions containing protein were collected. The fractions were then assayed by Coomassie-stained SDS-PAGE to identify fractions containing a polypeptide that migrates at the size of glycosylated sclerostin. The appropriate fractions from the column were combined to make the Heparin HP pool.

Cation Exchange Chromatography

[0449] The sclerostin eluted from the Heparin HP column was further purified by cation exchange chromatography using SP High Performance (SPHP) chromatography media (GE Healthcare, formerly Amersham Biosciences). The Heparin HP pool was buffer exchanged into PBS by dialysis using 10,000 MWCO membranes (Pierce Slide-A-Lyzer). The dialyzed Heparin HP pool was then loaded onto an SPHP column equilibrated in PBS. After loading, the column was washed with PBS until the absorbance at 280 nm of the flow-through returned to baseline. The sclerostin was then eluted from the SPHP column using a linear gradient from 150 mM to 1 M sodium chloride in PBS. The absorbance at 280 nm of the eluate was monitored and the eluted sclerostin was collected in fractions. The fractions were then assayed by Coomassie-stained SDS-PAGE to identify fractions containing a polypeptide that migrates at the size of glycosylated sclerostin. The appropriate fractions from the column were combined to make the SPHP pool.

Formulation

[0450] Following purification, the SPHP pool was formulated in PBS by dialysis using 10,000 MWCO membranes (Pierce Slide-A-Lyzer). If concentration of sclerostin was necessary, a centrifugal device (Amicon Centricon or Centriprep) with a 10,000 MWCO membrane was used. Following formulation the sclerostin was filtered through a sterile 0.2 µm filter and stored at 4°C or frozen.

EXAMPLE 3

PEPTIDE BINDING ELISA

[0451] A series of overlapping peptides (each peptide being approximately 20-25 amino acids long) were synthesized based on the known amino acid sequence of rat sclerostin (SEQ ID NO:98). The peptides were designed such that they all contained a reduced cysteine residue; an additional cysteine was included at the C-terminus of each peptide which did not already contain one in its sequence. This enabled the peptides to be bound to the assay plates by covalent coupling, using commercially available sulfhydryl binding plates (Costar), at a concentration of 1 µg/ml, in phosphate buffered saline (PBS: pH 6.5) containing 1 mM EDTA. Following incubation for 1 hour at room temperature, the plates were washed three times with PBS containing 0.5% Tween 20. The plates were blocked by incubation with a PBS solution containing 0.5% fish skin gelatin (Sigma) for 30 minutes at room temperature and then washed three times in PBS containing 0.5% Tween 20.

EP 2 251 351 B1

[0452] Antibodies to be tested were diluted to 1 µg/ml in PBS containing 0.5% fish skin gelatin and incubated with the peptide-coated plates for 1 hour at room temperature. Excess antibody was removed by three washes with PBS, 0.5% Tween 20. The plates were then incubated with an appropriate secondary antibody conjugated to horseradish peroxidase (diluted appropriately in PBS containing 0.5% Tween 20) and capable of binding to the antibody of interest. The plates were then washed three times: once with PBS containing 0.5% Tween 20, and twice with PBS. Finally the plates were incubated with a horseradish peroxidase chromogenic substrate (TMB-Stable Stop, RDI) for 5 minutes at room temperature, the color development was stopped with acid, and the plates' optical density measured at 450nm.

Materials

[0453]

Costar's Sulphydryl Binding Plates (VWR # 29442-278)
Coating Buffer: 1XPBS PH 6.5 + 1mM EDTA
Blocking Buffer: 1X PBS + 0.5% Fish Skin Gelatin (PBS from CS; FSG from Sigma# G 7765)
Wash Buffer: 1X PBS + 0.5% Tween 20
Rat Sclerostin peptides
Antibody Samples: Transient Ab, Purified recombinant Ab, rabbit Serum, etc.
Appropriate secondary Ab: Goat-anti-Rabbit/Mouse-HRP (Jackson Immuno Research, 115-036-072)
TMB-Stable Stop (RDI# RDI-TMBSX-1L) 0.5M HCl

Methods were as follows:

[0454]

1. Coat plates with 100 µl/well of rat sclerostin peptide diluted in 1XPBS PH 6.5 + 1mM EDTA at 1 µg/ml. Incubate plates 1 hour at room temperature. (Plates should be used within 30 minutes of opening).
2. Wash plates 3X with wash buffer.
3. Block plates with 200 µl/well blocking buffer. Incubate plates 30 minutes at room temp.
4. Repeat washing as described in (2).
5. Incubate plates with 50 µl/well of samples diluted in blocking buffer - Serum titers starting at 1:100; Transient Recombinant Ab use neat; Purified recombinant Ab use at 1 µg/ml (all samples run in duplicates). Incubate plates 1h at room temp.
6. Wash plates as described in (2).
7. Incubate plates with 50 µl/well of appropriate Secondary Antibody (HRP labeled) diluted 1:1600 in Blocking Buffer. Incubate plates 1 hour at room temperature.
8. Wash plates 1X wash buffer, 2x PBS
9. Incubate plates with 50 µl/well of TMB, 5 minutes at room temp.
10. Stop reaction with 50 µl/well 0.5M HCl.
11. Read plates at 450 nm wavelength.

[0455] The following peptides sequences were screened as described above:

QGWQAFKNDAT EII PGLREYPEPP (SEQ ID NO: 82)
TEII PGLREYPEPPQE LNN (SEQ ID NO:83)
PEPPQE LNNQTMNRAENG G (SEQ ID NO:84)
ENGGRPPHHPYDTKDVSEYS (SEQ ID NO:85)
CRELHYTRFVTDGP (SEQ ID NO:86)
CRELHYTRFVTDGPSRSAPVTELV (SEQ ID NO:87)
CRSAKPVTELVSSGQSGPRARLL (SEQ ID NO:88)
CGPARLLPNAIGRVKWWRPNGPDFR (SEQ ID NO:89)
RAQRVQLLCPPGAAPRSRKV (SEQ ID NO:90)
PGGAAPRSRKVRLVAS (SEQ ID NO:91)
KRLTRFHNQSELKDFGPETARPQ (SEQ ID NO:92)
IPDRYAQRVQLLSPGG (SEQ ID NO:93)
SELKDFGPETARPQKGRKPRPRAR (SEQ ID NO:94)
KGRKPRPRARGAKANQAELENAY (SEQ ID NO:95)
PNAIGRVKWWRPNGPDFR (SEQ ID NO:96)

KWWRPNGPDFRCIPDRYRAQRV (SEQ ID NO:97).

[0456] A high-affinity neutralizing antibody (Ab-19) bound to two overlapping peptide sequences: PNAIGRVKW-WRPNGPDFR (SEQ ID NO:96) and

KWWRPNGPDFRCIPDRYRAQRV (SEQ ID NO:97).

[0457] This procedure allows the recognition of epitopes for antibodies that react with apparent linear epitopes. Peptides that contain all or part of the antibody binding site will bind antibody and thus be detected.

EXAMPLE 4

IDENTIFICATION OF HUMAN SCLEROSTIN EPITOPES

Sclerostin structure

[0458] Mature form (signal peptide removed) human sclerostin is a 190 amino acid protein (Figure 8). Figure 9 shows a schematic of the general structure of sclerostin with an N-terminal arm (from the N-terminal Q to Cysteine1) and a C-terminal arm (from Cysteine8 to the terminal Y). Sandwiched in between these two arms there is the cystine-knot structure and three loops which are designated Loop1, Loop2 and Loop 3. The four disulfide bonds in sclerostin are Cys1 at sequence position 57 linked to Cys5 at sequence position 111 (referred to as C1-C5), Cys2 at sequence position 71 linked to Cys6 at sequence position 125 (referred to as C2-C6), Cys3 at sequence position 82 linked to Cys7 at sequence position 142 (referred to as C3-C7), Cys4 at sequence position 86 linked to Cys8 at sequence position 144 (referred to as C4-C8). The eight-membered ring structure is formed via C3-C7 and C4-C8 disulfide bonding. This ring structure, together with the C1-C5 disulfide bond penetrating through the ring, forms a typical cystine-knot. C2-C6, which is not part of the cystine-knot, brings two large loop structures, loop 1 (residues 57 to 82) and loop 3 (residues 111 to 142) close together. Loop 2 goes from C4 (residue 86) to C5 (residue 111).

Experimental

[0459] The general approach for characterizing the epitopes bound by anti-sclerostin monoclonal antibodies involved fragmenting human Sclerostin into peptides with different proteases, determining the sequence of the various human sclerostin peptides, isolating these peptides and testing each of them for their ability to bind to a particular monoclonal antibody using a Biacore-based "human sclerostin peptide epitope competition binding assay." The resulting data permitted the location of the binding epitope to be determined.

[0460] The peptide digests were subjected to HPLC peptide mapping; the individual peaks were collected, and the peptides identified and mapped by matrix assisted laser desorption mass spectrometry (MALDI-MS) and electrospray ionization LC-MS (ESI-LC-MS) analyses and/or by N-terminal sequencing. All HPLC analyses for these studies were performed using a reverse-phase C8 column (2.1 mm i.d. x 15 cm length). HPLC peptide mapping was performed with a linear gradient from 0.05% trifluoroacetic acid (mobile phase A) to 90% acetonitrile in 0.05% trifluoroacetic acid. Columns were developed over 50 minutes at a flow rate of 0.2 ml/min.

Trypsin and AspN Endoproteinase Digestions

[0461] Mature form human sclerostin was digested with trypsin, which cleaves after arginine and lysine, or with AspN. About 200 µg of sclerostin at 0.5-1.0 mg/ml was incubated in PBS (pH 7.2) for 20 hrs at 37°C with 8 µg of either trypsin or AspN.

Trypsin digestion

[0462] HPLC chromatography of the trypsin digests yielded several major peaks (Fig. 10A). Sequence analysis was conducted on the peptide peaks recovered from HPLC after trypsin digestion. On-line ESI LC-MS analysis of the peptide digest was also performed to determine the precise mass of the peptides that were separated by HPLC. The identity of the peptides present in the peptide peaks was thus determined (Fig. 11). Figure 13 shows the alignment of various peptide sequences (T19.2, T20, T20.6, T21-22) along the sclerostin sequence. The number following each T (e.g., T19.2) reflects the retention time. T19.2 contains two peptides (one from loop 1 and one from loop 3) linked by the C2-C6 disulfide bond. T20 contains two peptides held together by the cystine-knot structure, with intact loops 1 and 3 held together by the C2-C6 disulfide and with most of loop 2 absent. T20.6 contains four sequences held together by the cystine-knot structure, but is missing part of loop 1 and 3 (the T19.2 part) and is missing most of loop 2. T21-22 is almost identical to T20 but has 3 additional amino acids in the loop 2 region.

AspN Digestion

[0463] HPLC chromatography of the AspN digests yielded several major peaks (Fig. 10B). Sequence analysis was conducted on the peptide peaks recovered from HPLC. On-line ESI LC-MS analysis of the peptide digest was also performed to determine the precise mass of the peptides that were separated by HPLC. The identity of the peptides present in the peptide peaks from the AspN digestion was thus determined (Fig. 12). Figure 14 shows the alignment of various peptide sequences (AspN14.6, AspN18.6, AspN22.7-23.5) along the sclerostin sequence. The number following each AspN (e.g. AspN18.6) reflects the retention time. AspN14.6 contains three short peptides from both the N- and C-terminal arms of sclerostin, while AspN18.6 is a larger peptide from the N-terminal arm of sclerostin. AspN22.7-23.5 contains a single peptide fragment of 104 amino acids that encompasses all eight cysteines (the four disulfide bonds), the cystine-knot and all of loops 1, 2 and 3.

[0464] The strategy for characterizing the epitopes was to use these various trypsin and AspN generated human sclerostin peptides and determine which peptides could still be bound by the various Antibodies (Ab-A, Ab-B, Ab-C and Ab-D). Specifically this was tested in a Biacore-based "human sclerostin peptide epitope competition binding assay" where the binding of a particular monoclonal antibody to human sclerostin immobilized on the Biacore chip was determined in the presence or absence of each of the various isolated trypsin and AspN HPLC peptide fractions. In the absence of any competing peptides, the particular monoclonal antibody was able to bind the human sclerostin on the chip and produce a resonance unit, RU, response. Preincubation of the particular monoclonal antibody with intact human sclerostin in solution, followed by testing of binding to the chip, demonstrated that the binding of the Mab to human sclerostin in solution prevented the binding of the Mab to the human sclerostin on the chip, thus validating the general principle of this competition assay.

[0465] This general procedure was repeated individually for each peptide. A robust RU response was taken to indicate that the particular peptide being tested could not bind the Mab in solution (hence the Mab was free to bind the human sclerostin that had been immobilized on the chip). Conversely, the absence of a robust RU response indicated that the Mab was able to bind the sclerostin peptide in solution. These binding patterns, coupled with the known identity of the various sclerostin peptides, were used to determine the epitopes of sclerostin that were bound by anti-sclerostin antibodies Ab-A, Ab-B, Ab-C and Ab-D.

DIACORE-BASED HUMAN SCLEROSTIN PEPTIDE EPITOPE COMPETITION BINDING ASSAYPreparation of human sclerostin surface:

[0466] Immobilization of mature form human sclerostin to a Biacore sensor chip (CM5) surface was performed according to manufacturer's instructions. Briefly, carboxyl groups on the sensor chip surfaces were activated by injecting 60 μ L of a mixture containing 0.2 M N-ethyl-N'-(dimethylaminopropyl) carbodiimide (EDC) and 0.05 M N-hydroxysuccinimide (NHS). Human sclerostin was diluted in 10 mM sodium acetate, pH 4.0 at a concentration of 20 μ g/mL followed by injecting over the activated CM5 surface. Excess reactive groups on the surfaces were deactivated by injecting 60 μ L of 1 M ethanolamine. Final immobilized levels were ~ 5000 resonance units (RU) for the human sclerostin surface. A blank, mock-coupled reference surface was also prepared on the sensor chips.

Binding specificity analysis:

[0467] 1X Phosphate-buffered saline without calcium chloride or magnesium chloride was from Gibco/Invitrogen, Carlsbad, CA. Bovine serum albumin, fraction V, IgG-free was from Sigma-Aldrich, St. Louis, MO. Each Mab (2 nM) was separately incubated with 20 nM human sclerostin or a particular human sclerostin peptide (note: there are 3 unlinked peptides in AspN14.6) in sample buffer (1X PBS + 0.005% P-20 + 0.1 mg/mL BSA) before injection over the immobilized human sclerostin surface. The flow rate for sample injection was 5 μ L/min followed by surface regeneration using 1 M NaCl in 8 mM Glycine, pH 2.0 at 30 μ L/min for 30 seconds. The data was analyzed using BIAevaluation 3.2, and is presented in Figure 15 (Ab-A), Figure 16 (Ab-B), Figure 17 (Ab-C) and Figure 18 (Ab-D).

Loop 2 and T20.6 epitopes:

[0468] The sclerostin peptide binding pattern for two representative antibodies (Ab-A and Ab-B) were virtually identical (Fig. 15 and Fig. 16) and showed that both of these Antibodies could only bind the AspN22.7-23.5 peptide. The unique difference between AspN22.7-23.5 and all the other sclerostin peptides is that AspN22.7-23.5 contains an intact loop 2. This shows that Ab-A and Ab-B bind the loop 2 region of sclerostin thus defining the loop 2 epitope (Fig. 19A). The sclerostin peptide binding pattern for Ab-C and Ab-D were virtually identical to each other (Fig. 17 and Fig. 18) but completely distinct from that found for Ab-A and Ab-B. Of the peptides tested in this Example, the most diminutive peptide

that Ab-C and Ab-D could bind to was the T20.6 peptide. This result defines the T20.6 epitope (Fig. 19B).

Protease protection assay:

[0469] The general principle of this assay is that binding of a Mab to sclerostin can result in protection of certain specific protease cleavage sites and this information can be used to determine the region of sclerostin to where the Mab binds.

"T20.6 derivative 1 (cystine-knot + 4 arms)" epitope:

[0470] Figure 20 shows the HPLC peptide maps for a human sclerostin Ab-D complex (Fig 20A: human sclerostin was preincubated at a 1:1 molar ratio with Ab-D prior to digestion with trypsin as described above) and human sclerostin alone (Fig 20B: human sclerostin was digested with trypsin as described above). The peptide peaks of T19.2 and T20.6 in Figure 20A showed a clear reduction in their respective peak height, as compared to Figure 20B. This reduction in peak heights was accompanied by an increase in peak height for peptides T20 and T21-22. These data indicate that basic amino acid residues in loop 1 and loop 3, which in the absence of Ab-D were cleaved by trypsin to generate peptides T19.2 and T20.6, were resistant to cleavage by trypsin when Ab-D was prebound to sclerostin. The presence of T20, T20.6 and T21-22 indicates that loop 2 was still cleaved efficiently when Ab-D was prebound to sclerostin. These data indicate that Ab-D bound on the loop 1 and loop 3 side of the T20.6 epitope thus defining the smaller "T20.6 derivative 1 (cystine-knot + 4 arms)" epitope shown in Figure 21.

EXAMPLE 5

IN VIVO TESTING OF ANTI-SCLEROSTIN MONOCLONAL ANTIBODIES IN MICE

[0471] Four week-old BDF1 male mice were obtained from Charles River Laboratories (Raleigh, NC) and housed in clean caging, five animals per cage. Room temperature was maintained between 68 and 72°F, and relative humidity was maintained between 34 and 73%. The laboratory housing the cages had a 12-hour light/dark cycle and met all AAALAC specifications. Clinical observations of all mice on study occurred once daily.

[0472] Purified anti-sclerostin monoclonal antibodies (Ab-A Fig.1; Ab-B Fig.2; Ab-C Fig.3; Ab-D Fig.4) were diluted in sterile Dulbecco's phosphate buffered saline. Mice were injected with anti-sclerostin Antibodies or PBS vehicle subcutaneously at 21 μ l per gram body weight, two times per week (Monday and Thursday) at 25 mg/kg. Human PTH (1-34) was diluted in PTH buffer (0.001 N HCl, 0.15 M NaCl, 2% BSA), and dosed subcutaneously at 21 μ l per gram body weight five times per week (Monday, Tuesday, Wednesday, Thursday, Friday) at 100 μ g/kg as a positive control (Figures 5 and 6). Number of mice per group was N=5 in Fig 5 and 6, and N=6 in Figure 7.

PIXImus *in vivo* Bone Densitometry

[0473] Bone mineral density (BMD) was determined weekly at the proximal tibial metaphysis and lumbar vertebrae by peripheral Dual Energy X-ray Absorptometry (pDEXA) with the PIXImus2 system from GE/Lunar Medical Systems, Madison, WI. A 25mm² region of interest (ROI) was placed to include the proximal articular surface, the epiphysis, and the proximal end on the metaphysis of the tibia. A region of interest (ROI) was placed to include the lumbar vertebrae (L1-L5). The proximal tibia and lumbar regions were analyzed to determine total bone mineral density. Group means were reported $\pm$ Standard Deviation and compared to the vehicle treatment group for statistical analysis.

Statistical analysis

[0474] Statistical analysis was performed with a Dunnett's and Tukey-Kramer (using MS Excel and JMP v. 5.0. for the BMD data). Group means for each data set were considered significantly different when the P value was less than 0.05 ($P < 0.05$).

Sclerostin neutralizing activity of antibodies

[0475] The statistically significant increases in BMD as compared to vehicle seen for each of Ab-A (Figure 5), Ab-B (Figure 5), Ab-C (Figure 6) and Ab-D (Figure 7) demonstrates that these four antibodies are sclerostin neutralizing antibodies. Furthermore this data shows that, for anti-sclerostin antibodies that bind mouse sclerostin, treatment and analysis of mice as described above can be used to identify sclerostin neutralizing antibodies.

EXAMPLE 6

SCREENING FOR ANTIBODIES THAT BLOCK BINDING OF AN ANTIBODY TO HUMAN SCLEROSTIN

[0476] Human sclerostin was coupled to a CM5 Biacore chip using standard amine coupling chemistry to generate a sclerostin coated surface. 300 resonance units of sclerostin were coupled to the surface.

[0477] The antibodies to be tested were diluted to a concentration of 200ug/ml in HBS-EP buffer (being 10 mM HEPES pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.005% (v/v) Surfactant P20) and then mixed in a one to one molar ratio (on a binding site basis) to generate the test mixture. This test mixture thus contained each antibody at a concentration of 100ug/ml (1.3um on a binding site basis). Separate solutions containing each of the antibodies in the test mix alone were also prepared. These solutions contained the individual antibodies in HBS-EP buffer at a concentration of 100ug/ml (1.3um on a binding site basis).

[0478] 20 µL of the test mixture was passed over the sclerostin-coated chip at a flow rate of 10 µL/min and the amount of binding recorded. The chip was then treated with two 60 second pulses of 30 mM HCl to remove all of the bound antibody. A solution containing only one of the antibodies of the test mixture (at 1.3µM in the same buffer as the test mixture on a binding site basis) was then passed over the chip in the same manner as the test mixture and the amount of binding recorded. The chip was again treated to remove all of the bound antibody and finally a solution containing the other antibody from the test mixture alone (at 1.3µM in the same buffer as the test mixture on a binding site basis) was passed over the chip and the amount of binding recorded.

[0479] The table below show the results from cross-blocking assays on a range of different antibodies. The values in each square of the table represent the amount of binding (in RU) seen when the antibodies (at 1.3µM on a binding site basis) or buffer indicated in the top row of the table were mixed with the antibodies (at 1.3uM on a binding site basis) or buffer indicated in the first column of the table.

	Buffer	Ab-4	Ab-13	Ab-A	Ab-3	Ab-19
Buffer	-0.5	693	428.5	707.3	316.1	649.9
Ab-4	687.7	795.1	1018.2	860.5	869.3	822.5
Ab-13	425.6	1011.3	442.7	1108.4	431.9	1042.4
Ab-A	692.4	833.1	1080.4	738.5	946.2	868.1
Ab-3	305.5	845.1	428.2	952.2	344.4	895.7
Ab-19	618.1	788.6	1022.5	863.3	891.5	658.7

[0480] Using the mean binding value (in RU) for each combination of antibodies in the above table (since each combination appears twice) it is possible to calculate the percentage of the theoretical binding shown by each combination of antibodies. The theoretical binding being calculated as the sum of the average values for the components of each test mixture when assayed alone (*i.e.*, antibody and buffer).

	Buffer	Ab-4	Ab-13	Ab-A	Ab-3	Ab-19
Buffer						
Ab-4			90.75	60.45	85.4	60.75
Ab-13				96.9	58.0	97.0
Ab-A					93.5	65.0
Ab-3						94.4
Ab-19						

[0481] From the above data it is clear that Ab-4, Ab-A and Ab-19 cross-block each other. Similarly Ab-13 and Ab-3 cross block each other.

EXAMPLE 7

ELISA-BASED CROSS-BLOCKING

[0482] Liquid volumes used in this example would be those typically used in 96-well plate ELISAs (e.g. 50-200 μ l/well). Ab-X and Ab-Y, in this example are assumed to have molecular weights of about 145 Kd and to have 2 sclerostin binding sites per antibody molecule. An anti-sclerostin antibody (Ab-X) is coated (e.g. 50 μ l of 1 μ g/ml) onto a 96-well ELISA plate [e.g. Corning 96 Well EIA/RIA Flat Bottom Microplate (Product # 3590), Coming Inc., Acton, MA] for at least one hour. After this coating step the antibody solution is removed, the plate is washed once or twice with wash solution (e.g., PBS and 0.05% Tween 20) and is then blocked using an appropriate blocking solution (e.g., PBS, 1% BSA, 1% goat serum and 0.5% Tween 20) and procedures known in the art. Blocking solution is then removed from the ELISA plate and a second anti-sclerostin antibody (Ab-Y), which is being tested for its ability to cross-block the coated antibody, is added in excess (e.g. 50 μ l of 10 μ g/ml) in blocking solution to the appropriate wells of the ELISA plate. Following this, a limited amount (e.g. 50 μ l of 10 ng/ml) of sclerostin in blocking solution is then added to the appropriate wells and the plate is incubated for at least one hour at room temperature while shaking. The plate is then washed 2-4 times with wash solution. An appropriate amount of a sclerostin detection reagent [e.g., biotinylated anti-sclerostin polyclonal antibody that has been pre-complexed with an appropriate amount of a streptavidin-horseradish peroxidase (HRP) conjugate] in blocking solution is added to the ELISA plate and incubated for at least one hour at room temperature. The plate is then washed at least 4 times with wash solution and is developed with an appropriate reagent [e.g. HRP substrates such as TMB (colorimetric) or various HRP luminescent substrates]. The background signal for the assay is defined as the signal obtained in wells with the coated antibody (in this case Ab-X), second solution phase antibody (in this case Ab-Y), sclerostin buffer only (i.e. no sclerostin) and sclerostin detection reagents. The positive control signal for the assay is defined as the signal obtained in wells with the coated antibody (in this case Ab-X), second solution phase antibody buffer only (i.e. no second solution phase antibody), sclerostin and sclerostin detection reagents. The ELISA assay needs to be run in such a manner so as to have the positive control signal be at least 6 times the background signal.

[0483] To avoid any artifacts (e.g. significantly different affinities between Ab-X and Ab-Y for sclerostin) resulting from the choice of which antibody to use as the coating antibody and which to use as the second (competitor) antibody, the cross-blocking assay needs to be run in two formats:

- 1) format 1 is where Ab-X is the antibody that is coated onto the ELISA plate and Ab-Y is the competitor antibody that is in solution
- and
- 2) format 2 is where Ab-Y is the antibody that is coated onto the ELISA plate and Ab-X is the competitor antibody that is in solution.

[0484] Ab-X and Ab-Y are defined as cross-blocking if, either in format 1 or in format 2, the solution phase anti-sclerostin antibody is able to cause a reduction of between 60% and 100%, specifically between 70% and 100%, and more specifically between 80% and 100%, of the sclerostin detection signal (i.e. the amount of sclerostin bound by the coated antibody) as compared to the sclerostin detection signal obtained in the absence of the solution phase anti-sclerostin antibody (i.e. the positive control wells).

[0485] In the event that a tagged version of sclerostin is used in the ELISA, such as a N-terminal His-tagged Sclerostin (R&D Systems, Minneapolis, MN, USA; 2005 cat# 1406-ST-025) then an appropriate type of sclerostin detection reagent would include an HRP labeled anti-His antibody. In addition to using N-terminal His-tagged Sclerostin, one could also use C-terminal His-tagged Sclerostin. Furthermore, various other tags and tag binding protein combinations that are known in the art could be used in this ELISA-based cross-blocking assay (e.g., HA tag with anti-HA antibodies; FLAG tag with anti-FLAG antibodies; biotin tag with streptavidin).

EXAMPLE 8

CELL BASED MINERALIZATION FOR IDENTIFYING AGENTS ABLE TO ANTAGONIZE SCLEROSTIN ACTIVITY

Introduction

[0486] Mineralization by osteoblast-lineage cells in culture, either primary cells or cell lines, is used as an *in vitro* model of bone formation. Mineralization takes from about one to six weeks to occur beginning with the induction of osteoblast-lineage cell differentiation by one or more differentiation agents. The overall sequence of events involves cell proliferation, differentiation, extracellular matrix production, matrix maturation and finally deposition of mineral, which refers to crystallization and/or deposition of calcium phosphate. This sequence of events starting with cell proliferation and differen-

tiation, and ending with deposition of mineral is referred to herein as mineralization. Measurement of calcium (mineral) is the output of the assay.

[0487] Deposition of mineral has a strong biophysical characteristic, in that once mineral "seeds" begin to form, the total amount of mineral that will be deposited in the entire culture can sometimes be deposited quite rapidly, such as within a few days thereafter. The timing and extent of mineral deposition in culture is influenced, in part, by the particular osteoblast-lineage cells/cell-line being used, the growth conditions, the choice of differentiation agents and the particular lot number of serum used in the cell culture media. For osteoblast-lineage cell/cell-line mineralization cultures, at least eight to fifteen serum lots from more than one supplier should be tested in order to identify a particular serum lot that allows for mineralization to take place.

[0488] MC3T3-E1 cells (Sudo H et al., In vitro differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvaria. J. Cell Biol. 96:191-198) and subclones of the original cell line can form mineral in culture upon growth in the presence of differentiating agents. Such subclones include MC3T3-E1-BF (Smith E, Redman R, Logg C, Coetzee G, Kasahara N, Frenkel B. 2000. Glucocorticoids inhibit developmental stage-specific osteoblast cell cycle. J Biol Chem 275:19992-20001).

Identification of Sclerostin Neutralizing Antibodies

[0489] MC3T3-E1-BF cells were used for the mineralization assay. Ascorbic acid and B-glycerophosphate were used to induce MC3T3-E1-BF cell differentiation leading to mineral deposition. The specific screening protocol, in 96-well format, involved plating cells on a Wednesday, followed by seven media changes (as described further below) over a 12-day period with most of the mineral deposition taking place in the final approximately eighteen hours (e.g. Sunday night through Monday). For any given treatment, 3 wells were used (N=3). The specific timing, and extent, of mineral deposition may vary depending, in part, on the particular serum lot number being used. Control experiments will allow such variables to be accounted for, as is well known in the art of cell culture experimentation generally.

[0490] In this assay system sclerostin inhibited one or more of the sequence of events leading up to and including mineral deposition (*i.e.*, sclerostin inhibited mineralization). Anti-sclerostin antibodies that were able to neutralize sclerostin's inhibitory activity allowed for mineralization of the culture in the presence of sclerostin such that there was a statistically significant increase in deposition of calcium phosphate (measured as calcium) as compared to the amount of calcium measured in the sclerostin-only (*i.e.*, no antibody) treatment group. For statistical analysis (using MS Excel and JMP) a 1-way-ANOVA followed by Dunnett's comparison was used to determine differences between groups. Group means for each data set were considered significantly different when the P value was less than 0.05 ($P < 0.05$). A representative result from running this assay is shown in Figure 22. In the absence of recombinant mouse sclerostin, the sequence of events leading up to and including mineral deposition proceeded normally. Calcium levels in each treatment group are shown as means $\pm$ Standard Error of the Mean (SEM). In this exemplary experiment calcium levels from the calcium assay were $\sim 31 \mu\text{g/ml}$. However, addition of recombinant mouse sclerostin caused inhibition of mineralization, and calcium was reduced by $\sim 85\%$. Addition of anti-sclerostin monoclonal antibody Ab-19 or Ab-4 along with the recombinant sclerostin resulted in a statistically significant increase in mineral deposition, as compared to the sclerostin-only group, because the inhibitory activity of sclerostin was neutralized by either antibody. The results from this experiment indicate that Ab-19 and Ab-4 are sclerostin neutralizing monoclonal antibodies (Mabs).

[0491] Figure 23 shows a very similar result using recombinant human sclerostin and two humanized anti-sclerostin Mabs. Figure 24 also shows a very similar result using recombinant human sclerostin and mouse and humanized anti-sclerostin Mabs as indicated.

[0492] The antibodies used for the experiments shown in Fig 22, 23 and 24 have molecular weights of about 145 Kd and have 2 sclerostin binding sites per antibody molecule.

[0493] A detailed MC3T3-E1-BF cell culture protocol is described below.

Reagents and Medias

Reagents	Company	Catalog #
Alpha-MEM	Gibco-Invitrogen	12571-048
Ascorbic acid	Sigma	A4544
Beta-glycerophosphate	Sigma	G6376
100X PenStrepGlutamine	Gibco-Invitrogen	10378-016
Dimethylsulphoxide (DMSO)	Sigma	D5879 or D2650
Fetal bovine serum (FBS)	Cansera	CS-C08-500 (lot # SF50310)

EP 2 251 351 B1

(continued)

Reagents	Company	Catalog #
or Fetal bovine serum (FBS)	TerraCell Int.	CS-C08-1000A (lot # SF-20308)

Alpha-MEM is usually manufactured with a 1 year expiration date. Alpha-MEM that was not older than 6-months post-manufacture date was used for the cell culture.

[0494] Expansion Medium (Alpha-MEM/10%FBS/PenStrepGlu) was prepared as follows: A 500 ml bottle of FBS was thawed and filter sterilized through a 0.22 micron filter. 100 mls of this FBS was added to 1 liter of Alpha-MEM followed by the addition of 10 mls of 100x PenStrepGlutamine. Unused FBS was aliquoted and refrozen for later use.

[0495] Differentiation Medium (Alpha-MEM/10%FBS/PenStrepGlu, + 50 µg/ml ascorbic acid, + 10 mM beta-glycerophosphate) was prepared as follows:

100 mls of Differentiation Medium was prepared by supplementing 100 mls of Expansion Medium with ascorbic acid and beta-glycerophosphate as follows:

	Stock conc (see below)	Volume	Final Conc.
Ascorbic acid	10 mg/ml	0.5 mls	100 µg/ml (50ug/ml + 50µg/ml)
β-glycerophosphate	1M	1.0 mls	10 mM

[0496] Differentiation Medium was made by supplementing Expansion Medium only on the day that the Differentiation media was going to be used for cell culture. The final concentration of ascorbic acid in Differentiation medium is 100 µg/ml because Alpha-MEM already contains 50 µg/ml ascorbic acid. Ascorbic acid stock solution (10 mg/ml) was made and aliquoted for freezing at -80°C. Each aliquot was only used once (*i.e.* not refrozen). Beta-glycerophosphate stock solution (1 M) was made and aliquoted for freezing at -20°C. Each aliquot was frozen and thawed a maximum of 5 times before being discarded.

Cell Culture for expansion of MC3T3-E1-BF cells.

[0497] Cell culture was performed at 37°C and 5% CO₂. A cell bank was generated for the purposes of screening for sclerostin neutralizing antibodies. The cell bank was created as follows:

One vial of frozen MC3T3-E1-BF cells was thawed by agitation in a 37°C water bath. The thawed cells were put into 10 mls of Expansion Medium (Alpha-MEM/10%FBS/PenStrepGlu) in a 50 ml tube and gently spun down for 5 minutes. The cells were then resuspended in 4 mls of Alpha-MEM/10%FBS/PenStrepGlu. After determining the number of cells using trypan blue and hemacytometer, 1 x 10⁶ cells were plated in 50 mls Alpha-MEM/10%FBS/PenStrepGlu media in one T175 flask.

[0498] When this passage was confluent (at approximately 7 days), the cells were trypsinized with trypsin/EDTA (0.05% Trypsin; 0.53 mM EDTA), gently spun down for 5 minutes and then resuspended in 5 mls Alpha-MEM/10%FBS/PenStrepGlu. After determining the number of cells using trypan blue and hemacytometer, cells were plated at 1 x 10⁶ cells in 50 mls Alpha-MEM/10%FBS/PenStrepGlu media per one T175 flask. The number of T175 flasks used for plating at this point depended upon the total cell number available and the desired number of flasks that were to be taken forward to the next passage. Extra cells were frozen down at 1-2x10⁶ live cells/ml in 90%FBS/10%DMSO.

[0499] When this passage was confluent (about 3-4 days), the cells were trypsinized with trypsin/EDTA (0.05% Trypsin; 0.53 mM EDTA), gently spun down for 5 minutes and then resuspended in 5 mls Alpha-MEM/10%FBS/PenStrepGlu. After determining the number of cells using trypan blue and hemacytometer, cells were plated at 1 x 10⁶ cells in 50 mls Alpha-MEM/10%FBS/PenStrepGlu media per one T175 flask. The number of T175 flasks used for plating at this point depended upon the total cell number available and the desired number of flasks that were to be taken forward to the next passage. Extra cells were frozen down at 1-2x10⁶ live cells/ml in 90%FBS/10%DMSO.

[0500] When this passage was confluent (about 3-4 days), the cells were trypsinized with trypsin/EDTA (0.05% Trypsin; 0.53 mM EDTA), gently spun down for 5 minutes and then resuspended in 5 mls Alpha-MEM/10%FBS/PenStrepGlu. After determining the number of cells using trypan blue and hemacytometer, cells were plated at 1 x 10⁶ cells in 50 mls Alpha-MEM/10%FBS/PenStrepGlu media per one T175 flask. The number of T175 flasks used for plating at this point depended upon the total cell number available and the desired number of flasks that were to be taken forward to the next passage. Extra cells were frozen down at 1-2x10⁶ live cells/ml in 90%FBS/10%DMSO.

[0501] When this passage was confluent (about 3-4 days), the cells were trypsinized with trypsin/EDTA (0.05% Trypsin; 0.53 mM EDTA), gently spun down for 5 minutes and then resuspended in 5 mls Alpha-MEM/10%FBS/PenStrepGlu.

EP 2 251 351 B1

After determining the number of cells using trypan blue and hemacytometer, the cells were frozen down at $1\text{-}2 \times 10^6$ live cells/ml in 90%FBS/10%DMSO. This "final passage" of frozen cells was the passage that was used for the screening assay.

5 Cell Culture for mineralizing MC3T3-E1-BF cells.

[0502] Cell culture was performed at 37°C and 5% CO_2 . It is desirable to minimize temperature and % CO_2 fluctuations during the mineralization cell culture procedure. This can be achieved by minimizing the time that plates spend out of the incubator during feeding and also by minimizing the number of times the incubator door is opened and closed during the mineralization cell culture procedure. In this regard having a tissue culture incubator that is dedicated exclusively for the mineralization cell culture (and thus not opened and closed more than is necessary) can be helpful.

[0503] An appropriate number of "final passage" vials prepared as described above were thawed by agitation in a 37°C water bath. The thawed cells were put into 10 mls of Expansion Medium (Alpha-MEM/10%FBS/PenStrepGlu) in a 50 ml tube and gently spun down for 5 minutes. The cells were then resuspended in 4 mls of Alpha-MEM/10%FBS/Pen-StrepGlu. After determining the number of cells by trypan blue and hemacytometer, 2500 cells were plated in 200 microliters of Expansion media per well on collagen I coated 96-well plates (Becton Dickinson Labware, cat # 354407).

[0504] To avoid a mineralization plate-edge effect, cells were not plated in the outermost row/column all the way around the plate. Instead 200 microliters of PBS was added to these wells.

20 Exemplary cell culture procedure

[0505] In the following procedure, the starting day for plating the cells is indicated to be a Wednesday. If a different day of the week is used as the starting day for plating the cells, that day will trigger the daily schedule for removing and adding media during the entire process as indicated below. For example, if the cells are plated on a Tuesday, media should not be removed and added on the first Friday and Saturday, nor on the second Friday and Saturday. With a Tuesday start, the plates would be prepared for the calcium assay on the final Sunday.

Cells were plated on a Wednesday at 2500 cells in 200 μl of Expansion media.

On Thursday all of the Expansion media was removed and 200 μl of Differentiation Media was added.

On Friday 100 μl of media was removed and 100 μl of fresh Differentiation Media was added.

On Monday 100 μl of media was removed and 100 μl of fresh Differentiation Media was added.

On Tuesday 100 μl of media was removed and 100 μl of fresh Differentiation Media was added.

On Wednesday 100 μl of media was removed and 100 μl of fresh Differentiation Media was added.

On Thursday 100 μl of media was removed and 100 μl of fresh Differentiation Media was added.

On Friday 100 μl of media was removed and 100 μl of fresh Differentiation Media was added. On the following Monday plates were prepared for the calcium assay as follows:

Plates were washed once with 10 mM Tris, HCl pH 7-8.

Working under a fume hood, 200 μl of 0.5 N HCl was added per well. Plates were then frozen at -80°C .

[0506] Just prior to measuring calcium, the plates were freeze-thawed twice, and then trituration with a multichannel pipette was used to disperse the contents of the plate. The contents of the plate was then allowed to settle at 4°C for 30 minutes at which point an appropriate amount of supernatant was removed for measuring calcium using a commercially available calcium kit. An exemplary and not-limiting kit is Calcium (CPC) Liquicolor, Cat. No. 0150-250, Stanbio Laboratory, Boerne, TX.

[0507] In this cell based assay, sclerostin inhibits one or more of the sequence of events leading up to and including mineral deposition (*i.e.* sclerostin inhibits mineralization). Thus, in experiments where sclerostin was included in the particular cell culture experiment, the recombinant sclerostin was added to the media starting on the first Thursday and every feeding day thereafter. In cases where an anti-sclerostin monoclonal antibody (Mab) was being tested for the ability to neutralize sclerostin, *i.e.* allow for mineralization by neutralizing sclerostin's ability to inhibit mineralization, the Mab was added to the media starting on the first Thursday and every feeding day thereafter. According to the protocol, this was accomplished as follows: the Mab was preincubated with the recombinant sclerostin in Differentiation media for 45-60 minutes at 37°C and then this media was used for feeding the cells.

[0508] Described above is a 12-day mineralization protocol for MC3T3-E1-BF cells. Using the same reagents and feeding protocol, the original MC3T3-E1 cells (Sudo H, Kodama H-A, Amagai Y, Yamamoto S, Kasai S. 1983. In vitro Differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvaria. J Cell Biol 96:191-198) which we obtained from the RIKEN Cell Bank (RGB 1126, RIKEN BioResource Center 3-1-1 Koyadai, Tsukuba-shi, Ibaraki 305-0074 Japan) took longer to mineralize (20 days total for mineralization) than the MC3T3-E1-BF cells. Mineralization of the original MC3T3-E1 cells was inhibited by recombinant sclerostin and this inhibition was blocked

using a sclerostin neutralizing antibody.

EXAMPLE 9

ANTI-SCLEROSTIN ANTIBODY PROTECTS FROM INFLAMMATION-INDUCED BONE LOSS IN THE CD4 CD45RB^{HI} TRANSFER MODEL OF COLITIS IN SCID MICE

Summary of model

[0509] Injection of the CD45RB^{high} subset of CD4⁺ T cells into C.B-17 *scid* mice results in chronic intestinal inflammation with characteristics similar to those of human inflammatory bowel disease (IBD). Diarrhoea and wasting disease is noted 3-5 weeks after cell transfer with severe leukocyte infiltration into the colon accompanied by epithelial cell hyperplasia and granuloma formation. C.B-17 *scid* mice which receive the reciprocal subset of CD4⁺ cells, those which express CD45RB^{low}, do not exhibit colitis and have a weight gain indistinguishable from uninjected *scid* mice. In addition to colitis symptoms, the CD4⁺ CD45RB^{high} T cell transfer model of colitis is accompanied by a reduction in bone mineral density (BMD), thought to be primarily through inflammatory mechanisms rather than dietary malabsorption (Byrne, F. R. et al., Gut 54:78-86, 2005).

Induction of colitis and inflammation-induced bone loss

[0510] Spleens were taken from female balb/c mice and disrupted through a 70µm cell strainer. The CD4⁺ population was then enriched by negative selection with Dynabeads using antibodies against B220, MAC-1, CD8 and I-A^d. The enriched population was then stained with FITC conjugated anti-CD4 and PE conjugated anti-CD45RB and fractionated into CD4⁺CD45RB^{high} and CD4⁺CD45RB^{low} populations by two-color sorting on a Moflo (Dakocytomation). The CD45RB^{high} and CD45RB^{low} populations were defined as the brightest staining 40% and the dimmest staining 20% of CD4⁺ cells respectively. 5 x 10⁵ cells were then injected i.p. into C.B-17 *scid* mice on day 0 and the development of colitis was monitored through the appearance of soft stools or diarrhoea and weight loss. Bone mineral density measurements were taken at the termination of the study (day 88).

Effect of anti-Sclerostin treatment on colitis symptoms and BMD

[0511] Ab-A IgG was dosed at 10mg/kg s.c. from the day prior to CD4⁺CD45RB^{high} cell transfer and compared with mice which received the negative control antibody 101.4 also dosed at 10mg/kg s.c.. The antibodies were dosed weekly thereafter. A group of mice which received non-pathogenic CD4⁺CD45RB^{low} cells and were dosed with 10mg/kg 101.4 was studied as a control. At the termination of the study (day 88) the bone mineral density was measured and sections of the colon taken for analysis of cell infiltration and assessment of histological damage.

a) No effect on colitis symptoms

[0512] Typical colitis symptoms such as weight loss and infiltration of inflammatory cells into the colon were unaffected by treatment with Ab-A. Similarly there was no improvement of histological damage to the colon after treatment with Ab-A.

b) Inhibition of inflammation-induced loss of bone mineral density.

[0513] On day 88 after transfer of cells into C.B-17 *scid* mice, the bone mineral density was measured (total BMD, vertebrae BMD and femur BMD). In comparison to control mice which received CD4⁺CD45RB^{low} non-pathogenic cells, mice which received CD4⁺ CD45RB^{high} T cells and the negative control antibody 101.4 had reduced bone mineral density, as shown in Figure 25. In contrast, no reduction in BMD was noted after treatment with Ab-A. Total, vertebrae and femur measurements of BMD were significantly higher in mice receiving CD4⁺ CD45RB^{high} T cells and treated with Ab-A than mice receiving CD4⁺ CD45RB^{high} T cells and treated with 101.4 (P<0.001 by Bonferroni multiple comparison test).

EXAMPLE 10

KINEXA-BASED DETERMINATION OF AFFINITY (K_D) OF ANTI-SCLEROSTIN ANTIBODIES FOR HUMAN SCLEROSTIN

[0514] The affinity of several anti-sclerostin antibodies to human sclerostin was assessed by a solution equilibrium binding analysis using KinExA® 3000 (Sapidyne Instruments Inc., Boise, ID). For these measurements, Reacti-Gel 6x beads (Pierce, Rockford, IL) were pre-coated with 40 µg/ml human sclerostin in 50 mM Na₂CO₃, pH 9.6 at 4 °C overnight. The beads were then blocked with 1 mg/ml BSA in 1 M Tris-HCl, pH 7.5 at 4 °C for two hours. 10 pM, 30 pM, or 100 pM of the antibody was mixed with various concentrations of human sclerostin, ranging in concentration from 0.1 pM to 1 nM, and equilibrated at room temperature for over 8 hours in PBS with 0.1 mg/ml BSA and 0.005% P20. The mixtures were then passed over the human sclerostin coated beads. The amount of bead-bound anti-sclerostin antibody was quantified using fluorescent Cy5-labeled goat anti-mouse-IgG or fluorescent Cy5-labeled goat anti-human-IgG antibodies (Jackson Immuno Research, West Grove, PA) for the mouse or human antibody samples, respectively. The amount of fluorescent signal measured was proportional to the concentration of free anti-sclerostin antibody in each reaction mixture at equilibrium. The dissociation equilibrium constant (K_D) was obtained from nonlinear regression of the competition curves using a n-curve one-site homogeneous binding model provided in the KinExA Pro software. Results of the KinExA assays for the selected antibodies are summarized in the table below.

Antibodies	Antigen	K_D (pM)	95% confidence interval
Ab-13	Human Sclerostin	0.6	0.4 ~ 0.8 pM
Ab-4	Human Sclerostin	3	1.8 ~ 4pM
Ab-19	Human Sclerostin	3	1.7 ~ 4 pM
Ab-14	Human Sclerostin	1	0.5 ~ 2 pM
Ab-5	Human Sclerostin	6	4.3 ~ 8 pM
Ab-23	Human Sclerostin	4	2.1 ~ 8 pM

EXAMPLE 11

BIAcore METHOD FOR DETERMINING THE AFFINITY OF HUMANISED ANTI-SCLEROSTIN ANTIBODIES FOR HUMAN SCLEROSTIN.

[0515] The BIAcore technology monitors the binding between biomolecules in real time and without the requirement for labelling. One of the interactants, termed the ligand, is either immobilised directly or captured on the immobilised surface while the other, termed the analyte, flows in solution over the captured surface. The sensor detects the change in mass on the sensor surface as the analyte binds to the ligand to form a complex on the surface. This corresponds to the association process. The dissociation process is monitored when the analyte is replaced by buffer. In the affinity BIAcore assay, the ligand is the anti-sclerostin antibody and the analyte is sclerostin.

Instrument

[0516] Biacore ® 3000, Biacore AB, Uppsala, Sweden

Sensor chip

[0517] CM5 (research grade) Catalogue Number: BR-1001-14, Biacore AB, Uppsala, Sweden. Chips were stored at 4 °C.

BIAnormalising solution

[0518] 70% (w/w) Glycerol. Part of BIAmaintenance Kit Catalogue Number: BR-1002-51, Biacore AB, Uppsala, Sweden. The BIAmaintenance kit was stored at 4 °C.

EP 2 251 351 B1

Amine Complying Kit

[0519] Catalogue Number: BR-1000-50, Biacore AB, Uppsala, Sweden.

[0520] Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC). Made up to 75 mg/mL in distilled water and stored in 200 μ L aliquots at -70 °C.

[0521] N-Hydroxysuccinimide (NHS). Made up to 11.5 mg/mL in distilled water and stored in 200 μ L aliquots at -74 °C.

[0522] 1 M Ethanolamine hydrochloride-NaOH pH 8.5. Stored in 200 μ L aliquots at -70 °C.

Buffers

[0523] Running buffer for immobilising capture antibody: HBS-EP (being 0.01 M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005 % Surfactant P20). Catalogue Number: BR-1001-88, Biacore AB, Uppsala, Sweden. Buffer stored at 4 °C.

[0524] Immobilisation buffer: Acetate 5.0 (being 10 mM sodium acetate pH 5.0). Catalogue number: BR-1003-51, Biacore AB, Uppsala, Sweden. Buffer stored at 4 °C.

[0525] Running buffer for binding assay: HBS-EP (being 0.01 M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005 % Surfactant P20, Catalogue Number: BR-1001-88, Biacore AB, Uppsala, Sweden) with CM-Dextran added at 1 mg/mL (Catalogue Number 27560, Fluka BioChemika, Buchs, Switzerland). Buffer stored at 4 °C.

Ligand capture

[0526] Affinipure F(ab')₂ fragment goat anti-human IgG, Fc fragment specific. Jackson ImmunoResearch Inc (Pennsylvania, USA) Catalogue number: 109-006-098. Reagent stored at 4 °C.

Ligand

[0527] Humanised anti-human sclerostin antibodies Ab5, Ab14 and Ab20.

Analyte

[0528] Recombinant human sclerostin. Aliquots stored at -70°C and thawed once for each assay.

Regeneration Solution

[0529] 40 mM HCl prepared by dilution with distilled water from an 11.6 M stock solution (BDH, Poole, England. Catalogue number: 101254H).

[0530] 5 mM NaOH prepared by dilution with distilled water from a 50 mM stock solution. Catalogue number: BR-1003-58, Biacore AB, Uppsala, Sweden.

Assay Methods

[0531] The assay format was capture of the anti-sclerostin antibody by immobilised anti-human IgG-Fc then titration of the sclerostin over the captured surface.

[0532] An example of the procedure is given below:

BIA (Biomolecular Interaction Analysis) was performed using a BIAcore 3000 (BIAcore AB). Affinipure F(ab')₂ Fragment goat anti-human IgG, Fc fragment specific (Jackson ImmunoResearch) was immobilised on a CM5 Sensor Chip via amine coupling chemistry to a capture level of $\approx$ 4000 response units (RUs). HBS-EP buffer (10mM HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005 % Surfactant P20, BIAcore AB) containing 1 mg/mL CM-Dextran was used as the running buffer with a flow rate of 10 μ L/min. A 10 μ L injection of the anti-sclerostin antibody at $\sim$ 5 μ g/mL was used for capture by the immobilised anti-human IgG-Fc. Antibody capture levels were typically 100-200 RU. Sclerostin was titrated over the captured anti-sclerostin antibody at various concentrations at a flow rate of 30 μ L/min. The surface was regenerated by two 10 μ L injections of 40 mM HCl, followed by a 5 μ L injection of 5 mM NaOH at a flowrate of 10 μ L/min.

[0533] Background subtraction binding curves were analysed using the BIAevaluation software (version 3.2) following standard procedures. Kinetic parameters were determined from the fitting algorithm.

[0534] The kinetic data and calculated dissociation constants are given in Table 2.

TABLE 2: Affinity of anti-sclerostin antibodies for sclerostin

Antibody	ka (1/Ms)	kd (1/s)	Kd(pM)
Ab-5	1.78E+06	1.74E-04	97.8
Ab-14	3.30E+06	4.87E-06	1.48
Ab-20	2.62E+06	4.16E-05	15.8

EXAMPLE 12

IN VIVO TESTING OF ANTI-SCLEROSTIN MONOCLONAL ANTIBODIES IN CYNOMOLGOUS MONKEYS

[0535] Thirty-three, approximately 3-5 year old, female cynomolgus monkeys (*Macaca fascicularis*) were used in this 2- month study. The study contained 11 groups:

- Group 1: vehicle (N=4)
- Group 2: Ab-23 (N=2, dose 3 mg/kg)
- Group 3: Ab-23 (N=3, dose 10 mg/kg)
- Group 4: Ab-23 (N=3, dose 30 mg/kg)
- Group 5: Ab-5 (N=3, dose 3 mg/kg)
- Group 6: Ab-5 (N=3, dose 10 mg/kg)
- Group 7: Ab-5 (N=3, dose 30 mg/kg)
- Group 8: Ab-14 (N=3, dose 3 mg/kg)
- Group 9: Ab-14 (N=3, dose 10 mg/kg)
- Group 10: Ab-14 (N=3, dose 30 mg/kg)
- Group 11: Parathyroid Hormone (1-34) [PTH (1-34)] (N=3, dose 10 ug/kg)

[0536] All dosing was subcutaneous. PTH (1-34) was dosed everyday, monoclonal antibodies (Mabs) were dosed twice (first dose at the beginning of the study and second dose at the one month time point). For assessment of bone parameters (e.g. bone mineral density) pQCT (peripheral quantitative computed tomography) and DXA (dual energy X-ray absorptiometry) scans were performed prior to the beginning of the study (to obtain baseline values) and after a month (prior to the second dose of Mab) and finally at the end of the study (2-month time point) at which point the monkeys were necropsied for further analysis (e.g. histomorphometric analysis).

[0537] Animals were fluorochrome labeled (days 14,24,47, and 57) for dynamic histomorphometry. Serum was collected at various time points during the study [day 1 pre-dose (the day of the first Mab dose), day 1 twelve hours post-dose, day 2, day 3, day 5, day 7, day 14, day 21, day 28, day 29 twelve hours post-dose (day 29 was the day of the second and final Mab dose), day 30, day 31, day 33, day 35, day 42, day 49 and day 56].

[0538] Three bone-related serum biomarkers were measured using commercially available kits:

Osteocalcin (OC) (DSL Osteocalcin Radioimmunoassay Kit; Diagnostic Systems Laboratories, Inc., Webster, TX, USA)

N-terminal Propeptide of Type I Procollagen (P1NP) (P1NP Radioimmunoassay Kit; Orion Diagnostica, Espoo, Finland)

C-telopeptide fragments of collagen type I α 1 chains (sCTXI) (Serum CrossLaps® ELISA; Nordic Bioscience Diagnostics A/S, Herlev, Denmark).

[0539] pQCT and DXA scans yielded data on various bone parameters (including bone mineral density (BMD) and bone mineral content) across numerous skeletal sites (including tibial metaphysis and diaphysis, radial metaphysis and diaphysis, femur neck, lumbar vertebrae). Analysis of this bone data (percent change from baseline for each animal) and the anabolic (OC, P1NP) serum biomarker data (percent change from baseline for each animal) revealed statistically significant increases, versus the vehicle group, in some parameters at some of the time points and doses for each Mab. This bone parameter data, serum biomarker data, as well as the histomorphometric data, indicated that each of the 3 Mabs (Ab-23, Ab-5 and Ab-14) was able to neutralize sclerostin in cynomolgous monkeys. This activity was most robust for Ab-23 and Ab-5, particularly at the highest dose (30 mg/kg), with a clear increase in bone formation (anabolic effect) as well as net gains in bone (e.g. BMD). Statistically significant increases in bone parameters and anabolic histomorphometric parameters were also found for the positive control group (PTH (1-34)).

[0540] Serum bone formation markers (P1NP, osteocalcin) were increased ($p < 0.05$ vs vehicle (VEH)) at various time points and doses, but particularly in the 30 mg/kg groups for Ab-23 and Ab-5. Histomorphometric analysis revealed dramatic increases ($p < 0.05$ vs VEH) in bone formation rates in cancellous bone at lumbar vertebra and proximal tibia (up to 5-fold increase), as well as at the endocortical surface of the femur midshaft (up to 10-fold increase) at the higher doses of Ab-23 and Ab-5. Trabecular thickness was increased with high dose Ab-23 and Ab-5 in lumbar vertebrae ($> 60\%$, $p < 0.05$ vs VEH). By study end (2 months), areal BMD, as percent change from baseline, was increased ($p < 0.05$ vs VEH) at the femur neck, ultra-distal radius (Ab-23, 30 mg/kg), and lumbar vertebrae (Ab-5, 30 mg/kg). The increases in areal BMD at the lumbar vertebrae were accompanied by increases in vertebral strength (97% increase in vertebral maximal load for Ab-23, 30 mg/kg; $p < 0.05$ vs VEH); baseline values for lumbar areal BMD prior to Mab dosing were statistically similar across all groups. In summary, short-term administration of sclerostin-neutralizing Mabs in cynomolgous monkeys resulted, in part, in increases in bone formation, BMD and vertebral bone strength.

[0541] From the foregoing, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

Aspects of the disclosure

[0542] The following are aspects of the disclosure:

1. A composition comprising a polypeptide having the amino acid sequence of SEQ ID NO: 6.
2. A composition comprising a polypeptide having the amino acid sequence of SEQ ID NO: 63, 64, 65, 66, 67, 68 or 69.
3. A composition comprising at least one, at least two, at least three or all four of the polypeptides of the amino acid sequences SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5.
4. A composition comprising a polypeptide having the amino acid sequences of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5, wherein SEQ ID NO: 2 and 4 are joined by a disulfide bond at amino acid positions 57 and 111 with reference to SEQ ID NO: 1, and SEQ ID NO: 3 and 5 are joined by at least one of (a) a disulfide bond at amino acid positions 82 and 142 with reference to SEQ ID NO: 1, and (b) a disulfide bond at amino acid positions 86 and 144 with reference to SEQ ID NO: 1.
5. A polypeptide consisting essentially of a multiply truncated human sclerostin protein of SEQ ID NO: 1, wherein amino acids 1-50, 65-72, 91-100, 118-137, and 150-190 of SEQ ID NO: 1 are absent from said polypeptide.
6. A composition comprising at least one, at least two, at least three or all four of the polypeptides of the amino acid sequences SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72 and SEQ ID NO: 73.
7. A composition comprising a polypeptide having the amino acid sequences of SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72 and SEQ ID NO: 73, wherein SEQ ID NO: 72 and 73 are joined by a disulfide bond at amino acid positions 57 and 111 with reference to SEQ ID NO: 1, and SEQ ID NO: 70 and 71 are joined by at least one of (a) a disulfide bond at amino acid positions 82 and 142 with reference to SEQ ID NO: 1, and (b) a disulfide bond at amino acid positions 86 and 144 with reference to SEQ ID NO: 1.
8. The composition of any one of aspects 1-3, 6 and 7 wherein each of said polypeptides retains the tertiary structure of the corresponding polypeptide region of human sclerostin of SEQ ID NO: 1.
9. A polypeptide consisting essentially of a multiply truncated human sclerostin protein of SEQ ID NO: 1, wherein amino acids 1-56, 65-72, 87-110, 118-137, and 145-190 of SEQ ID NO: 1 are absent from said polypeptide.
10. The polypeptide of aspect 9, wherein said polypeptide is obtained by tryptic digestion of human sclerostin.
11. The polypeptide of aspect 10, wherein said human sclerostin is treated with trypsin to achieve complete trypsin digestion and said polypeptide is isolated by HPLC.
12. A portion of human sclerostin comprising amino acids 51-64, 73-90, 101-117, and 138-149 of SEQ ID NO: 1, wherein said portion has at least one, at least two or all three of:

- (a) a disulfide bond between amino acids 57 and 111;
- (b) a disulfide bond between amino acids 82 and 142; and
- (c) a disulfide bond between amino acids 86 and 144.

5 13. A portion of human sclerostin comprising amino acids 57-64, 73-86, 111-117, and 138-144 of SEQ ID NO: 1, wherein said portion has at least one, at least two, or all three of:

- (a) a disulfide bond between amino acids 57 and 111;
- (b) a disulfide bond between amino acids 82 and 142; and
- 10 (c) a disulfide bond between amino acids 86 and 144.

14. A polypeptide consisting essentially of a human sclerostin protein of SEQ ID NO: 1 truncated at the C-terminal and N-terminal ends, wherein amino acids 1-85 and 112-190 of SEQ ID NO: 1 are absent from said polypeptide.

15 15. A portion of human sclerostin, comprising amino acids 86-111 of SEQ ID NO: 1.

16. A portion of human sclerostin, comprising SEQ ID NO: 6.

17. A portion of human sclerostin, comprising SEQ ID NO: 63, 64, 65, 66, 67, 68 or 69.

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18. A portion of rat sclerostin, comprising SEQ ID NO: 96 or 97.

19. A method of producing a portion of human sclerostin, comprising the steps of:

- 25 (a) treating human sclerostin with trypsin to achieve complete tryptic digestion;
- (b) collecting the tryptic digest sample having average molecular mass of 7122.0D (theoretical mass 7121.5D) or retention time of about 20.6 minutes as determined by elution from a reverse-phase HPLC column with linear gradient from 0.05% trifluoroacetic acid to 90% acetonitrile in 0.05% TFA at a flow rate of 0.2ml/min; and
- (c) purifying said portion.

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20. A polypeptide of

SEQ ID NO: 6;

SEQ ID NO: 2;

SEQ ID NO: 3;

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SEQ ID NO: 5;

SEQ ID NO: 2, SEQ ID NO: 3; SEQ ID NO: 4 and SEQ ID NO: 5;

SEQ ID NO: 96;

SEQ ID NO: 97;

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SEQ ID NO: 64;

SEQ ID NO: 65;

SEQ ID NO: 66;

SEQ ID NO: 67;

45 SEQ ID NO: 68;

SEQ ID NO: 69;

SEQ ID NO: 70;

SEQ ID NO: 71;

SEQ ID NO: 72;

50 SEQ ID NO: 73; or

SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72 and SEQ ID NO: 73.

21. A polypeptide according to any of aspects 1-18 and 20, for use in a method of generating an antibody comprising administering the polypeptide to an animal.

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22. The polypeptide according to aspect 21, for use in said method wherein the animal is a mammal.

23. A vaccine comprising at least one polypeptide comprising one or more of the epitopes of SEQ ID NO: 2, 3, 4,

5, 6, 70, 71, 72, and 73.

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EP 2 251 351 B1

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EP 2 251 351 B1

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EP 2 251 351 B1

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<210> 13
 <211> 462
 <212> PRT
 <213> Mus musculus
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20      25      30
Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35      40      45
Thr Asp His Tyr Met Ser Trp Val Lys Gln Ser His Gly Lys Ser Leu
50      55      60
Glu Trp Ile Gly Asp Ile Asn Pro Tyr Ser Gly Glu Thr Thr Tyr Asn
65      70      75      80
Gln Lys Phe Lys Gly Thr Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
85      90      95

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	Tyr	Tyr	Cys 115	Ala	Arg	Asp	Asp	Tyr 120	Asp	Ala	Ser	Pro	Phe 125	Ala	Tyr	Trp
	Gly	Gln 130	Gly	Thr	Leu	Val	Thr 135	Val	Ser	Ala	Ala	Lys 140	Thr	Thr	Pro	Pro
	Ser 145	Val	Tyr	Pro	Leu	Ala 150	Pro	Gly	Ser	Ala	Ala 155	Gln	Thr	Asn	Ser	Met 160
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	Pro	Ser 210	Ser	Thr	Trp	Pro	Ser 215	Glu	Thr	Val	Thr	Cys 220	Asn	Val	Ala	His
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	Gly	Cys	Lys	Pro	Cys 245	Ile	Cys	Thr	Val	Pro 250	Glu	Val	Ser	Ser	Val 255	Phe
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	Lys	Val	Thr 275	Cys	Val	Val	Val	Asp 280	Ile	Ser	Lys	Asp	Asp 285	Pro	Glu	Val
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	Gln 305	Pro	Arg	Glu	Glu	Gln 310	Phe	Asn	Ser	Thr	Phe 315	Arg	Ser	Val	Ser	Glu 320
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	Arg	Val	Asn	Ser 340	Pro	Ala	Phe	Pro	Ala 345	Pro	Ile	Glu	Lys	Thr 350	Ile	Ser
30	Lys	Thr	Lys 355	Gly	Arg	Pro	Lys	Ala 360	Pro	Gln	Val	Tyr	Thr 365	Ile	Pro	Pro
	Pro	Lys 370	Glu	Gln	Met	Ala	Lys 375	Asp	Lys	Val	Ser	Leu 380	Thr	Cys	Met	Ile
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	Gln	Pro	Ala	Glu	Asn 405	Tyr	Lys	Asn	Thr	Gln 410	Pro	Ile	Met	Asp	Thr 415	Asp
35	Gly	Ser	Tyr	Phe 420	Ile	Tyr	Ser	Lys	Leu 425	Asn	Val	Gln	Lys	Ser 430	Asn	Trp
	Glu	Ala	Gly 435	Asn	Thr	Phe	Thr	Cys 440	Ser	Val	Leu	His	Glu 445	Gly	Leu	His
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<210> 14
<211> 1389
<212> DNA
<213> Mus musculus

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	gagatccgcy	gcctgacatc	tgaggactct	gcagtctatt	actgtgcaag	agatgattac	360
	gacgcctctc	cgtttgctta	ctggggccaa	gggactctgg	tcactgtctc	tgcagccaaa	420
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55	tctggatccc	tgtccacgcy	tggtcacacc	ttcccagctg	tcttcgagtc	tgacctctac	600
	actctgagca	gctcagtgac	tgtcccctcc	agcacctggc	ccagcgagac	cgtcacctgc	660
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	ggttgtaagc	cttgcatatg	tacagtccca	gaagtatcat	ctgtcttcat	cttcccccca	780
	aaagcccaagg	atgtgctcac	cattactctg	actcctaagg	ctgcgttgtgt	tgtggtagac	840

EP 2 251 351 B1

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<210> 15
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 <212> PRT
 <213> Mus musculus

<400> 15

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20 25 30
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35 40 45
Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60
Arg Phe Ser Gly Asn Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80
Pro Val Glu Glu Glu Asp Ala Val Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
115 120 125
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
130 135 140
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145 150 155 160
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
165 170 175
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
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Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
210 215

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 <212> DNA
 <213> Mus musculus

<400> 16

EP 2 251 351 B1

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<211> 238

<212> PRT

15 <213> Mus musculus

<400> 17

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 20 25
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 35 40 45
 25 Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
 50 55 60
 Gly Gln Pro Pro Lys Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
 65 70 75 80
 Gly Ile Pro Ala Arg Phe Ser Gly Asn Gly Ser Gly Thr Asp Phe Thr
 85 90 95
 30 Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Val Thr Tyr Tyr Cys
 100 105 110
 Gln Gln Ser Asn Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
 115 120 125
 Glu Ile Lys Arg Ala Asp Ala Pro Thr Val Ser Ile Phe Pro Pro
 130 135 140
 35 Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu
 145 150 155 160
 Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly
 165 170 175
 Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser
 180 185 190
 Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp
 195 200 205
 40 Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr
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<212> DNA

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50 <400> 18

EP 2 251 351 B1

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<211> 449

<212> PRT

15 <213> Mus musculus

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

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30

35

40

45

50

55

Lys 65 Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 Met Gln Leu Asn Ser 70 Leu Thr Ser Asp Asp 75 Ser Ala Val Tyr Tyr Cys
 5 Ala Arg Ser His 85 Tyr Tyr Phe Asp Gly 90 Arg Val Pro Trp Asp 95 Ala Met
 Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr
 Thr Pro Pro Ser Val Tyr Pro 105 Leu Ala Pro Gly Ser Ala Ala Gln Thr
 10 Asn 130 Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
 145 150 Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
 Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
 15 Val Thr Val 165 Pro Ser Ser Thr Trp 170 Pro Ser Glu Thr Val Thr Cys Asn
 Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
 Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
 20 Ser Val Phe Ile Phe 200 Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
 Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
 Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
 25 Ala Gln Thr Gln Pro Arg Glu Gln Phe Asn Ser Thr Phe Arg Ser
 Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
 Phe Lys Cys Arg Val 325 Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
 30 Thr Ile Ser Lys Thr Lys Gly Arg Pro 340 Lys Asp Lys Val Ser Leu Thr
 Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
 Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
 35 Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
 385 390 Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys
 Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
 40 Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
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<210> 20

<211> 1350

<212> DNA

<213> Mus musculus

<400> 20

EP 2 251 351 B1

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 <212> PRT
 <213> Mus musculus

<400> 21

EP 2 251 351 B1

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				20					25					30		
5	Pro	Gly	Thr	Ser	Val	Lys	Met	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe
			35					40					45			
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				85						90					95	
	Thr	Ala	Tyr	Met	Gln	Leu	Asn	Ser	Leu	Thr	Ser	Asp	Asp	Ser	Ala	Val
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15	Ala	Lys	Thr	Thr	Pro	Pro	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala
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				180					185					190		
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			195					200					205			
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			355					360					365			
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		370					375					380				
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	Glu	Trp	Gln	Trp	Asn	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln
				405						410					415	
45	Pro	Ile	Met	Asp	Thr	Asp	Gly	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn
				420					425					430		
	Val	Gln	Lys	Ser	Asn	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val
			435					440					445			
	Leu	His	Glu	Gly	Leu	His	Asn	His	His	Thr	Glu	Lys	Ser	Leu	Ser	His
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<210> 22

<211> 1407

<212> DNA

55 <213> Mus musculus

<400> 22

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 20 ggaaatactt tcacctgctc tgtgttcat gagggcctgc acaaccacca tactgagaag 1380
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<210> 23

<211> 217

25 <212> PRT

<213> Rabbit-Mouse chimera

<400> 23

30 Ala Gln Val Leu Thr Gln Thr Pro Ala Ser Val Ser Ala Ala Val Gly
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 Gly Thr Val Thr Ile Asn Cys Gln Ser Ser Gln Ser Val Tyr Asp Asn
 20 25 30
 Asn Trp Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
 35 35 40 45
 Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val Pro Ser Arg Phe
 50 55 60
 Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Gly Val
 65 70 75 80
 Gln Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gly Ala Tyr Asn Asp
 85 90 95
 40 Val Ile Tyr Ala Phe Gly Gly Gly Thr Glu Val Val Val Lys Arg Thr
 100 105 110
 Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu
 115 120 125
 Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro
 45
 130 135 140
 Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn
 145 150 155
 Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr
 165 170 175
 50 Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His
 180 185 190
 Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile
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 Val Lys Ser Phe Asn Arg Asn Glu Cys
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<210> 24

<211> 654

<212> DNA

EP 2 251 351 B1

<213> Rabbit-Mouse Chimera

<400> 24

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      aactttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat 480
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      accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacttg tgaggccact 600
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<210> 25

<211> 239

<212> PRT

<213> Rabbit-Mouse Chimera

<400> 25

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

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<210> 26

<211> 720

<212> DNA

<213> Rabbit-Mouse Chimera

<400> 26


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gtcaccatca attgccagtc cagtcagagt gtttatgata acaactgggt agcctgggtt 180
cagcagaaac cagggcagcc tcccaagctc ctgatttatg atgcatccga tctggcatct 240
5 ggggtcccat cgcggttcag tggcagtgga tctgggacac agttcactct caccatcagc 300
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tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480
ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 540
10 caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600
agcagcacc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660
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<210> 27

<211> 433

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody

<400> 27

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20
Met Asn Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Ile Gly
35
Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser Trp Ala Lys Gly
50
30 Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Met Asp Leu Lys Met Thr
65
Ser Leu Thr Thr Gly Asp Thr Ala Arg Tyr Phe Cys Ala Arg Asn Trp
85
Asn Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
100
35 Lys Gly Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
115
Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
130
Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
145
40 Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
165
Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
180
Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
195
45 Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
210
Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
225
Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
245
50 Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
260
Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
275
Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
290
55

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EP 2 251 351 B1

5 Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
 305 310 315 320
 Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
 325 330 335
 Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
 340 345 350
 Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
 355 360 365
 Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
 370 375 380
 10 Asn Thr Asn Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys
 385 390 395 400
 Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
 405 410 415
 Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
 420 425 430
 15 Lys

<210> 28

<211> 1302

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody

<400> 28

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 caaggcaccc tcgtcaccgt ctcgagcgct tctacaaagg gcccatctgt ctatccactg 360
 gcccctggat ctgctgcccc aactaactcc atggtgacct tgggatgcct ggtcaagggc 420
 tatttccctg agccagtgc agtgacctgg aactctggat cctgtccag cggtgtgcac 480
 accttcccag ctgtcctgca gtctgacctc tacactctga gcagctcagt gactgtcccc 540
 35 tccagcacct ggcccagcga gaccgtcacc tgcaacgttg cccaccggc cagcagcacc 600
 aagggtggaca agaaaattgt gcccagggat tgtggttgta agccttgcat atgtacagtc 660
 ccagaagtat catctgtctt catcttcccc ccaaagcccc aggatgtgct caccattact 720
 ctgactccta aggtcacgtg tgttggtgta gacatcagca aggatgatcc cgagggtccag 780
 ttcagctgggt ttgtagatga tgtggagggt cacacagctc agacgcaacc ccgggaggag 840
 cagttcaaca gcactttccg ctgagtcagt gaacttcccc tcatgcacca ggactggctc 900
 40 aatggcaagg agttcaaatt caggggtcaac agtgcagctt tccctgcccc catcgagaaa 960
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 cagcccatca tggacacaga tggctcttac ttcgtctaca gcaagctcaa tgtgcagaag 1200
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<210> 29

<211> 452

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody

<400> 29

EP 2 251 351 B1

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20 25 30
5 Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35 40 45
Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu

50 55 60
10 Trp Ile Gly Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Met Asp Leu
85 90 95
Lys Met Thr Ser Leu Thr Thr Gly Asp Thr Ala Arg Tyr Phe Cys Ala
100 105 110
15 Arg Asn Trp Asn Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125
Ala Ser Thr Lys Gly Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
130 135 140
Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
145 150 155 160
20 Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
165 170 175
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
180 185 190
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
195 200 205
25 Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
210 215 220
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
225 230 235 240
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
245 250 255
30 Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
260 265 270
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
275 280 285 290
Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
295 300 305
Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
310 315 320
35 Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
325 330 335
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
340 345 350
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
355 360 365
40 Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
370 375 380
Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
385 390 395 400
Pro Ile Met Asn Thr Asn Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
405 410 415
45 Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
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435 440 445
Ser Pro Gly Lys
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50 <210> 30
<211> 1359
<212> DNA
<213> Artificial Sequence

55 <220>
<223> Humanized antibody

<400> 30

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 gaggggctgg aatggatcgg aaccattgat tctgggtgta ggacgggacta cgcgagctgg 240
 gcaaaaggcc gattcaccat ctccagaacc tcgactacga tggatctgaa aatgaccagt 300
 ctgacgaccg gggacacggc ccgttatttc tgtgccagaa attggaactt gtggggccaa 360

ggcacccctg tcaccgtctc gagcgcttct acaaagggcc catctgtcta tccactggcc 420
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 agcacctggc ccagcgagac cgtcacctgc aacgttgccc acccggccag cagcaccaag 660
 gtggacaaga aaattgtgcc cagggattgt ggttgtaagc cttgcatatg tacagtccca 720
 gaagtatcat ctgtcttcat ctcccccca aagcccaagg atgtgctcac cattactctg 780
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<210> 31

<211> 213

<212> PRT

<213> Mus musculus

<400> 31

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 Glu Lys Val Thr Leu Ile Cys Ser Ala Ser Ser Ser Val Ser Phe Val
 20 25 30
 Asp Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Arg Trp Ile Tyr
 35 40 45
 Arg Thr Ser Asn Leu Gly Phe Gly Val Pro Ala Arg Phe Ser Gly Gly
 50 55 60
 Gly Ser Gly Thr Ser His Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
 65 70 75 80
 Asp Ala Ala Thr Tyr Cys Gln Gln Arg Ser Thr Tyr Pro Pro Thr
 85 90 95
 Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
 100 105 110
 Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
 115 120 125
 Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
 130 135 140
 Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
 145 150 155 160
 Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
 165 170 175
 Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
 180 185 190
 Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
 195 200 205
 Asn Arg Asn Glu Cys
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<210> 32

<211> 642

<212> DNA

<213> Mus musculus

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15

<210> 33

 $\langle 211 \rangle$ 235

<212> PRT

<213> Mus musculus

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<400> 33

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	Val	Ser	Ala 35	Ser	Pro	Gly	Glu	Lys 40	Val	Thr	Leu	Ile	Cys 45	Ser	Ala	Ser
	Ser	Ser	Val	Ser	Phe	Val	Asp 55	Trp	Phe	Gln	Gln	Lys 60	Pro	Gly	Thr	Ser
30	Pro 65	Lys	Arg	Trp	Ile 70	Tyr	Arg	Thr	Ser	Asn	Leu 75	Gly	Phe	Gly	Val	Pro 80
	Ala	Arg	Phe	Ser	Gly 85	Gly	Gly	Ser	Gly	Thr 90	Ser	His	Ser	Leu	Thr 95	Ile
	Ser	Arg	Met	Glu 100	Ala	Glu	Asp	Ala	Ala 105	Thr	Tyr	Tyr	Cys	Gln 110	Gln	Arg
35	Ser	Thr	Tyr 115	Pro	Pro	Thr	Phe	Gly 120	Ala	Gly	Thr	Lys	Leu 125	Glu	Leu	Lys
	Arg	Ala 130	Asp	Ala	Ala	Pro	Thr 135	Val	Ser	Ile	Phe	Pro 140	Pro	Ser	Ser	Glu
	Gln 145	Leu	Thr	Ser	Gly	Gly 150	Ala	Ser	Val	Val	Cys 155	Phe	Leu	Asn	Asn	Phe 160
40	Tyr	Pro	Lys	Asp	Ile 165	Asn	Val	Lys	Trp	Lys 170	Ile	Asp	Gly	Ser	Glu 175	Arg
	Gln	Asn	Gly	Val 180	Leu	Asn	Ser	Trp	Thr 185	Asp	Gln	Asp	Ser	Lys 190	Asp	Ser
	Thr	Tyr	Ser 195	Met	Ser	Ser	Thr	Leu 200	Thr	Leu	Thr	Lys	Asp 205	Glu	Tyr	Glu
45	Arg	His 210	Asn	Ser	Tyr	Thr	Cys 215	Glu	Ala	Thr	His	Lys 220	Thr	Ser	Thr	Ser
	Pro 225	Ile	Val	Lys	Ser	Phe 230	Asn	Arg	Asn	Glu	Cys 235					

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45

<210> 34

<211> 708

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<212> DNA

<213> Mus musculus

<400> 34

EP 2 251 351 B1

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	gtcaccctaa	tctgcagtgc	cagttcaagt	gtaagtttcg	tggactgggt	ccagcagaag	180
	ccaggcactt	ctcccaaacy	ctggatttac	agaacatcca	acctggggtt	tggagtccct	240
5	gctcgcttca	gtggcggttg	atctgggacc	tctcactctc	tcacaatcag	ccgaatggag	300
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	gctgggacca	agctggaact	gaaacgggct	gatgctgcac	caactgtatc	catcttccca	420
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	taccccaaag	acatcaatgt	caagtgggaag	attgatggca	gtgaacgaca	aaatggcgtc	540
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10	acgttgacca	aggacgagta	tgaacgacat	aacagctata	cctgtgaggg	cactcacaag	660
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<210> 35

<211> 449

<212> PRT

15 <213> Mus musculus

<400> 35

20 Gln val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln

25

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35

40

45

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55

EP 2 251 351 B1

1 Thr Leu Ser Leu 5 Thr Cys Ser Phe 10 Gly Phe Ser Leu 15 Thr Ser
 Gly Met Gly 20 Val Gly Trp Ile Arg 25 His Pro Ser Gly Lys 30 Asn Leu Glu
 5 Trp Leu Ala 35 His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Val
 50 Leu Lys Ser Arg Leu Thr 55 Ile Ser Lys Asp Thr Ser Asn Ser Gln Val
 65 Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
 10 Cys Ala Arg Ile 85 Glu Asp Phe Asp Tyr Asp Glu Glu Tyr Tyr Ala Met
 100 Asp Tyr Trp 115 Gly Gln Gly Thr Ser Val Ile Val Ser Ser Ala Lys Thr
 130 Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
 15 Asn Ser Met Val Thr Leu 135 Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
 145 Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
 165 Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
 180 Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
 195 Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
 210 Arg Asp Cys Gly Cys Lys 215 Pro Cys Ile Cys Thr Val Pro Glu Val Ser
 225 Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
 245 Leu Thr Pro Lys Val Thr Cys Val Val Asp Ile Ser Lys Asp Asp
 260 Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
 275 Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
 290 Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
 305 Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
 325 Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
 340 Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
 355 Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
 370 Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
 385 Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys
 405 Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
 420 Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
 435 Lys 440 445

<210> 36

<211> 1350

<212> DNA

<213> Mus musculus

<400> 36

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EP 2 251 351 B1

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EP 2 251 351 B1

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 20 Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
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 115 Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Ile Val Ser Ser
 130 Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
 145 Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
 160 Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
 180 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
 195 Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
 210 Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
 225 Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
 240 Glu Val Ser Ser Val Phe Ile Phe Pro Lys Pro Lys Asp Val Leu
 260 Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
 275 Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
 290 Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
 305 Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
 325 330 335
 340 Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
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 360 Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
 370 Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
 385 Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
 400 Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
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EP 2 251 351 B1

<400> 38

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EP 2 251 351 B1

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EP 2 251 351 B1

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	<213> Rabbit-Mouse Chimera	
	<400> 51	
40	Ser Tyr Trp Met Asn	1 5
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45	<211> 16	
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55	<211> 4	
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EP 2 251 351 B1

<400> 53

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<211> 13

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<213> Rabbit-Mouse chimera

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<213> Rabbit-Mouse chimera

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Asp Ala Ser Asp Leu Ala Ser
1 5

25

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<211> 10

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<213> Rabbit-Mouse chimera

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<400> 56

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<211> 7

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<213> Mus musculus

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<400> 57

Thr Ser Gly Met Gly Val Gly
1 5

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<212> PRT

<213> Mus musculus

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His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Val Leu Lys Ser
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EP 2 251 351 B1

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<400> 59

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<210> 60

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<400> 60

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1 5 10

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<400> 61

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Arg Thr Ser Asn Leu Gly Phe
1 5

30 <210> 62

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<212> PRT

<213> Mus musculus

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Gln Gln Arg Ser Thr Tyr Pro Pro Thr
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<212> PRT

<213> Homo sapiens

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Trp Arg Pro Ser
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55 <213> Homo sapiens

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EP 2 251 351 B1

Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp
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 Arg Pro Ser Gly
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Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg
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 Pro Ser Gly Pro
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Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro
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Ser Gly Pro Asp
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 <213> Homo sapiens

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 Gly Pro Asp Phe
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Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser Gly
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 Pro Asp Phe Arg
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EP 2 251 351 B1

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<213> Homo sapiens

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Leu Val Ala Ser Cys Lys Cys
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<211> 8

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<213> Homo sapiens

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Cys Arg Glu Leu His Phe Thr Arg
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<210> 73

<211> 7

<212> PRT

<213> Homo sapiens

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<400> 73

Cys Ile Pro Asp Arg Tyr Arg
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<211> 399

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<213> Artificial sequence

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EP 2 251 351 B1

<220>

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    gtgactatta cctgtcaatc tagtcagagc gtgtatgata acaattggct ggcgtggtac 180
    cagcaaaaac cgggcaaagc cccgaagctg ctcatctatg acgcgtccga tctggctagc 240
10  ggtgtgccaa gccgtttcag tggcagtggc agcgggtactg actttaccct cacaatttcg 300
    tctctccagc cggaagattt cgccacttac tattgtcaag gtgcttacia cgatgtgatt 360
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<213> Artificial sequence

<220>

20 <223> Humanized antibody sequence

<400> 75

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

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40 <210> 76
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<212> DNA

<213> Artificial sequence

45 <220>

<223> Humanized antibody sequence

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gggaaggggc tggagtgggt gggcaccatt gattccggag gccgtacaga ctacgcgtct 240
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<213> Artificial Sequence

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20      25      30
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu
35      40      45
Ser Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50      55      60
Glu Trp Val Gly Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser
65      70      75      80
Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
85      90      95
Met Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Arg Tyr
100      105      110
Tyr Cys Ala Arg Asn Trp Asn Leu Trp Gly Gln Gly Thr Leu Val Thr
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Val Ser Ser
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<211> 11

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<400> 78

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Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1      5      10

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<210> 79

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Tyr Thr Ser Arg Leu Leu Ser
1      5

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EP 2 251 351 B1

<213> Mus musculus

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Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

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<211> 11

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1 5 10

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Leu Arg Glu Tyr Pro Glu Pro Pro
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<213> Rattus norvegicus

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Thr Glu Ile Ile Pro Gly Leu Arg Glu Tyr Pro Glu Pro Pro Gln Glu
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Leu Glu Asn Asn
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<210> 84

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EP 2 251 351 B1

<213> Rattus norvegicus

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EP 2 251 351 B1

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Arg Ala Gln Arg Val Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg
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Ser Arg Lys Val
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<210> 93

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<213> Rattus norvegicus

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EP 2 251 351 B1

<213> Rattus norvegicus

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 Ala Glu Leu Glu Asn Ala Tyr
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 Phe Arg

20 <210> 97
 <211> 22
 <212> PRT
 <213> Rattus norvegicus

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 Lys Trp Trp Arg Pro Asn Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg
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30 Tyr Arg Ala Gln Arg Val
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 <210> 98
 <211> 213
35 <212> PRT
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<400> 98

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45

50

55

EP 2 251 351 B1

Ala 1nr Glu 35 Ile Ile Pro Gly 40 Leu Arg Glu Tyr Pro 45 Glu Pro Pro Gln
 Glu 50 Leu Glu Asn Asn Gln Thr 55 Met Asn Arg Ala 60 Glu Asn Gly Gly Arg
 5 Pro Pro His His Pro Tyr 70 Asp Thr Lys Asp Val 75 Ser Glu Tyr Ser Cys
 65 Arg Glu Leu His Tyr 85 Thr Arg Phe Val Thr 90 Asp Gly Pro Cys Arg Ser
 Ala Lys Pro Val 100 Thr Glu Leu Val Cys 105 Ser Gly Gln Cys Gly 95 Pro Ala
 10 Arg Leu Leu 115 Pro Asn Ala Ile Gly 120 Arg Val Lys Trp Trp 125 Arg Pro Asn
 Gly Pro Asp Phe Arg Cys Ile 135 Pro Asp Arg Tyr Arg 140 Ala Gln Arg Val
 Gln 145 Leu Leu Cys Pro Gly 150 Gly Ala Ala Pro Arg 155 Ser Arg Lys Val Arg
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 <213> Mus musculus

EP 2 251 351 B1

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1 5

5

<210> 103

<211> 9

<212> PRT

<213> Mus musculus

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<400> 103

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

15

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<212> PRT

<213> Mus musculus

20

<400> 104

Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

25

<210> 105

<211> 7

<212> PRT

<213> Mus musculus

30

<400> 105

Tyr Thr Ser Arg Leu Leu Ser
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<400> 107

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<211> 7

EP 2 251 351 B1

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EP 2 251 351 B1

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<400> 116

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<400> 117

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EP 2 251 351 B1

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 20 25 30
 His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Ile Tyr
 35 40 45
 Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
 50 55 60
 Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Thr Arg Val Glu Ala Glu
 65 70 75 80
 10 Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
 85 90 95
 Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
 100 105 110
 Thr Val Ser Ile Phe Pro Pro Ser Glu Gln Leu Thr Ser Gly Gly
 115 120 125
 15 Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
 130 135 140
 Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
 145 150 155 160
 Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
 165 170 175
 20 Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
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 Asn Arg Asn Glu Cys
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<210> 118
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 <212> DNA
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<400> 118

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<400> 119

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 Leu Ser Thr Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
 35 40 45

EP 2 251 351 B1

Ser Ser Val Tyr Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Ser Ser
 50 55 60
 Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro
 65 70 75 80
 Val Arg Phe Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
 85 90 95
 Thr Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
 100 105 110
 Ser Ser Asp Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
 115 120 125
 Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
 130 135 140
 Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
 145 150 155 160
 Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
 165 170 175
 Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
 180 185 190
 Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
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<210> 120

<211> 708

<212> DNA

<213> Mus musculus

<400> 120

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<211> 445

<212> PRT

<213> Mus musculus

<400> 121

EP 2 251 351 B1

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 Gly Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala Pro Lys Phe
 Gln Asp Lys Ala Ile Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
 10 65 Leu Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
 Glu Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Phe Phe Pro Tyr Trp Gly
 Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser
 15 Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
 130 Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
 145 Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
 20 Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
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 25 Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
 Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
 Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
 30 Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
 Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
 Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
 35 Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
 Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
 40 Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
 Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
 Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
 45 Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
 Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
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50 <210> 122
 <211> 1338
 <212> DNA
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55 <400> 122

EP 2 251 351 B1

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	cctgaacagg	gcctggagtg	gattggaagg	cttgatcctg	aggatgggtga	aagtgattat	180
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	cttcagctca	gaagcctgac	atctgaggac	actgccatct	attattgtga	gagagaggac	300
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25 <211> 464

<212> PRT

<213> Mus musculus

<400> 123

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EP 2 251 351 B1

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	Val	Asn	Ser	Glu	Val	Gln	Val	Gln	Gln	Ser	Gly	Pro	Glu	Leu	Val	Lys
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	Pro	Gly	Ala	Ser	Val	Lys	Leu	Ser	Cys	Thr	Ala	Ser	Gly	Phe	Asn	Ile
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	Lys	Asp	Tyr	Phe	Ile	His	Trp	Val	Lys	Gln	Arg	Pro	Glu	Gln	Gly	Leu
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	Glu	Trp	Ile	Gly	Arg	Leu	Asp	Pro	Glu	Asp	Gly	Glu	Ser	Asp	Tyr	Ala
10	65					70				75						80
	Pro	Lys	Phe	Gln	Asp	Lys	Ala	Ile	Met	Thr	Ala	Asp	Thr	Ser	Ser	Asn
				85						90					95	
	Thr	Ala	Tyr	Leu	Gln	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Thr	Ala	Ile
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	Tyr	Tyr	Cys	Glu	Arg	Glu	Asp	Tyr	Asp	Gly	Thr	Tyr	Thr	Phe	Phe	Pro
			115					120					125			
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	130						135					140				
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	145					150					155					160
	Ser	Met	Val	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro	Glu	Pro
				165						170					175	
20	Val	Thr	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val	His	Thr
				180					185					190		
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			195					200					205			
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		210					215					220				
25	Ala	His	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Val	Pro	Arg
	225					230					235					240
	Asp	Cys	Gly	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Val	Pro	Glu	Val	Ser	Ser
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	Val	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile	Thr	Leu
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30	Thr	Pro	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp	Asp	Pro
			275					280					285			
	Glu	Val	Gln	Phe	Ser	Trp	Phe	Val	Asp	Asp	Val	Glu	Val	His	Thr	Ala
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	Ser	Glu	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Phe
				325						330					335	
	Lys	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	Lys	Thr
				340					345					350		
	Ile	Ser	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	Thr	Ile
			355					360					365			
40	Pro	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr	Cys
		370					375					380				
	Met	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln	Trp
	385					390					395					400
	Asn	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	Met	Asp
45				405						410					415	
	Thr	Asp	Gly	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys	Ser
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	Asn	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu	Gly
		435						440					445			
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<211> 1395

<212> DNA

55 <213> Mus musculus

<400> 124

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<212> PRT

<213> Mus musculus

<400> 125

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 Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
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 145 150 155 160
 Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met
 165 170 175
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<211> 648

<212> DNA

EP 2 251 351 B1

<213> Mus musculus

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<212> PRT

<213> Mus musculus

<400> 127

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      35      40      45
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      50      55      60
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      65      70      75      80
      Val Pro Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
      85      90      95
      Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
      100      105      110
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      Leu Arg Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
      130      135      140
      Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
      145      150      155      160
40     Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
      165      170      175
      Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
      180      185      190
      Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
      195      200      205
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<212> DNA

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EP 2 251 351 B1

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 aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat 540
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15 <210> 129
 <211> 449
 <212> PRT
 <213> Mus musculus

20 <400> 129

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EP 2 251 351 B1

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	Leu	Val	Lys	Leu	Ser	Cys	Thr	Ala	Ser	Asp	Phe	Asn	Ile	Lys	Asp	Phe
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5	Tyr	Leu	His	Trp	Met	Arg	Gln	Arg	Pro	Glu	Gln	Gly	Leu	Asp	Trp	Ile
			35					40					45			
	Gly	Arg	Ile	Asp	Pro	Glu	Asn	Gly	Asp	Thr	Leu	Tyr	Asp	Pro	Lys	Phe
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	Gln	Asp	Lys	Ala	Thr	Leu	Thr	Thr	Asp	Thr	Ser	Ser	Asn	Thr	Ala	Tyr
	65					70					75					80
10	Leu	Gln	Leu	Ser	Gly	Leu	Thr	Ser	Glu	Thr	Ala	Val	Tyr	Tyr	Cys	
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			115					120					125			
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20	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Asp	Leu	Tyr	Thr	Leu	Ser	Ser	Ser
				180					185					190		
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	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile	Thr
					245					250					255	
	Leu	Thr	Pro	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp	Asp
				260					265					270		
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35	Phe	Lys	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	Lys
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	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	Thr
				340					345					350		
	Ile	Pro	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr
			355					360					365			
40	Cys	Met	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln
		370					375					380				
	Trp	Asn	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	Met
	385					390					395					400
	Asp	Thr	Asp	Gly	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys
					405					410					415	
45	Ser	Asn	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu
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Lys 435

440

445

<210> 130
 <211> 1350
 55 <212> DNA
 <213> Mus musculus
 <400> 130

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 cctgaacagg gcctggactg gattggaagg attgatcctg agaatggtga tactttatat 180
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<210> 131

<211> 468

<212> PRT

<213> Mus musculus

<400> 131

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

210 215 220
 Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
 225 230 235 240
 Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
 5 Glu Val Ser Ser Val Phe Ile Phe Pro 250 255
 Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
 10 Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
 290 295 300
 Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
 305 310 315 320
 Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
 325 330 335
 Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
 15 Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
 340 345 350
 Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
 355 360 365
 Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
 20 385 390 395 400
 Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
 405 410 415
 Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
 420 425 430
 Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
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<210> 132

<211> 1407

<212> DNA

<213> Mus musculus

<400> 132

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EP 2 251 351 B1

<210> 133
 <211> 214
 <212> PRT
 <213> Mus musculus

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<400> 133

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        Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile
        35      40      45
        Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
        50      55      60
        Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
        65      70      75      80
        Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
        85      90      95
        Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
        100     105     110
        Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115     120     125
        Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
        130     135     140
        Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
        145     150     155     160
        Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
        165     170     175
        Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
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        195     200     205
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<210> 134
 <211> 645
 <212> DNA
 <213> Mus musculus

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<400> 134

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        gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180
        aggttcagtg gcagtgggtc tggaaacagat tattctctca ccatttacaa cctggagcaa 240
        gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300
        gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttccacca 360
        tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
        cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
        aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
        ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
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<210> 135
 <211> 234
 <212> PRT
 <213> Mus musculus

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<400> 135

EP 2 251 351 B1

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 20 25 30
 Ala Ser Leu Gly Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp
 35 40 45
 Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
 50 55 60
 Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser
 65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr
 85 90 95
 Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp
 100 105 110
 Thr Leu Pro Tyr Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Arg
 115 120 125
 Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
 130 135 140
 Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
 145 150 155 160
 Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
 165 170 175
 Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
 180 185 190
 Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
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 His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
 210 215 220
 Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
 225 230

<210> 136
 <211> 705
 <212> DNA
 <213> Mus musculus

<400> 136

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 aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
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 <211> 447
 <212> PRT
 <213> Mus musculus

<400> 137

EP 2 251 351 B1

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				20					25					30		
5	Asn	Met	His	Trp	Val	Lys	Gln	Asn	Gln	Gly	Lys	Thr	Leu	Glu	Trp	Ile
			35					40					45			
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		50					55					60				
	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Thr	Thr	Ala	Tyr
	65					70					75					80
10	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Leu	Gly	Tyr	Asp	Asp	Ile	Tyr	Asp	Asp	Trp	Tyr	Phe	Asp	Val
				100					105					110		
	Trp	Gly	Ala	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Lys	Thr	Thr	Pro
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15	Pro	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala	Ala	Gln	Thr	Asn	Ser
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	Thr	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val	His	Thr	Phe
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					165					170					175	
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				180					185					190		
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			195					200					205			
25	His	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Val	Pro	Arg	Asp
		210					215					220				
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	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile	Thr	Leu	Thr
					245					250					255	
30	Pro	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp	Asp	Pro	Glu
				260					265					270		
	Val	Gln	Phe	Ser	Trp	Phe	Val	Asp	Asp	Val	Glu	Val	His	Thr	Ala	Gln
			275					280					285			
	Thr	Gln	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Ser	Val	Ser
		290					295					300				
35	Glu	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Phe	Lys
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	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
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	Ser	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	Thr	Ile	Pro
				340					345					350		
40	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr	Cys	Met
			355					360					365			
	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln	Trp	Asn
		370					375					380				
	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	Met	Asp	Thr
						390					395					400
45	Asp	Gly	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys	Ser	Asn
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	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu	Gly	Leu
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<211> 1344

<212> DNA

55 <213> Mus musculus

<400> 138

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5	aaccagaagt	tcaagggcaa	ggccacattg	actgtagaca	agtcctccac	cacagcctac	240
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	caaactaact	ccatgggtgac	cctgggatgc	ctgggtcaagg	gctatttccc	tgagccagtg	480
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	cagtctgacc	tctacactct	gagcagctca	gtgactgtcc	cctccagcac	ctggcccagc	600
10	gagaccgtca	cctgcaacgt	tgcccacccg	gccagcagca	ccaaggtgga	caagaaaatt	660
	gtgcccaggg	attgtggttg	taagccttgc	atatgtacag	tcccagaagt	atcatctgtc	720
	ttcatcttcc	ccccaaagcc	caaggatgtg	ctcaccatta	ctctgactcc	taaggtcacg	780
	tgtgttgtgg	tagacatcag	caaggatgat	cccaggtgcc	agttcagctg	gtttgtagat	840
	gatgtggagg	tgcacacagc	tcagacgcaa	ccccgggagg	agcagttcaa	cagcactttc	900
	cgctcagtca	gtgaacttcc	catcatgcac	caggactggc	tcaatggcaa	ggagttcaaa	960
15	tgccaggtca	acagtgcagc	tttccctgcc	cccatcgaga	aaaccatctc	caaaaccaaa	1020
	ggcagaccga	aggctccaca	ggtgtacacc	attccacctc	ccaaggagca	gatggccaag	1080
	gataaagtca	gtctgacctg	catgataaca	gacttcttcc	ctgaagacat	tactgtggag	1140
	tgccagtggg	atgggcagcc	agcggagaa	tacaagaaca	ctcagcccat	catggacaca	1200
	gatggctctt	acttcatcta	cagcaagctc	aatgtgcaga	agagcaactg	ggaggcagga	1260
	aatactttca	cctgctctgt	gttacatgag	ggcctgcaca	accaccatac	tgagaagagc	1320
20	ctctcccact	ctcctggtaa	atga				1344

<210> 139

<211> 466

<212> PRT

25 <213> Mus musculus

<400> 139

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EP 2 251 351 B1

	Met	Gly	Trp	Ser	Trp	Thr	Phe	Leu	Phe	Leu	Leu	Ser	Gly	Thr	Ala	Gly
	1				5					10					15	
	Val	Leu	Ser	Glu	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Leu	Met	Lys
5				20				25						30		
	Pro	Gly	Ala	Ser	Val	Lys	Met	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe
			35					40					45			
	Thr	Asp	Tyr	Asn	Met	His	Trp	Val	Lys	Gln	Asn	Gln	Gly	Lys	Thr	Leu
		50					55					60				
	Glu	Trp	Ile	Gly	Glu	Ile	Asn	Pro	Asn	Ser	Gly	Gly	Ala	Gly	Tyr	Asn
10						70					75					80
	Gln	Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Thr
					85					90					95	
	Thr	Ala	Tyr	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val
				100					105					110		
	Tyr	Tyr	Cys	Ala	Arg	Leu	Gly	Tyr	Asp	Asp	Ile	Tyr	Asp	Asp	Trp	Tyr
			115					120					125			
15	Phe	Asp	Val	Trp	Gly	Ala	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Lys
		130					135					140				
	Thr	Thr	Pro	Pro	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala	Ala	Gln
					150					155						160
	Thr	Asn	Ser	Met	Val	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro
					165					170					175	
20	Glu	Pro	Val	Thr	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val
				180					185					190		
	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Asp	Leu	Tyr	Thr	Leu	Ser	Ser
			195					200					205			
	Ser	Val	Thr	Val	Pro	Ser	Ser	Thr	Trp	Pro	Ser	Glu	Thr	Val	Thr	Cys
		210					215					220				
25	Asn	Val	Ala	His	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Val
		225				230					235				240	
	Pro	Arg	Asp	Cys	Gly	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Val	Pro	Glu	Val
				245						250					255	
	Ser	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile
				260					265					270		
30	Thr	Leu	Thr	Pro	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp
			275					280					285			
	Asp	Pro	Glu	Val	Gln	Phe	Ser	Trp	Phe	Val	Asp	Asp	Val	Glu	Val	His
		290					295					300				
	Thr	Ala	Gln	Thr	Gln	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg
					310						315					320
35	Ser	Val	Ser	Glu	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
					325					330					335	
	Glu	Phe	Lys	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu
				340					345					350		
	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr
			355					360					365			
40	Thr	Ile	Pro	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu
		370					375					380				
	Thr	Cys	Met	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp
					390						395				400	
	Gln	Trp	Asn	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile
					405					410				415		
45	Met	Asp	Thr	Asp	Gly	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln
				420					425					430		
	Lys	Ser	Asn	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His
			435					440					445			
	Glu	Gly	Leu	His	Asn	His	His	Thr	Glu	Lys	Ser	Leu	Ser	His	Ser	Pro
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50	Gly	Lys														
	465															

<210> 140

<211> 1401

55 <212> DNA

<213> Mus musculus

<400> 140

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 gtccaactgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
 tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa 180
 ggaagaccc tagagtggat aggagaaatt aatcctaaca gtgggtgggtc tggctacaac 240
 5 cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
 gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
 gatgatattc acgacgactg gtacttcgat gtctggggcg caggggaccac ggtcaccgtc 420
 tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccac 480
 actaactcca tggtgaccct gggatgcctg gtcaagggtt atttccctga gccagtgaac 540
 gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgcctgcag 600
 10 tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gccagcgag 660
 accgtcacct gcaacgttgc ccacccggcc agcagacca aggtggacaa gaaaattgtg 720
 cccagggtt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
 atcttccccc caaagcccaa ggatgtgtc accattactc tgactcctaa ggtcacgtgt 840
 gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctgggtt tgtagatgat 900
 gtggaggtgc acacagctca gacgcaacc cgggaggagc agttcaacag cactttccgc 960
 tcagtcaagt aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
 15 aggggtcaaca gtgcagcttt ccctgcccc atcgagaaaa ccatctccaa aaccaaaggc 1080
 agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
 aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
 cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
 ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
 20 actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
 tcccactctc ctggtaaaatg a 1401

<210> 141

<211> 214

<212> PRT

25 <213> Artificial sequence

<220>

<223> Humanized antibody sequence

30 <400> 141

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

<210> 142

<211> 642

EP 2 251 351 B1

<212> DNA

<213> Artificial Sequence

<220>

5 <223> Humanized antibody sequence

<400> 142

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10  gacatccaga tgacccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc 60
    ataacatgta gagcatctca agatatttcc aactatttga attggtacca acaaaaaccc 120
    ggcaaagcac ctaaactcct catttactat acatcaagac tcctctccgg cgttccatca 180
    cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca 240
    gaagattttg caaccctatta ctgtcaacaa ggcgatacac tcccatacac attcggcggc 300
    ggcacaaaag ttgaaattaa acgtacggtg gctgcacat ctgtcttcat cttcccgcga 360
15  tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
    cccagagagg ccaaagtaca gtggaagggt gataacgccc tccaatcggg taactcccag 480
    gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
    ctgagcaaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
    ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

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20 <210> 143

<211> 236

<212> PRT

<213> Artificial Sequence

25 <220>

<223> Humanized antibody sequence

<400> 143

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

```

<210> 144

<211> 708

EP 2 251 351 B1

<212> DNA

<213> Artificial sequence

<220>

5 <223> Humanized antibody sequence

<400> 144

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10      atggacatga ggggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc 60
      agatgtgaca tccagatgac ccagtctcca tcctccctct ccgcatccgt aggcgaccgc 120
      gtaaccataa catgtagagc atctcaagat atttccaact atttgaattg gtaccaacaa 180
      aaacccggca aagcacctaa actcctcatt tactatacat caagactcct ctccggcggt 240
      ccatcacgat tctcaggctc cggctccggc acagatttca cactcactat ttcctccctc 300
      caaccagaag attttgcaac ctattactgt caacaaggcg atacactccc atacacattc 360
15      ggcggcgga caaaagttga aattaaacgt acggtggctg caccatctgt cttcatcttc 420
      ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480
      ttctatccca gagaggccaa agtacagtgg aagggtggata acgccctcca atcgggtaac 540
      tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600
      ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660
      cagggcctga gctcgcccgt cacaagagc ttcaacaggg gagagtgt 708

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20

<210> 145

<211> 449

<212> PRT

<213> Artificial sequence

25

<220>

<223> Humanized antibody sequence

<400> 145

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35

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45

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EP 2 251 351 B1

	Glu	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	Asp	Tyr
5				20					25					30		
	Asn	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Glu	Ile	Asn	Pro	Asn	Ser	Gly	Gly	Ala	Gly	Tyr	Asn	Gln	Lys	Phe
		50					55					60				
	Lys	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
	65					70					75				80	
10	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Leu	Gly	Tyr	Asp	Asp	Ile	Tyr	Asp	Asp	Trp	Tyr	Phe	Asp	Val
				100					105					110		
	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly
			115					120					125			
15	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser
		130					135					140				
	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val
	145					150					155				160	
	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe
					165					170				175		
20	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val
				180					185					190		
	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val
			195					200					205			
	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys
		210					215					220				
25	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro
	225					230					235				240	
	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
					245					250				255		
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
				260					265					270		
30	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
			275					280					285			
	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val
		290					295					300				
	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305					310					315				320	
35	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys
					325					330					335	
40	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
			355					360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu
	385					390					395				400	
45	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
					405					410					415	
	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420					425					430		
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
			435					440					445			
50	Lys															

<210> 146

<211> 1347

55 <212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 146

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      ccaggacaag  gattggaatg  gatgggcgaa  attaacccta  atagtggagg  agcaggctac  180
      aatcaaaaat  tcaaagggag  agttacaatg  acaacagaca  caagcacttc  aacagcatat  240
      atggaactgc  gatcacttag  aagcgacgat  acagctgtat  actattgcgc  acgacttggg  300
10     tatgatgata  tatatgatga  ctggtatttc  gatgtttggg  gccaggggaa  aacagttacc  360
      gtctctagtg  cctccacca  gggcccatcg  gtcttcccc  tggcgccctg  ctccaggagc  420
      acctccgaga  gcacagcggc  cctgggctgc  ctggtcaagg  actacttccc  cgaaccgggtg  480
      acgggtgtcgt  ggaactcagg  cgctctgacc  agcggcgtgc  acaccttccc  agctgtccta  540
      cagtcctcag  gactctactc  cctcagcagc  gtggtgaccg  tgccctccag  caacttcggc  600
      acccagacct  acacctgcaa  cgtagatcac  aagcccgaca  acaccaaggt  ggacaagaca  660
15     gttgagcgca  aatgttgtgt  cgagtgccca  ccgtgccag  caccacctgt  ggcaggaccg  720
      tcagtcttcc  tcttcccccc  aaaacccaag  gacaccctca  tgatctcccg  gacccttgag  780
      gtcacgtgcg  tgggtggtgga  cgtgagccac  gaagaccccg  aggtccagtt  caactggtac  840
      gtggacggcg  tggaggtgca  taatgccaa  acaaagccac  gggaggagca  gttcaacagc  900
      acgttccgtg  tggtcagcgt  cctcacggt  gtgcaccagg  actggctgaa  cggcaaggag  960
      tacaagtgca  aggtctccaa  caaaggcctc  ccagcccca  tcgagaaaac  catctccaaa  1020
20     accaaagggc  agccccgaga  accacaggtg  tacaccctgc  ccccatcccg  ggaggagatg  1080
      accaagaacc  aggtcagcct  gacctgcctg  gtcaaaggct  tctacccag  cgacatcgcc  1140
      gtggagtggg  agagcaatgg  gcagccggag  aacaactaca  agaccacacc  tcccatgctg  1200
      gactccgacg  gctccttctt  cctctacagc  aagctcaccg  tggacaagag  cagggtggcag  1260
      caggggaacg  tcttctcatg  ctccgtgatg  catgaggctc  tgcacaacca  ctacacgcag  1320
      aagagcctct  ccctgtctcc  gggtaaa  1347

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<210> 147

<211> 468

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 147

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

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[illegible]

45

<210>	148
<211>	1404
<212>	DNA
<213>	Mus musculus

50 <400> 148

55

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tgtaaagcaa	gcgatatac	atttacagat	tacaacatgc	attgggtaag	acaagcgcca	180
ggacaaggat	tggaatggat	gggcgaaatt	aaccctaata	gtggaggagc	aggctacaat	240
caaaaattca	aaggggagagt	tacaatgaca	acagacacaa	gcacttcaac	agcatatatg	300
gaactgcgat	cacttagaag	cgacgatac	gctgtatact	attgcgcacg	acttgggtat	360
gatgatatat	atgatgactg	gtatttcgat	gtttggggcc	agggaaacaac	agttaccgtc	420
tctaagtgcct	ccaccaaggg	cccatcggtc	ttccccctgg	cgccctgctc	caggagcacc	480

EP 2 251 351 B1

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tccgagagca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540
gtgtcgtgga actcaggcgc tctgaccagc ggcgtgcaca ccttcccagc tgtcctacag 600
tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcaa cttcggcacc 660
cagacctaca cctgcaacgt agatcacaag cccagcaaca ccaaggtgga caagacagtt 720
gagcgcaaat gttgtgtcga gtgcccaccg tgcccagcac cacctgtggc aggaccgtca 780
gtcttctctt tcccccaaa acccaaggac accctcatga tctcccgac ccctgaggtc 840
acgtgcgtgg tgggtggacgt gagccacgaa gaccccgagg tccagttcaa ctggtacgtg 900
gacggcgtgg aggtgcataa tgccaagaca aagccacggg aggagcagtt caacagcacg 960
ttccgtgtgg tcagcgtcct caccgttgtg caccaggact ggctgaacgg caaggagtac 1020
aagtgaagg tctccaacaa aggcctccca gccccatcg agaaaacat ctccaaaacc 1080
aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc 1140
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gagtgggaga gcaatgggca gccggagaac aactacaaga ccacacctcc catgctggac 1260
tccgacggct ccttcttctt ctacagcaag ctcaccgtgg acaagagcag gtggcagcag 1320
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<210> 149

<211> 214

<212> PRT

<213> Mus musculus

<400> 149

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

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<210> 150

<211> 645

<212> DNA

<213> Mus musculus

<400> 150

EP 2 251 351 B1

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 gatggaactc ttaaaactcct gatcttctac acatcaagat tacactcagg agttccatca 180
 aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 240
 gaagatatatt ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcgggggg 300
 gggaccaagc tggaaataag acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
 tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
 aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gtttag 645

<210> 151
 <211> 234
 <212> PRT
 <213> Mus musculus

<400> 151

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

<210> 152
 <211> 705
 <212> DNA
 <213> Mus musculus

<400> 152

EP 2 251 351 B1

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	atcagttgca	gggcaagtca	ggacattagc	aattatttaa	actggtttca	gcagaaacca	180
5	gatggaactc	ttaaactcct	gatcttctac	acatcaagat	tacactcagg	agttccatca	240
	aggttcagtg	gcagtgggtc	tggaacagat	tattctctca	ccattagcaa	cctggagcaa	300
	gaagatattg	ccacttactt	ttgccaacag	ggtgatacgc	ttccgtacac	gttcggggggg	360
	gggaccaagc	tggaataaag	acgggctgat	gctgcaccaa	ctgtatccat	cttccacca	420
	tccagtgagc	agttaacatc	tggaggtgcc	tcagtcgtgt	gcttcttgaa	caacttctac	480
	cccaaagaca	tcaatgtcaa	gtggaagatt	gatggcagtg	aacgacaaaa	tggcgtcctg	540
10	aacagttgga	ctgatcagga	cagcaaagac	agcacctaca	gcatgagcag	caccctcacg	600
	ttgaccaagg	acgagtatga	acgacataac	agctatacct	gtgaggccac	tcacaagaca	660
	tcaacttcac	ccattgtcaa	gagcttcaac	aggaatgagt	gttag		705

<210> 153

<211> 447

15 <212> PRT

<213> Mus musculus

<400> 153

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	1				5					10					15	

25

30

35

40

45

50

55

EP 2 251 351 B1

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

<210> 154
 <211> 1344
 <212> DNA
 <213> Mus musculus

<400> 154

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 tcctgcaagg ctcttgata cacattcact gactacaaca tgcactgggt gaaacagaac 120
 caaggaaaga gcctagagtg gataggagaa attaataccta acagtgggtg tagtggctac 180
 aaccaaaagt tcaaaggcaa ggccacattg actgtagaca agtcttcag cacagcctac 240
 atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggtc 300
 tacgatggca gctacgagga ctggtacttc gatgtctg99 gcgaggagac cacggctacc 360

EP 2 251 351 B1

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gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
caaaactaact ccatgggtgac cctgggatgc ctgggtcaagg gctattttccc tgagccagtg 480
acagtgcact ggaactctgg atccctgtcc agcgggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taagggtcacg 780
tgtgttggtg tagacatcag caaggatgat cccgaggtcc agttcagctg gttttagat 840
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cgctcagtcg gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
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gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
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gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgtctctg gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctccact ctcctggtaa atga 1344

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<210> 155

<211> 466

<212> PRT

<213> Mus musculus

<400> 155

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Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35
Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Ser Leu
50
Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn
65
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
85
Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
100
Tyr Tyr Cys Ala Arg Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr
115
Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ala Lys
130
Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
165
Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
180
His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
195
Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
210
Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225
Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
245
Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
260
Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
275
Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
290
Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305
Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
325
Glu Phe Lys Cys Arg Val Asn Ser Ala Phe Pro Ala Pro Ile Glu
340
345
350

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Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
 355 360 365
 Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
 370 375 380
 Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
 385 390 395 400
 Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
 405 410 415
 Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
 420 425 430
 Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
 435 440 445
 Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
 450 455 460
 Gly Lys
 465

<210> 156
 <211> 1401
 <212> DNA
 <213> Mus musculus

<400> 156

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 tgcaaggctt ctggatacac attcactgac tacaacatgc actgggtgaa acagaaccaa 180
 ggaaagagcc tagagtggat aggagaaatt aatcctaaca gtggtggtag tggctacaac 240
 caaaagttca aaggcaaggc cacattgact gtagacaagt ctccagcac agcctacatg 300
 gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attggtctac 360
 gatggcagct acgaggactg gtacttcgat gtctggggcg cagggaccac ggtcacgctc 420
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 gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
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 accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
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 gtggagggtc acacagctca gacgcaacct cgggaggagc agttcaacag cactttccgc 960
 tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
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 agaccgaagg ctccacaggt gtacaccatt ccacctcca aggagcagat ggccaaggat 1140
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 cagtggaaat ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
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 tcccactctc ctggtaaatg a
 1401

<210> 157
 <211> 214
 <212> PRT
 <213> Mus musculus

<400> 157

EP 2 251 351 B1

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

15 Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
 100 105 110
 Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
 115 120 125
 Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
 130 135 140
 20 Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
 145 150 155 160
 Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
 165 170 175
 Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
 180 185 190
 Phe Asn Arg Asn Glu Cys 200 205
 25 210

<210> 158
 <211> 642
 <212> DNA
 30 <213> Mus musculus
 <400> 158

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 gatggaactt ttaaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180
 aggttcagtg gcagtggtgc tggaaacagat tattctctca ccattagcaa cctggaacag 240
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 40 tccagtgagc agttaacatc tggagggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaa tggcgctcctg 480
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45 <210> 159
 <211> 234
 <212> PRT
 <213> Mus musculus
 50 <400> 159

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EP 2 251 351 B1

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

210 215 220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230

<210> 160
<211> 702
<212> DNA
<213> Mus musculus

<400> 160

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atctgttgca gggcaagtca gggtcattacc aattatttat actggtatca gcagaaacca 180
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tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 702

<210> 161
<211> 447
<212> PRT
<213> Mus musculus

<400> 161

EP 2 251 351 B1

1 Glu Val Gln Leu 5 Gln Ser Gly Pro 10 Glu Leu Met Lys Pro 15 Gly Ala
 2 Ser Val Lys Met 20 Ser Cys Lys Ala 25 Ser Gly Tyr Thr Phe Thr Asp Tyr
 3 Asn Met His 35 Trp Met Lys Gln Asn 40 Gln Gly Lys Ser 45 Leu Gln Trp Ile
 4 Gly Glu Ile Asn Pro Asn 55 Ser Gly Gly Ala Gly Tyr Asn Gln Gln Phe
 5 Lys 60 Gly Lys Ala Thr 65 Leu Thr Val Asp Lys 70 Ser Ser Arg Thr Ala Tyr
 6 Met Glu Leu Arg 85 Ser 90 Thr Ser Glu Asp 95 Ser Ala Val Tyr Tyr Cys
 7 Ala Arg Leu Gly Tyr Val Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
 8 Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys 110 Thr Thr Pro
 9 Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser
 10 Met 130 Val Thr Leu Gly Cys 135 Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
 11 Thr Val Thr Trp Asn 150 Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
 12 Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
 13 Val Pro Ser 180 Thr Trp Pro Ser Glu Thr Val Thr Cys 190 Asn Val Ala
 14 His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
 15 Cys Gly Cys Lys Pro Cys 230 Ile Cys Thr Val Pro Glu Val Ser Ser Val
 16 Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
 17 Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
 18 Val Gln Phe 260 Ser Trp Phe Val Asp 265 Val Glu Val His Thr Ala Gln
 19 Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
 20 290 295 300
 21
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 <212> DNA
 <213> Mus musculus

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 caaggaaaga gcctagaatg gataggagaa attaataccta acagtgggtg tgctggctac 180
 aaccagcagt tcaaaggcaa ggccacattg actgtagaca agtcctccag gacagcctac 240
 atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
 tacgttggtta attacgagga ctgggtactt gatgtctggg gcgcagggac cacggtcacc 360
 gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
 caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
 acagtgaact ggaactctgg atccctgtcc agcgggtgtg acaccttccc agctgtcctg 540
 cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
 gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaagggtga caagaaaatt 660
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<210> 163

<211> 466

<212> PRT

<213> Mus musculus

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

5 Tnr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
 Tyr Tyr Cys 100 Ala Arg Leu Gly Tyr 105 Val Gly Asn Tyr Glu 110 Asp Trp Tyr
 Phe Asp 115 Val Trp Gly Ala Gly 120 Thr Thr Val Thr Val 125 Ser Ser Ala Lys
 Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
 145 Thr Asn Ser Met Val 150 Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe 160 Pro
 10 Glu Pro Val Thr 165 Val Thr Trp Asn Ser 170 Gly Ser Leu Ser Ser Gly Val
 His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
 Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
 210 Asn Val Ala His Pro Ala 215 Ser Ser Thr Lys Val Asp Lys Lys Ile Val
 225 Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
 Ser Ser Val Phe Ile Phe Pro Pro Lys 235 Pro Lys Asp Val Leu Thr Ile
 260 Thr Leu Thr Pro Lys Val Thr Cys 265 Val Val Val Asp Ile Ser Lys Asp
 Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
 290 Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
 305 Ser Val Ser Glu Leu Pro Ile Met His Gln 315 Asp Trp Leu Asn Gly Lys
 325 Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
 Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
 355 Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
 370 Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
 385 Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
 405 Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
 420 Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
 435 Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
 450 Gly Lys
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<210> 164

<211> 1398

<212> DNA

<213> Mus musculus

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 gagctccgca gcctgacatc tgaggactct gcagctctatt actgtgcaag attgggctac 360
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 gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
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cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
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 gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctgggt tgtagatgat 900
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 <212> PRT
 <213> Mus musculus

<400> 165

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 35 40 45
 Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
 100 105 110
 Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
 115 120 125
 Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
 130 135 140
 Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
 145 150 155 160
 Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
 165 170 175
 Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
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 Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
 195 200 205
 Phe Asn Arg Asn Glu Cys
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<210> 166
 <211> 645
 <212> DNA

EP 2 251 351 B1

<213> Mus musculus

<400> 166

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      gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180
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10     gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttccacca 360
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<210> 167

<211> 234

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<400> 167

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      Ala Ser Leu Gly Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp
      35
      Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
      50
30     Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser
      65
      Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr
      85
      Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp
      100
35     Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
      115
      Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
      130
      Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
      145
40     Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
      165
      Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
      180
      Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
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      Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
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<211> 705

<212> DNA

<213> Mus musculus

<400> 168

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	gatggaactt	ttaaactcct	tatcttctac	acatcaagat	tactctcagg	agtcccatca	240
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<211> 447

<212> PRT

15 <213> Mus musculus

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			20						25					30		
	Asn	Met	His	Trp	Val	Lys	Gln	Asn	Gln	Gly	Lys	Thr	Leu	Asp	Trp	Ile
			35					40					45			

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	Gly	Glu	Ile	Asn	Pro	Asn	Ser	Gly	Gly	Ala	Gly	Tyr	Asn	Gln	Lys	Phe
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15	Pro	Ala	Val	Leu	Gln	Ser	135	Asp	Leu	Tyr	Thr	Leu	Ser	Ser	Ser	Val
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	Pro	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp	175	Asp	Pro
25	Val	Gln	Phe	Ser	Trp	Phe	Val	Asp	180	Asp	Val	Glu	Val	185	Thr	Ala
	Thr	Gln	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	190	Ser	Val
	Glu	Leu	Pro	Ile	Met	His	Gln	Asp	200	Trp	Leu	Asn	Gly	205	Lys	Glu
30	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	210	Lys	Thr
	Ser	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	215	Thr	Ile
	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	220	Thr	Cys
35	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	225	Gln	Trp
	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	230	Met	Asp
	Asp	Gly	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln	235	Lys	Ser
40	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	240	Glu	Gly
	His	Asn	His	His	Thr	Glu	Lys	Ser	Leu	Ser	His	Ser	Pro	245	Gly	Lys
45	<210> 170															
	<211> 1344															
	<212> DNA															
	<213> Mus musculus															
50	<400> 170															
55																

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 aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240
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<210> 171

<211> 466

<212> PRT

<213> Mus musculus

<400> 171

Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1 Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
 5 Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
 Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu
 10 Asp Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
 Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
 Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
 Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
 15 Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
 Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
 Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
 20 Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
 His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
 Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
 25 Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
 Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
 Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
 Thr Leu Thr Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
 30 Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
 Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
 35 Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
 Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
 Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
 40 Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
 Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
 45 Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
 Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
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<210> 17,2

<211> 1401

<212> DNA

<213> Mus musculus

<400> 172

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    tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa 180
    ggaaagaccc tagactggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
    cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
    gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attggggtac 360
    gatgatatct acgacgactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420
    tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgcctgccc 480
10  actaactcca tgggtgaccct gggatgcctg gtcaagggtt atttccctga gccagtgaca 540
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    tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 660
    accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
    cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
15  atcttcccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
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    agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
20  aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
    cagtggaaat ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
    ggctcttact tcattctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
    actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
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25 <210> 173

<211> 214

<212> PRT

<213> Mus musculus

30 <400> 173

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

    130          135          140
50  Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
    145         150         155         160
    Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
    165         170         175
    Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
    180         185         190
55  Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
    195         200         205
    Phe Asn Arg Asn Glu Cys
    210

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EP 2 251 351 B1

<210> 174
 <211> 642
 <212> DNA
 <213> Mus musculus

5

<400> 174

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      atcagttgca gggcaagtca agacattagc aattatttaa attggtatca gcagaaacca 120
      gatggaactt ttaaactcct tatcttctac acatcaagat tattttcagg agtcccatca 180
      aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttaca cctggagcaa 240
      gaagattttg ccacttactt ttgccaaacag ggagatacgc ttccgtacac tttcggaggg 300
      gggaccaagg tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttccacca 360
      tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
      cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
15      aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
      ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
      tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642
    
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<210> 175
 <211> 234
 <212> PRT
 <213> Mus musculus

20

<400> 175

25

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      Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ile Thr Ser Ser Leu Ser
      20      25      30
30      Ala Ser Leu Gly Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp
      35      40      45
      Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
      50      55      60
      Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu Phe Ser Gly Val Pro Ser
      65      70      75      80
35      Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr
      85      90      95
      Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp
      100      105      110
      Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
      115      120      125
40      Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
      130      135      140
      Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
      145      150      155      160
      Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
      165      170      175
45      Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
      180      185      190
      Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
      195      200      205
      His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
      210      215      220
50      Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
      225      230
    
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<210> 176
 <211> 702
 <212> DNA
 <213> Mus musculus

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<400> 176

EP 2 251 351 B1

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	gatatccaga	tgacacagat	tacatcctcc	ctgtctgcct	ctctgggaga	caggggtctcc	120
	atcagttgca	gggcaagtca	agacattagc	aattatttaa	attggtatca	gcagaaacca	180
	gatggaactt	ttaaactcct	tatctttctac	acatcaagat	tattttcagg	agtcccatca	240
5	aggttcagtg	gcagtggggtc	tggaacagat	tattctctca	ccattttacaa	cctggagcaa	300
	gaagattttg	ccacttactt	ttgccaacag	ggagatacgc	ttccgtacac	tttcggaggg	360
	gggaccaagg	tggaataaaa	acgggctgat	gctgcaccaa	ctgtatccat	cttcccacca	420
	tccagtgagc	agttaacatc	tggaagggtgc	tcagtcgtgt	gcttcttgaa	caacttctac	480
	cccaaagaca	tcaatgtcaa	gtggaagatt	gatggcagtg	aacgacaaaa	tggcgtcctg	540
	aacagttgga	ctgatcagga	cagcaaagac	agcacctaca	gcatgagcag	caccctcacg	600
10	ttgaccaagg	acgagtatga	acgacataac	agctatacct	gtgaggccac	tcacaagaca	660
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<210> 177

<211> 450

<212> PRT

15 <213> Mus musculus

<400> 177

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	Ser	Val	Lys	Met	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Tyr
			20						25					30		
	Asn	Met	His	Trp	Val	Lys	Gln	Thr	Gln	Gly	Lys	Thr	Leu	Glu	Trp	Ile
			35					40					45			
	Gly	Glu	Ile	Asn	Pro	Asn	Ser	Gly	Gly	Ala	Gly	Tyr	Asn	Gln	Lys	Phe
25		50				55						60				
	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Thr	Thr	Ala	Tyr
	65					70					75				80	
	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys
				85						90				95		
	Ala	Lys	Leu	Gly	Tyr	Asp	Asp	Ile	Tyr	Asp	Asp	Trp	Tyr	Phe	Asp	Val
			100						105					110		
30	Trp	Gly	Ala	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Lys	Thr	Thr	Ala
			115						120				125			
	Pro	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Val	Cys	Gly	Asp	Thr	Thr	Gly	Ser
		130					135					140				
	Ser	Val	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro	Glu	Pro	Val
35		145				150					155				160	
	Thr	Leu	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Asp	Val	His	Thr	Phe
				165						170				175		
	Pro	Ala	Leu	Leu	Gln	Ser	Gly	Leu	Tyr	Thr	Leu	Ser	Ser	Ser	Val	Thr
			180						185					190		
	Val	Thr	Thr	Trp	Pro	Ser	Gln	Thr	Ile	Thr	Cys	Asn	Val	Ala	His	Pro
			195					200					205			
40	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Glu	Pro	Arg	Gly	Ser	Pro
		210					215					220				
	Thr	His	Lys	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Asn	Leu	Leu	Gly	Gly
		225				230					235				240	
	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys	Ile	Lys	Asp	Val	Leu	Met	Ile
				245						250				255		
45	Ser	Leu	Ser	Pro	Met	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Glu	Asp
			260						265					270		
	Asp	Pro	Asp	Val	His	Val	Ser	Trp	Phe	Val	Asn	Asn	Val	Glu	Val	His
			275					280					285			
	Thr	Ala	Gln	Thr	Gln	Thr	His	Arg	Glu	Asp	Tyr	Asn	Ser	Thr	Ile	Arg
		290					295					300				
50	Val	Val	Ser	Ala	Leu	Pro	Ile	Gln	His	Gln	Asp	Trp	Met	Ser	Gly	Lys
		305				310					315				320	
	Glu	Phe	Lys	Cys	Lys	Val	Asn	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
				325						330				335		

55

Arg Thr Ile Ser Lys Pro Lys Gly Pro Val Arg Ala Pro Gln Val Tyr
 Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
 Thr Cys Met Ile Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp
 Thr Asn Asn Gly Gln Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val
 Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
 Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
 Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
 Gly Lys

<210> 178

<211> 1350

<212> DNA

<213> Mus musculus

<400> 178

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 caaggaaaga ccctagagtg gataggagaa attaatccta acagtgggtg tgctggctac 180
 aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240
 atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aaaattgggc 300
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 gtctcctcag ccaaaacaac agccccatcg gtctatccac tggccccctgt gtgtggagat 420
 acaactggct cctcggtgac tctaggatgc ctgggtcaagg gttatttccc tgagccagtg 480
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 cagtctggcc tctacaccct cagcagctca gtgactgtaa ccacctggcc cagccagacc 600
 atcacctgca atgtggccca cccggcaagc agcaccaaag tggacaagaa aattgagccc 660
 agaggggtccc caacacataa accctgtcct ccatgcccag ctccctaacct cttgggtgga 720
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 atggtcacgt gtgtgggtgt ggatgtgagc gaggatgacc cagatgtcca tgtcagctgg 840
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<210> 179

<211> 469

<212> PRT

<213> Mus musculus

<400> 179

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

Tyr Tyr Cys Ala Lys Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
 115 120 125
 Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
 130 135 140
 20 Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr
 145 150 155 160
 Thr Gly Ser Ser Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
 165 170 175
 Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser Leu Ser Ser Asp Val
 180 185 190
 25 His Thr Phe Pro Ala Leu Leu Gln Ser Gly Leu Tyr Thr Leu Ser Ser
 195 200 205
 Ser Val Thr Val Thr Thr Trp Pro Ser Gln Thr Ile Thr Cys Asn Val
 210 215 220
 Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg
 225 230 235 240
 30 Gly Ser Pro Thr His Lys Pro Cys Pro Pro Cys Pro Ala Pro Asn Leu
 245 250 255
 Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val
 260 265 270
 Leu Met Ile Ser Leu Ser Pro Met Val Thr Cys Val Val Val Asp Val
 275 280 285
 35 Ser Glu Asp Asp Pro Asp Val His Val Ser Trp Phe Val Asn Asn Val
 290 295 300
 Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser
 305 310 315 320
 Thr Ile Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met
 325 330 335
 40 Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Ala Leu Pro Ala
 340 345 350
 Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Pro Val Arg Ala Pro
 355 360 365
 Gln Val Tyr Val Leu Pro Pro Glu Glu Glu Met Thr Lys Lys Gln
 370 375 380
 45 Val Thr Leu Thr Cys Met Ile Thr Asp Phe Met Pro Glu Asp Ile Tyr
 385 390 395 400
 Val Glu Trp Thr Asn Asn Gly Gln Thr Glu Leu Asn Tyr Lys Asn Thr
 405 410 415
 Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
 420 425 430
 50 Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser
 435 440 445
 Val Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser
 450 455 460
 Arg Thr Pro Gly Lys
 465

<210> 180
 <211> 1407
 <212> DNA

EP 2 251 351 B1

<213> Mus musculus

<400> 180

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      tgcaaggcct ctggatatac attcactgac tacaacatgc actgggtgaa gcagacccaa 180
      ggaaagaccc tagagtggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
      cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
10     gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaaa attggggtac 360
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      tcctcagcca aaacaacagc cccatcggtc tatccactgg cccctgtgtg tggagataca 480
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15     acctgcaatg tggccacccc ggcaagcagc accaaagtgg acaagaaaat tgagcccaga 720
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<210> 181

30 <211> 214

<212> PRT

<213> Mus musculus

<400> 181

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EP 2 251 351 B1

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 Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile
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 Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
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 Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
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 Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
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 Pro Thr Val Ser Ile Phe Pro Leu Ser Ser Glu Gln Leu Thr Ser Gly
 115 120 125
 Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
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 Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
 145 150 155 160
 Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
 165 170 175
 Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
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 Phe Asn Arg Asn Glu Cys
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<210> 182
 <211> 645
 <212> DNA
 <213> Mus musculus

<400> 182

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<210> 183
 <211> 234
 <212> PRT
 <213> Mus musculus

<400> 183

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 35 40 45
 Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
 50 55 60
 Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser
 65 70 75 80
 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr
 85 90 95
 Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp
 100 105 110
 Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
 115 120 125
 Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Leu Ser Ser Glu Gln
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 145 150 155 160
 Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
 165 170 175
 Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
 180 185 190
 Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
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<210> 184

<211> 705

<212> DNA

<213> Mus musculus

<400> 184

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<210> 185

<211> 447

<212> PRT

<213> Mus musculus

<400> 185

EP 2 251 351 B1

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10	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Thr	Thr	Ala	Tyr
	65					70					75					80
	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys
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	Thr	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val	His	Thr	Phe
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		210					215					220				
	Cys	Gly	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Val	Pro	Glu	Val	Ser	Ser	Val
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	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile	Thr	Leu	Thr
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	Glu	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Phe	Lys
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	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
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	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr	Cys	Met
			355					360					365			
	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln	Trp	Asn
						375						380				
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	Asp	Gly	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys	Ser	Asn
					405					410					415	
	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu	Gly	Leu
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<210> 186

<211> 1344

<212> DNA

55 <213> Mus musculus

<400> 186

EP 2 251 351 B1

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caaggaaaga ccctagaatg gataggagaa attaataccta acagtgggtg tgctggctac 180
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caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
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<210> 187
<211> 466
<212> PRT
<213> Mus musculus

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<400> 187

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	Thr	Asp	Tyr	Asn	Met	His	Trp	Val	Lys	Gln	Asn	Gln	Gly	Lys	Thr	Leu
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	Glu	Trp	Ile	Gly	Glu	Ile	Asn	Pro	Asn	Ser	Gly	Gly	Ala	Gly	Tyr	Asn
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	Gln	Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Thr
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	Thr	Ala	Tyr	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val
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			195					200					205			
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	Glu	Phe	Lys	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu
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<210> 188

<211> 1401

<212> DNA

<213> Mus musculus

<400> 188

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<210> 189

25 <211> 213

<212> PRT

<213> Mus musculus

30 <400> 189

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    35      40      45
    Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Gly Arg Phe Ser Gly Ser
    50      55      60
    Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
    65      70      75      80
40  Asp Ala Ala Thr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
    85      90      95
    Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
    100      105      110
    Thr Val Ser Ile Phe Pro Pro Ser Glu Gln Leu Thr Ser Gly Gly
    115      120      125
45  Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
    130      135      140
    Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn

145      150      155      160
    Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
    165      170      175
50  Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
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<210> 190

<211> 642

EP 2 251 351 B1

<212> DNA
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      tcctcccccga gatcctggat ttatgccaca tccaacctgg cttctggagt ccctgggtcgc 180
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      accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 360
      agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
      aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480
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<210> 191
<211> 235
<212> PRT
20 <213> Mus musculus

<400> 191

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

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<210> 192
<211> 708
<212> DNA
55 <213> Mus musculus

<400> 192

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agaggacaaa ttgttctctc ccagctctcca gcattcctgt ctgtatctcc aggggataag 120
gtcacaatga ctgtcagggc cagctcaagt ataagttaca tacactgggt tcagcagaag 180
ccaggatcct cccccagatc ctggatttat gccacatcca acctggcttc tggagtcctt 240
5 ggtcgcttca gtggcagtggt gtctgggacc tcttactctc tcacaatcag cagagtggag 300
gctgaggatg ctgccactta ttactgccag cagtggagta gtgaccact cacgttcggt 360
gctgggacca agctggagct gaaacgggct gatgctgcac caactgtatc catcttccca 420
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 480
taccctaaag acatcaatgt caagtggaaag attgatggca gtgaacgaca aaatggcgtc 540
10 ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccttc 600
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660
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<210> 193

<211> 445

<212> PRT

<213> Mus musculus

<400> 193

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Glu Val Gln Leu Gln Gln Ser Gly Ala Asp Leu Val Gln Pro Gly Ala
1      5      10
Ser Val Lys Val Ser Cys Thr Ala Ser Gly Phe Asp Ile Lys Asp Tyr
20
Tyr Ile His Trp Met Lys Gln Arg Pro Asp Gln Gly Leu Glu Trp Ile
35
25 Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
50
Pro Gly Lys Ala Thr Phe Thr Thr Asp Thr Ser Asn Thr Ala Tyr
65
Leu Gln Leu Arg Gly Leu Thr Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85
30 Gly Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
100
Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser
115
Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
130
35 Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
145
Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
165
40 Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
180
Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
195
Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
210
45 Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
225
Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
245
Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
260
Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
275
50 Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
290
Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
305
Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
325
55 Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
340
345

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Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
 355 360 365
 Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
 370 375 380
 Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
 385 390 395 400
 Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
 405 410 415
 Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
 420 425 430
 His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
 435 440 445

<210> 194

<211> 1338

<212> DNA

<213> Mus musculus

<400> 194

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 tcctgcacag cttctggctt cgacattaag gactactata tacactggat gaaacagagg 120
 cctgaccagg gcctggagtg gattggaagg gttgatcctg acaatgggtga gactgaattt 180
 gccccgaagt tcccgggcaa ggccactttt acaacagaca catcctccaa cacagcctac 240
 ctacaactca gaggcctgac atctgaggac actgccatct attactgtgg gagagaagac 300
 tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt cactgtctct 360
 gcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaact 420
 aactccatgg tgaccctggg atgcctggtc aagggtatt tccctgagcc agtgacagtg 480
 acctggaact ctggatccct gtccagcggg gtgcacacct tcccagctgt cctgcagtct 540
 gacctctaca ctctgagcag ctcaagtact gtcccctcca gcacctggcc cagcgagacc 600
 gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
 agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcac 720
 ttcccccaa agcccaagga tgtgctcacc attactctga ctctaagggt cacgtgtgtt 780
 gtggtagaca tcagcaagga tgatcccag gtccagttca gctggtttgt agatgatgtg 840
 gaggtgcaca cagctcagac gcaaccccg gaggagcagt tcaacagcac tttccgctca 900
 gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960
 gtcaacagtg cagctttccc tgcccccac gagaaaaacca tctccaaaac caaaggcaga 1020
 ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080
 gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1140
 tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1200
 tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggagggc aggaaatact 1260
 ttcacctgtc ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320
 cactctcctg gtaaatga 1338

<210> 195

<211> 464

<212> PRT

<213> Mus musculus

<400> 195

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

Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
 145 150 155 160
 Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
 165 170 175
 Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
 180 185 190
 Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
 195 200 205
 Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
 210 215 220
 Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
 225 230 235 240
 Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
 245 250 255
 Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
 260 265 270
 Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
 275 280 285
 Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
 290 295 300
 Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
 305 310 315 320
 Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
 325 330 335
 Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
 340 345 350
 Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
 355 360 365
 Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
 370 375 380
 Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
 385 390 395 400
 Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
 405 410 415
 Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
 420 425 430
 Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
 435 440 445
 Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
 450 455 460

<210> 196

<211> 1395

<212> DNA

<213> Mus musculus

<400> 196

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	tgcacagctt	ctggcttcga	cattaaggac	tactatatac	actggatgaa	acagaggcct	180
	gaccagggcc	tggagtggat	tggaagggtt	gacccctgaca	atggtgagac	tgaatttgcc	240
	ccgaagtcc	cgggcaaggc	cactttttaca	acagacacat	cctccaacac	agcctaccta	300
	caactcagag	gcctgacatc	tgaggacact	gccatctatt	actgtgggag	agaagactac	360
	gatggtacct	acacctgggt	tccttatttg	ggccaaggga	ctctggtcac	tgtctctgca	420
10	gccaaaacga	cacccccatc	tgtctatcca	ctggcccctg	gatctgctgc	ccaaactaac	480
	tccatggtga	ccctgggatg	cctggtcaag	ggctattttc	ctgagccagt	gacagtgacc	540
	tggaactctg	gatccctgtc	cagcgggtgtg	cacaccttcc	cagctgtcct	gcagtctgac	600
	ctctacactc	tgagcagctc	agtgactgtc	ccctccagca	cctggcccag	cgagaccgtc	660
	acctgcaacg	ttgcccaccc	ggccagcagc	accaagggtg	acaagaaaat	tgtgcccagg	720
	gattgtgggt	gtaagccttg	catatgtaca	gtcccagaag	tatcatctgt	cttcatcttc	780
15	cccccaaagc	ccaaggatgt	gctcaccatt	actctgactc	ctaagggtcac	gtgtgtttgtg	840
	gtagacatca	gcaaggatga	tcccagaggtc	cagttcagct	ggtttgtaga	tgatgtggag	900
	gtgcacacag	ctcagacgca	accccgggag	gagcagttca	acagcacttt	ccgctcagtc	960
	agtgaacttc	ccatcatgca	ccaggactgg	ctcaatggga	aggagttcaa	atgcagggtc	1020
	aacagtgcag	ctttccctgc	ccccatcgag	aaaaccatct	ccaaaaccaa	aggcagaccg	1080
	aaggctccac	aggtgtacac	cattccacct	cccaaggagc	agatggccaa	ggataaagtc	1140
20	agtctgacct	gcatgataac	agacttcttc	cctgaagaca	ttactgtgga	gtggcagtg	1200
	aatgggcagc	cagcggagaa	ctacaagaac	actcagccca	tcatggacac	agatggctct	1260
	tacttcatct	acagcaagct	caatgtgcag	aagagcaact	gggaggcagg	aaatactttc	1320
25	acctgctctg	tgttacatga	gggcctgcac	aaccaccata	ctgagaagag	cctctcccac	1380
	tctcctggta	aatga					1395

<210> 197

<211> 214

<212> PRT

30 <213> Mus musculus

<400> 197

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

<210> 198
 <211> 645
 <212> DNA
 <213> Mus musculus

5
 <400> 198

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gatggaactg ttaagctcct gatcttctac acatcaacat tacagtcagg agtcccacg 180
aggttcagtg gcagtggtgc tggacaacaa tattctctca ccattaccaa cctggagcaa 240
gatgatgctg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg 300
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag          645

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<210> 199
 <211> 234
 <212> PRT
 <213> Mus musculus

20
 <400> 199

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Gly Ser Arg Cys Asp Leu Gln Met Thr Gln Thr Thr Ser Ser Leu Ser

30
Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp
 20    35    40    45
Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
 50    55    60
Lys Leu Leu Ile Phe Tyr Thr Ser Thr Leu Gln Ser Gly Val Pro Ser
 65    70    75    80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asn Tyr Ser Leu Thr Ile Thr
 85    90    95
Asn Leu Glu Gln Asp Asp Ala Ala Thr Tyr Phe Cys Gln Gln Gly Asp
100   105   110
Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
115   120   125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
130   135   140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145   150   155   160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
165   170   175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
180   185   190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
195   200   205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
210   215   220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225   230

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55
 <210> 200
 <211> 705
 <212> DNA
 <213> Mus musculus

EP 2 251 351 B1

<400> 200

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      atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 180
      gatggaactg ttaagctcct gatcttctac acatcaacat tacagtcagg agtcccatcg 240
      aggttcagtg gcagtgggtc tggaacaaat tattctctca ccattaccaa cctggagcaa 300
      gatgatgctg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg 360
      gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
10     tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
      cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
      aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
      ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
      tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 705

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15 <210> 201
 <211> 447
 <212> PRT
 <213> Mus musculus

20 <400> 201

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

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35

40

45

50

55

EP 2 251 351 B1

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

<210> 202

<211> 1344

40 <212> DNA

<213> Mus musculus

<400> 202

45

50

55

EP 2 251 351 B1

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	tcctgcaagg	cttctggata	cacattcact	gactacaaca	tgcactggat	gaagcagaac	120
	caaggaaaga	gcctagagtg	gataggagag	attaatccta	acagtgggtg	ttctgggttac	180
5	aaccagaagt	tcaaaggcaa	ggccacattg	actgtagaca	agtcctccag	cacagcctac	240
	atggagctcc	gcagcctgac	atctgaggac	tctgcagtct	attactgtgc	aagattgggc	300
	tactatggta	actacgagga	ctgggtatttc	gatgtctggg	gcgcagggac	cacggtcacc	360
	gtctcctctg	ccaaaacgac	acccccatct	gtctatccac	tggccccctgg	atctgctgcc	420
	caaactaact	ccatggtgac	cctgggatgc	ctggtcaagg	gctatttccc	tgagccagtg	480
	acagtgcact	ggaactctgg	atccctgtcc	agcgggtgtgc	acaccttccc	agctgtcctg	540
	cagtctgacc	tctacactct	gagcagctca	gtgactgtcc	cctccagcac	ctggcccagc	600
10	gagaccgtca	cctgcaacgt	tgcccacccg	gccagcagca	ccaaggtgga	caagaaaatt	660
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	ttcatcttcc	ccccaaagcc	caaggatgtg	ctcaccatta	ctctgactcc	taagggtcacg	780
	tgtgttgtgg	tagacatcag	caaggatgat	cccagggtcc	agttcagctg	gtttgtagat	840
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	cgctcagtca	gtgaacttcc	catcatgcac	caggactggc	tcaatggcaa	ggagttcaaa	960
15	tgagggtca	acagtgcagc	tttccctgcc	ccatcgaga	aaaccatctc	caaaaccaa	1020
	ggcagaccga	aggctccaca	ggtgtacacc	attccacctc	ccaaggagca	gatggccaag	1080

	gataaagtca	gtctgacctg	catgataaca	gacttcttcc	ctgaagacat	tactgtggag	1140
20	tggcagtgga	atgggcagcc	agcggagaac	tacaagaaca	ctcagcccat	catggacaca	1200
	gatggctctt	acttcattca	cagcaagctc	aatgtgcaga	agagcaactg	ggaggcagga	1260
	aatactttca	cctgctctgt	gttacatgag	ggcctgcaca	accaccatac	tgagaagagc	1320
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<210> 203

<211> 466

<212> PRT

<213> Mus musculus

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<400> 203

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	Val	Leu	Ser	Glu	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Leu	Met	Lys
5				20					25					30		
	Pro	Gly	Ala	Ser	Val	Lys	Met	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe
			35					40					45			
	Thr	Asp	Tyr	Asn	Met	His	Trp	Met	Lys	Gln	Asn	Gln	Gly	Lys	Ser	Leu
		50					55					60				
	Glu	Trp	Ile	Gly	Glu	Ile	Asn	Pro	Asn	Ser	Gly	Gly	Ser	Gly	Tyr	Asn
10						70					75				80	
	Gln	Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser
					85					90					95	
	Thr	Ala	Tyr	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val
				100					105					110		
	Tyr	Tyr	Cys	Ala	Arg	Leu	Gly	Tyr	Tyr	Gly	Asn	Tyr	Glu	Asp	Trp	Tyr
			115					120					125			
15	Phe	Asp	Val	Trp	Gly	Ala	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Lys
		130					135					140				
	Thr	Thr	Pro	Pro	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala	Ala	Gln
						150					155					160
	Thr	Asn	Ser	Met	Val	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro
					165					170					175	
20	Glu	Pro	Val	Thr	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val
				180					185					190		
	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Asp	Leu	Tyr	Thr	Leu	Ser	Ser
			195					200					205			
	Ser	Val	Thr	Val	Pro	Ser	Ser	Thr	Trp	Pro	Ser	Glu	Thr	Val	Thr	Cys
			210				215					220				
25	Asn	Val	Ala	His	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Val
						230					235					240
	Pro	Arg	Asp	Cys	Gly	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Val	Pro	Glu	Val
					245					250					255	
	Ser	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile
				260					265					270		
30	Thr	Leu	Thr	Pro	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp
			275					280					285			
	Asp	Pro	Glu	Val	Gln	Phe	Ser	Trp	Phe	Val	Asp	Asp	Val	Glu	Val	His
							295					300				
	Thr	Ala	Gln	Thr	Gln	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg
35						310					315					320
	Ser	Val	Ser	Glu	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
					325					330					335	
	Glu	Phe	Lys	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu
				340					345					350		
	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr
			355					360					365			
40	Thr	Ile	Pro	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu
							375					380				
	Thr	Cys	Met	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp
						390					395					400
	Gln	Trp	Asn	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile
					405					410					415	
45	Met	Asp	Thr	Asp	Gly	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln
				420					425					430		
	Lys	Ser	Asn	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His
			435					440					445			
50																
	Glu	Gly	Leu	His	Asn	His	His	Thr	Glu	Lys	Ser	Leu	Ser	His	Ser	Pro
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	Gly	Lys														
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<210> 204
 <211> 1401
 <212> DNA
 <213> Mus musculus

<400> 204

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   tgcaaggcct ctggatacac attcactgac tacaacatgc actggatgaa gcagaaccaa 180
   ggaaagagcc tagagtggat aggagagatt aatcctaaca gtggtgggtc tggttacaac 240
   cagaagttca aaggcaaggc cacattgact gtagacaagt cctccagcac agcctacatg 300
   gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
   tatggtaact acgaggactg gtaattcgat gtctggggcg cagggaccac ggtcaccgtc 420
   tcctctgcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgcctgccaa 480
10  actaactcca tgggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
   gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgcctctgcag 600
   tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 660
   accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
   cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
   atcttcccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
15  gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctgggt tgtagatgat 900
   gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
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   agaccgaagg ctccacaggt gtacaccatt ccacctcca aggagcagat ggccaaggat 1140
   aaagtcagtc tgacctgcat gataacagac ttcttcctg aagacattac tgtggagtgg 1200
20  cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
   ggctcttact tcacttacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
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25 <210> 205

<211> 215

<212> PRT

<213> Mus musculus

30 <400> 205

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

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195 200 205
 Ser Phe Asn Arg Asn Glu Cys
 210 215

EP 2 251 351 B1

<210> 206
 <211> 645
 <212> DNA
 <213> Mus musculus

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 <400> 206

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atgacctgca gggccagctc aagtgttaact tccagttact tgaactggta ccagcagaag 120
ccaggatctt cccccaact ctggatttat agcacatcca acctggcttc aggagtcca 180
gctcgcttca gtggcagtggt gtctgggacc tcttactctc tcacaatcag cagtgtggag 240
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ggaggcacca agctggaaat caagcgggct gatgtctgcac caactgtatc catcttcca 360
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ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccttc 540
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 600
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<210> 207
 <211> 237
 <212> PRT
 <213> Mus musculus

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 <400> 207

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20     25     30
Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
35     40     45
Ser Ser Val Thr Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
50     55     60
Ser Ser Pro Lys Leu Trp Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly
65     70     75     80
Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
85     90     95
Thr Ile Ser Ser Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
100    105    110
Gln Tyr Asp Phe Phe Pro Ser Thr Phe Gly Gly Gly Thr Lys Leu Glu
115    120    125
Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
130    135    140
Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
145    150    155    160
Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
165    170    175
Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
180    185    190
Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
195    200    205
Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser
210    215    220
Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225    230    235
  
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<210> 208
 <211> 711
 <212> DNA
 <213> Mus musculus

<400> 208

EP 2 251 351 B1

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	gtcaccatga	cctgcagggc	cagctcaagt	gtaacttcca	gttacttgaa	ctggtaccag	180
	cagaagccag	gatcttcccc	caaactctgg	atttatagca	catccaacct	ggcttcagga	240
	gtcccagctc	gcttcagtgg	cagtgggtct	gggacctctt	actctctcac	aatcagcagt	300
	gtggaggctg	aggatgctgc	cacttattac	tgccagcagt	atgatttttt	cccatcgacg	360
	ttcgggtggag	gcaccaagct	ggaaatcaag	cgggctgatg	ctgcaccaac	tgtatccatc	420
10	ttcccaccat	ccagtgcagca	gttaacatct	ggagggtgcct	cagtcgtgtg	cttcttgaac	480
	aactttctacc	ccaaagacat	caatgtcaag	tggaagattg	atggcagtga	acgacaaaat	540
	ggcgtcctga	acagtgggac	tgatcaggac	agcaaagaca	gcacctacag	catgagcagc	600
	accctcacgt	tgaccaagga	cgagtatgaa	cgacataaca	gctataacctg	tgaggccact	660
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15 <210> 209
 <211> 445
 <212> PRT
 <213> Mus musculus

20 <400> 209

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

<211> 1335

<212> DNA

55 <213> Mus musculus

<400> 210

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 catggagaga gccttgagtg gattggagat attaatcctt acaacgatga tactacctac 180
 aaccacaagt tcaagggcaa ggccacattg actgtagaca aatcctccaa cacagcctac 240
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 gccgttatta ctacgaatgc tatggactac tgggggtcaag gaacctcagt caccgtctcc 360
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 aactccatgg tgaccctggg atgcctggtc aagggtctatt tccctgagcc agtgacagtg 480
 acctggaact ctggatccct gtccagcggg gtgcacacct tcccagctgt cctgcagtct 540
 gacctctaca ctctgagcag ctccagtact gtccctcca gcacctggcc cagcgagacc 600
 gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
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 tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaataact 1260
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<210> 211

<211> 464

<212> PRT

<213> Mus musculus

<400> 211

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

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
 Thr Val 195 Ser Ser Thr Trp 200 Pro Ser Glu Thr Val 205 Thr Cys Asn Val
 Ala 210 His Pro Ala Ser Ser 215 Lys Val Asp Lys 220 Lys Ile Val Pro Arg
 225 Asp Cys Gly Cys Lys 230 Pro Cys Ile Cys Thr Val 235 Pro Glu Val Ser Ser
 Val Phe Ile Phe 245 Pro Pro Lys Pro Lys 250 Asp Val Leu Thr Ile Thr Leu
 260 Thr Pro Lys Val Thr Cys Val Val 265 Asp Ile Ser Lys 270 Asp Asp Pro
 275 Glu Val Gln Phe Ser Trp Phe 280 Val Asp Asp Val Glu Val His Thr Ala
 290 Gln Thr Gln Pro Arg Glu 295 Gln Phe Asn Ser Thr Phe Arg Ser Val
 305 Ser Glu Leu Pro Ile Met His Gln Asp Trp 315 Leu Asn Gly Lys Glu Phe
 325 Lys Cys Arg Val Asn Ser Ala Ala Phe 330 Pro Ala Pro Ile Glu Lys Thr
 340 Ile Ser Lys Thr Lys Gly Arg Pro 345 Lys Ala Pro Gln Val Tyr Thr Ile
 355 Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val 365 Ser Leu Thr Cys
 370 Met Ile Thr Asp Phe Phe 375 Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
 385 Asn Gly Gln Pro Ala 390 Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
 405 Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
 420 Asn Trp Glu Ala Gly Asn Thr Phe 425 Thr Cys Ser Val Leu His Glu Gly
 435 Leu His 440 Lys Ser Leu Ser His 445 Pro Gly Lys
 450 455 460

<210> 212
 <211> 1392
 <212> DNA
 <213> Mus musculus

<400> 212

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 gtccagctgc aacaatctgg acctgagctg gtgaagcctg gggcttcagt gaagatgtcc 120
 tgtaaggctt ctggatacac attcactgac tactacatga actgggtgaa gcagagccat 180
 ggagagagcc ttgagtggat tggagatatt aatccttaca acgatgatac tacctacaac 240
 cacaagttca agggcaaggc cacattgact gtagacaaat cctccaacac agcctacatg 300
 cagctcaaca gcctgacatc tgaggactct gcagtctatt actgtgcaag agagacggcc 360
 gttattacta cgaatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 420
 gccaaaacga caccctcatc tgtctatcca ctggcccctg gatctgctgc ccaaaactaac 480
 tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 540
 tggaactctg gatccctgtc cagcgggtgtg cacaccttcc cagctgtcct gcagtctgac 600
 ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 660
 acctgcaacg ttgcccaccc ggccagcagc accaagggtg acaagaaaaa tgtgcccagg 720
 gattgtgggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780
 ccccaaagc ccaaggatgt gctcaccatt actctgactc ctaagggtcac gtgtgttgtg 840
 gtagacatca gcaaggatga tcccagaggtc cagttcagct ggtttgtaga tgatgtggag 900
 gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 960
 agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 1020
 aacagtgcag ctttccctgc ccccctcag aaaaaccatc ccaaaaccaa aggcagaccg 1080
 aaggctccac aggtgtacac cattccacct ccgaaggagc agatggccaa ggataaagtc 1140
 agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtg 1200
 aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1260
 tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1320
 acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380
 tctcctggtg aa 1392

EP 2 251 351 B1

<210> 213
 <211> 215
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Humanized antibody sequence

<400> 213

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1      5      10      15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Thr Ser Ser
20      25      30
Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
35      40      45
Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50      55      60
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65      70      75      80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Phe Phe Pro
85      90      95
Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100      105      110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115      120      125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130      135      140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145      150      155      160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165      170      175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180      185      190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195      200      205
Ser Phe Asn Arg Gly Glu Cys
210      215
  
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<210> 214
 <211> 645
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Humanized antibody sequence

<400> 214

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atcacatgcc ggcgctcatc ttcagttaca tcttcttatc ttaattggta tcaacaaaaa 120
ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatc aggagttccc 180
tctcgatttt caggatctgg atcaggcaca gaatttacac ttactatatc atcactccaa 240
ccagaagact tcgccactta ttactgccaa caatacgatt tttttccaag cacattcgga 300
ggaggtacaa aagtagaaat caagcgtacg gtggctgcac catctgtctt catcttcccg 360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420
tatccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcacctcg 540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 600
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 645
  
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<210> 215
 <211> 237

EP 2 251 351 B1

<212> PRT

<213> Artificial Sequence

<220>

5 <223> Humanized antibody sequence

<400> 215

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

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35

<210> 216

<211> 711

<212> DNA

<213> Artificial sequence

40

<220>

<223> Humanized antibody sequence

<400> 216

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      agatgtgaca tccagctgac ccagagcccc agcttccttt ccgcatccgt tgggtgaccga 120
      gtaacaatca catgccgcgc ctcattctta gttacatctt cttatcttaa ttggtatcaa 180
      caaaaaccag gaaaagcacc taaacttctt atatactcta catctaattc cgcatacagga 240
      gttccctctc gattttcagg atctggatca ggcacagaat ttacacttac tatatcatca 300
      ctccaaccag aagacttcgc cacttattac tgccaacaat acgatttttt tccaagcaca 360
      ttcggaggag gtacaaaagt agaaatcaag cgtacggtgg ctgcaccatc tgtcttcatc 420
      ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat 480
      aacttctatc ccagagaggc caaagtacag tggaagggtg ataacgccct ccaatcgggt 540
      aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 600
      accctgacgc tgagcaaaag agactacgag aaacacaaag tctacgcctg cgaagtcacc 660
      catcagggcc tgagctcgcc cgtcacaaaag agcttcaaca ggggagagtg t 711

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<210> 217

EP 2 251 351 B1

<211> 447
 <212> PRT
 <213> Artificial sequence

5 <220>
 <223> Humanized antibody sequence

<400> 217

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

15

20

25

30

35

40

45

50

55

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

<210> 218

<211> 1341

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 218

EP 2 251 351 B1

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cctggacaaa gacttgaatg gatgggagac attaacctt ataacgacga cactacatac 180
aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat 240
atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact 300
gccgttatta ctactaacgc tatggattac tgggggtcaag gaaccactgt taccgtctct 360

10 agtgcctcca ccaagggccc atcgggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctgggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtgggtg accgtgccct ccagcaactt cggcaccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgaaatggt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgctgtgggtg tggacgtgag ccacgaagac cccgagggtcc agttcaactg gtacgtggac 840
15 ggctgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtgggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaagggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccagggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
20 tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc 1200
gacggctcct tcttctctta cagcaagctc accgtggaca agagcagggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa a 1341

25 <210> 219
<211> 466
<212> PRT
<213> Artificial sequence

30 <220>
<223> Humanized antibody sequence

<400> 219

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45

50

55

EP 2 251 351 B1

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	1				5					10					15	
	Ala	His	Ser	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys
				20					25					30		
5	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe
			35					40					45			
	Thr	Asp	Tyr	Tyr	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Arg	Leu
		50				55					60					
	Glu	Trp	Met	Gly	Asp	Ile	Asn	Pro	Tyr	Asn	Asp	Asp	Thr	Thr	Tyr	Asn
		65				70				75						80
10	His	Lys	Phe	Lys	Gly	Arg	Val	Thr	Ile	Thr	Arg	Asp	Thr	Ser	Ala	Ser
					85					90					95	
	Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val
				100					105					110		
	Tyr	Tyr	Cys	Ala	Arg	Glu	Thr	Ala	Val	Ile	Thr	Thr	Asn	Ala	Met	Asp
			115					120					125			
15	Tyr	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys
		130					135					140				
	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu
		145				150				155						160
	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro
					165					170					175	
20	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr
				180					185					190		
	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val
			195					200					205			
	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn
		210					215					220				
25	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg
		225				230					235				240	
	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly
					245					250					255	
	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
				260					265					270		
30	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
			275					280					285			
	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
		290					295					300				
	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg
		305				310					315					320
35	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
					325					330					335	
	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu
				340					345					350		
40	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
			355					360					365			
	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
		370					375					380				
	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
						390				395					400	
45	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met
					405					410					415	
	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
				420					425					430		
	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His
			435					440					445			
50	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro
		450					455					460				
	Gly	Lys														
		465														

55 <210> 220
 <211> 1398
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 220

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      tgcaaaagcat ctggatacac atttaccgac tactacatga attgggtacg acaagcccct 180
10     ggacaaagac ttgaatggat gggagacatt aacccttata acgacgacac tacatacaat 240
      cataaattta aaggaagagt tacaattaca agagatacat ccgcatcaac cgcctatatg 300
      gaactttcct cattgagatc tgaagacact gctgtttatt actgtgcaag agaaactgcc 360
      gttattacta ctaacgctat ggattactgg ggtcaaggaa ccactgttac cgtctctagt 420
      gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cactcccgag 480
      agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggg gacggtgtcg 540
15     tggaaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 600
      ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg caccagacc 660
      tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 720
      aaatgttgtg tcgagtgcc accgtgcccc gcaccacctg tggcaggacc gtcagtcttc 780
      ctcttcccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacgtgc 840
      gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 900
20     gtggaggtgc ataatgcca gacaaagcca cgggaggagc agttcaacag cacgttcgt 960
      gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 1020
      aaggtctcca acaaaggcct cccagcccc atcgagaaaa ccatctccaa aaccaaggg 1080
      cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac 1140
      caggtcagcc tgacctgcct ggtcaaaggc ttctaccca gcgacatcgc cgtggagtgg 1200
      gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1260
25     ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1320
      gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380
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<210> 221

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 221

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40     Asp Arg Val Thr Ile Thr Cys Ser Val Ser Ser Thr Ile Ser Ser Asn
           20           25           30

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His Leu His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu
 Ile Tyr³⁵ Gly Thr Ser Asn⁴⁰ Leu⁴⁵ Ala Ser Gly Val⁵⁰ Pro⁵⁵ Ser Arg Phe Ser
 Gly⁶⁰ Ser Gly Ser Gly Thr⁶⁵ Asp Phe Thr Leu Thr⁷⁰ Ile Ser Ser Leu Gln⁷⁵
 Pro Glu Asp Phe⁸⁰ Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro⁸⁵
 Leu Thr Phe Gly⁹⁰ Gly Gly Thr Lys Val⁹⁵ Glu Ile Lys Arg Thr Val Ala¹⁰⁰
 Ala Pro Ser Val¹⁰⁵ Phe Ile Phe Pro¹¹⁰ Ser Asp Glu Gln¹¹⁵ Leu Lys Ser
 Gly Thr Ala Ser Val Val Cys¹²⁰ Leu Leu Asn Asn Phe Tyr Pro Arg Glu¹²⁵
 Ala Lys Val Gln Trp Lys¹³⁰ Val Asp Asn Ala Leu¹³⁵ Gln Ser Gly Asn Ser¹⁴⁰
 Gln Glu Ser Val Thr¹⁴⁵ Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu¹⁵⁰
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val¹⁵⁵
 Tyr Ala Cys¹⁶⁰ Glu Val Thr His Gln¹⁶⁵ Gly Leu Ser Ser Pro¹⁷⁰ Val Thr Lys¹⁷⁵
 Ser Phe¹⁸⁰ Asn Arg Gly Glu Cys¹⁸⁵
 Ser Phe¹⁹⁰ Asn Arg Gly Glu Cys¹⁹⁵
 Ser Phe²⁰⁰ Asn Arg Gly Glu Cys²⁰⁵
 Ser Phe²¹⁰ Asn Arg Gly Glu Cys²¹⁵

<210> 222

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 222

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 cccggcaag cacctaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct 180
 tcaagatttt caggctctgg ctcaggcacc gactttactc ttacaatatc ctccctccaa 240
 cccgaagact tgcgaaccta ttactgtcaa caatgggtcct catatccact cacatttggc 300
 ggcggcacia aagtagaaat taaacgtacg gtggctgcac catctgtcct catcttccc 360
 ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420
 tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480
 caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540
 acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 600
 ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 645

<210> 223

<211> 237

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 223

EP 2 251 351 B1

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

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
 100 105 110
 Gln Trp Ser Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
 115 120 125
 Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
 130 135 140
 Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
 145 150 155 160
 Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
 165 170 175
 Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys
 180 185 190
 Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp
 195 200 205
 Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
 210 215 220
 Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235

<210> 224
 <211> 711
 <212> DNA
 <213> Artificial sequence

<220>
 <223> Humanized antibody sequence

<400> 224

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 agatgtgaca tccagatgac ccagttctca tctctcctct cagcatccgt aggcgataga 120
 gttacaataa catgcagcgt atcatcaact atatacatcaa atcatcttca ttgggttcaa 180
 cagaaacccg gcaaagcacc taaatcactt atatacggca catcaaactc cgcatacaggc 240
 gttccttcaa gattttcagg ctctggctca ggcaccgact ttactcttac aatatacctcc 300
 ctccaacccg aagacttcgc aacctattac tgtcaacaat ggtcctcata tccactcaca 360
 tttggcgggc gcacaaaagt agaaattaaa cgtacgggtg ctgcaccatc tgtcttcac 420
 ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat 480
 aactttctatc ccagagaggc caaagtacag tggaggtggg ataacgccct ccaatcgggt 540
 aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 600
 accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc 660
 catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t 711

<210> 225
 <211> 451
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Humanized antibody sequence

<400> 225

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

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

<210> 226

<211> 1353

<212> DNA

<213> Artificial sequence

EP 2 251 351 B1

<220>

<223> Humanized antibody sequence

<400> 226

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      tcctgcaagg  cttctgactt  caacattaaa  gacttctatc  tacactgggt  gcgacaggcc  120
      cctggacaag  ggcttgagtg  gattggaagg  attgatcctg  agaatgggtg  tactttatat  180
      gacccgaagt  tccaggacaa  ggtcaccatg  accacagaca  cgtccaccag  cacagcctac  240
10     atggagctga  ggagcctgag  atctgacgac  acggccgtgt  attactgtgc  gagagaggcg  300
      gattatttcc  acgatggtag  ctctacttgg  tacttcgatg  tctggggccg  tggcaccctg  360
      gtcaccgtct  ctagtgcctc  caccaagggc  ccatcggtct  tccccctggc  gccctgctcc  420
      aggagcacct  ccgagagcac  agcggccctg  ggctgcctgg  tcaaggacta  cttccccgaa  480
      ccggtgacgg  tgtcgtggaa  ctcaggcgct  ctgaccagcg  gcgtgcacac  cttcccagct  540
15     gtcctacagt  cctcaggact  ctactccctc  agcagcgtgg  tgaccgtgcc  ctccagcaac  600
      ttccgcaccc  agacctacac  ctgcaacgta  gatcacaagc  ccagcaacac  caagggtggac  660
      aagacagttg  agcgcaaatg  ttgtgtcgag  tgcccaccgt  gccagcacc  acctgtggca  720
      ggaccgtcag  tcttcctctt  ccccccaaaa  cccaaggaca  ccctcatgat  ctcccggacc  780
      cctgaggtca  cgtgcgtggt  ggtggacgtg  agccacgaag  accccgaggt  ccagttcaac  840
      tggtagctgg  acggcgtgga  ggtgcataat  gccaaagaca  agccacggga  ggagcagttc  900
20     aacagcacgt  tccgtgtggt  cagcgtcctc  accgttgtgc  accaggactg  gctgaacggc  960

      aaggagtaca  agtgcaaggc  ctccaacaaa  ggcctcccag  ccccatcga  gaaaaccatc  1020
      tccaaaacca  aagggcagcc  ccgagaacca  caggtgtaca  ccctgcccc  atcccgggag  1080
      gagatgacca  agaaccaggc  cagcctgacc  tgcctggtca  aaggcttcta  ccccagcgac  1140
25     atcgccgtgg  agtgggagag  caatgggcag  ccggagaaca  actacaagac  cacacctccc  1200
      atgctggact  ccgacggctc  cttcttcctc  tacagcaagc  tcaccgtgga  caagagcagg  1260
      tggcagcagg  ggaacgtctt  ctcatgctcc  gtgatgcatg  aggctctgca  caaccactac  1320
      acgcagaaga  gcctctccct  gtctccgggt  aaa
      . 1353

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<210> 227

<211> 470

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 227

EP 2 251 351 B1

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	Ala	His	Ser	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys
5				20					25					30		
	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Asp	Phe	Asn	Ile
			35					40					45			
	Lys	Asp	Phe	Tyr	Leu	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu
		50					55					60				
	Glu	Trp	Ile	Gly	Arg	Ile	Asp	Pro	Glu	Asn	Gly	Asp	Thr	Leu	Tyr	Asp
10	65					70					75					80
	Pro	Lys	Phe	Gln	Asp	Lys	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser
					85					90					95	
	Thr	Ala	Tyr	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val
				100					105					110		
	Tyr	Tyr	Cys	Ala	Arg	Glu	Ala	Asp	Tyr	Phe	His	Asp	Gly	Thr	Ser	Tyr
			115					120					125			
15	Trp	Tyr	Phe	Asp	Val	Trp	Gly	Arg	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser
		130					135					140				
	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
	145					150					155					160
	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
					165					170					175	
20	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
				180					185					190		
	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
			195					200					205			
	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr
		210					215					220				
25	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
	225					230					235					240
	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro
					245					250					255	
	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp
				260					265					270		
30	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp
			275					280					285			
	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly
		290					295					300				
	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn
		305				310					315					320
35	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp
					325					330					335	
	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro
				340					345					350		
	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu
			355					360					365			
40	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	
		370					375				380					
	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
					390						395					400
	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
45																
					405					410					415	
	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
				420					425					430		
	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys
			435					440					445			
50	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
		450					455					460				
	Ser	Leu	Ser	Pro	Gly	Lys										
					470											
55																

<210> 228

<211> 1410

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 228

5
10
15
20
25

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tgcaaggctt ctgacttcaa cattaaagac ttctatctac actgggtgcg acaggcccct 180
ggacaagggc ttgagtggat tggaaggatt gatcctgaga atggtgatac tttatatgac 240
ccgaagttcc aggacaaggt caccatgacc acagacacgt ccaccagcac agcctacatg 300
gagctgagga gcctgagatc tgacgacacg gccgtgtatt actgtgagag agaggcggat 360
tatttccacg atggtacctc ctactggtac ttcgatgtct ggggccgtgg caccctgggtc 420
accgtctcta gtgcctccac caagggccca tcggtcttcc ccctggcgcc ctgctccagg 480
agcacctccg agagcacagc ggccctgggc tgcctggtca aggactactt cccgaaccg 540
gtgacggtgt cgtggaactc aggcgtcttg accagcggcg tgcacacctt ccagctgtc 600
ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcaacttc 660
ggcaccaga cctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag 720
acagttgagc gcaaattgtt tgctgagtgcc caccgtgcc cagcaccacc tgtggcagga 780
ccgtcagctc tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccctc 840
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tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cacgggagga gcagttcaac 960
agcacgttcc gtgtggtcag cgtcctcacc gttgtgcacc aggactggct gaacggcaag 1020
gagtacaagt gcaaggtctc caacaaaggc ctcccagccc ccacgagaa aaccatctcc 1080
aaaaccaaag ggcagccccg agaaccacag gtgtacaccc tgccccatc ccgggaggag 1140
atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctaccc cagcgacatc 1200
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac acctcccatg 1260
ctggactccg acggctcctt ctccctctac agcaagctca ccgtggacaa gagcaggtgg 1320
cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1380
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<210> 229

<211> 213

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 229

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45
50
55

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

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EP 2 251 351 B1

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
 115 120 125
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
 130 135 140
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
 145 150 155 160
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
 165 170 175
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
 180 185 190
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
 195 200 205
 Asn Arg Gly Glu Cys
 210

15 <210> 230
 <211> 639
 <212> DNA
 <213> Artificial sequence

20 <220>
 <223> Humanized antibody sequence

<400> 230

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 atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg 120
 aaagccccta agctcctgat ctatgccaca tccaacctgg cttctggggg cccatcaagg 180
 ttcagcggca gtggatctgg gacagaattc actctcaca tcagcagcct gcagcctgaa 240
 gattttgcaa cttattactg tcagcagtgg agtagtgacc cactcacgtt cggcggaggg 300
 30 accaagggtg agatcaaactg tacgggtggc gcaccatctg tcttcatctt cccgccatct 360
 gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
 agagaggcca aagtacagt gaaggtggat aacgcccctc aatcgggtaa ctcccaggag 480
 agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540
 agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600
 agctcgcccc tcacaaagag cttcaacagg ggagagtgt 639

35 <210> 231
 <211> 235
 <212> PRT
 <213> Artificial Sequence

40 <220>
 <223> Humanized antibody sequence

<400> 231

45

50

55

EP 2 251 351 B1

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

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210 215 220
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 232
<211> 705
<212> DNA
<213> Artificial sequence

<220>
<223> Humanized antibody sequence

<400> 232

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gtcaccatca cttgcagggc cagctcaagt ataagttaca tacactggta tcagcaaaaa 180
ccagggaaag cccctaagct cctgatctat gccacatcca acctggcttc tgggggtcca 240
tcaaggttca gcggcagtg atctgggaca gaattcactc tcacaatcag cagcctgcag 300
cctgaagatt ttgcaactta ttactgtcag cagtggagta gtgaccact cagttcggc 360
ggagggacca aggtggagat caaacgtacg gtggctgcac catctgtctt catcttccg 420
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 480
tatccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggttaactcc 540
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 600
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 660
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 705

<210> 233
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody sequence

<400> 233

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 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asp Ile Lys Asp Tyr
 20 25 30
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Trp Ile
 35 40 45
 Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
 50 55 60
 10 Pro Gly Lys Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
 100 105 110
 15 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
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 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
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 195 200 205
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 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 260 265 270
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 275 280 285
 Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
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 Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 305 310 315 320
 40 Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
 325 330 335
 Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
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 Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
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 45 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
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 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
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EP 2 251 351 B1

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	Pro	Lys	Phe	Pro	Gly	Lys	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Ile	Ser
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	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
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	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu
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	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
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	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His
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EP 2 251 351 B1

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EP 2 251 351 B1

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EP 2 251 351 B1

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Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr
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EP 2 251 351 B1

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Asp Tyr Tyr Met Asn
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EP 2 251 351 B1

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Ser Ser Ile Ser Ser Ser Asn Leu His Trp Ser Gln Gln Lys Ser Gly
50 55 60
Thr Ser Pro Lys Leu Trp Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly
65 70 75 80
Val Pro Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
85 90 95
Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
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Lys Arg
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gtccctgttc gcttcagtgg cagtggatct gggacctctt attctctcac aatcagcagc 300
atggaggctg aagatgctgc cacttattac tgtcaacagt ggactactac gtatacgttc 360
ggatcggggga ccaagctgga gctgaaacgt 390

<210> 301

<211> 141

<212> PRT

<213> Mus musculus

<400> 301

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

<210> 302

<211> 423

<212> DNA

<213> Mus musculus

<400> 302

```

5
    atgggatgga actggatcat cttcttcctg atggcagtgg ttacaggggt caattcagag 60
    gtgcagttgc ggcagtctgg ggcagacctt gtgaagccag gggcctcagt caagttgtcc 120
    tgcacagctt ctggcttcaa cattaagac tactatatac actgggtgaa gcagaggcct 180
    gaacagggcc tggagtggat tgggaaggatt gatcctgata atggtgaaag tacatatgtc 240
10  ccgaagttcc agggcaaggc cactataaca gcagacacat catccaacac agcctaccta 300
    caactcagaa gcctgacatc tgaggacact gccatctatt attgtgggag agaggggctc 360
    gactatgggtg actactatgc tgtggactac tgggggtcaag gaacctcggg cacagtctcg 420
    agc                                     423

```

<210> 303

<211> 130

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 303

```

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

```

<210> 304

<211> 390

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 304

```

55  atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gccgggcgcg 60
    cgctgcgata ttcagctgac ccagagcccg agctttctga gcgcgagcgt gggcgatcgc 120
    gtgaccatta cctgcagcgt gagcagcagc attagcagca gcaacctgca ttggtatcag 180
    cagaaaccgg gcaaagcgcc gaaactgctg atttatggca ccagcaacct ggcgagcggc 240
    gtgccgagcc gcttttagcgg cagcggcagc ggcaccgaat ttaccctgac cattagcagc 300
    ctgcagccgg aagattttgc gacctattat tgccagcagt ggaccaccac ctataccttt 360
    ggccagggca ccaaactggg aattaaactg
    390

```

EP 2 251 351 B1

<210> 305
 <211> 141
 <212> PRT
 <213> Artificial sequence

5

<220>
 <223> Humanized antibody sequence

10

```

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

```

25

<210> 306
 <211> 423
 <212> DNA
 <213> Artificial sequence

30

<220>
 <223> Humanized antibody sequence

35

<400> 306

```

atggattgga cctggagcat tctgtttctg gtggcgggcg cgaccggcg ccatagcgaa 60
gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc 120
tgcaaagcga gcggctttaa cattaaagat tattatattc attgggtgcg ccaggcgccg 180
ggccagggcc tggaatggat gggccgcatt gatccggata acggcgaaag cacctatgtg 240
ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg 300
gaactgcgca gcctgcgag cgatgatacc gcggtgtatt attgcgcgcg cgaaggcctg 360
gattatggcg attattatgc ggtggattat tggggccagg gcaccctggt gaccgtctcg 420
agc

```

45

<210> 307
 <211> 127
 <212> PRT
 <213> Mus musculus

50

<400> 307

55

EP 2 251 351 B1

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

<210> 308
<211> 381
<212> DNA
<213> Mus musculus
<400> 308

atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcaac 120
atcagctgca gggcaagtca ggacattagc agttatttaa actggtatca gcagaaacca 180
gatggaactg tttaaactcct gatctactcc acatcaagat taaactcagg agtcccatca 240
aggttcagtg gcagtggtgc tgggacagat tattctctca ctattagcaa cctggcacia 300
gaagatatgg ccacttactt ttgccaacag gatattaagc atccgacgtt cgggtggaggc 360
accaagttgg agctgaaacg t 381

<210> 309
<211> 139
<212> PRT
<213> Mus musculus
<400> 309

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

<210> 310
<211> 417
<212> DNA
<213> Mus musculus

EP 2 251 351 B1

<400> 310

```

5      atggaatgga tctggatatt tctcttcctc ctgtcaggaa ctgcaggtgt ccactctgag 60
      gtccagctgc agcagtctgg acctgagctg gtaaagcctg gggcttcagt gaagatgtcc 120
      tgcaaggcctt ctgggttcac attcactgac tacattatgc actgggtgaa gcagaagcct 180
      gggcagggccc ttgagtggat tggatatatt aatccttaca atgatgatac tgaatacaat 240
      gagaagttca aaggcaaggc cacactgact tcagacaaat cctccagcac agcctacatg 300
      gatctcagca gtctgacctc tgagggctct gcggtctatt actgtgcaag atcgatttat 360
      tactacgatg ccccgtttgc ttactggggc caaggggactc tggtcacagt ctcgagc 417

```

10

<210> 311

<211> 127

<212> PRT

<213> Artificial Sequence

15

<220>

<223> Humanized antibody sequence

<400> 311

20

```

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

```

30

```

      Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
      85      90      95
      Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Ile
      100      105      110
35      Lys His Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
      115      120      125

```

35

<210> 312

<211> 381

<212> DNA

<213> Artificial Sequence

40

<220>

<223> Humanized antibody sequence

45

<400> 312

```

50      atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
      gatatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggatga ccgtgtcacc 120
      atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca 180
      gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca 240
      cgcttcagtg gcagtggctc tgggacagat ttactctca ccatcagcag tctgcaacct 300
      gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggatcaaggc 360
      accaagggtgg agatcaaacg t

```

55

<210> 313

<211> 139

<212> PRT

EP 2 251 351 B1

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

5

<400> 313

```

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

```

25 <210> 314

<211> 107

<212> PRT

<213> Mus musculus

30 <400> 314

```

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

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Ala Gln
 65      70      75      80
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile Lys His Pro Thr
 85      90      95
Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg
100      105

```

<210> 315

<211> 128

<212> PRT

<213> Mus musculus

<400> 315

55

EP 2 251 351 B1

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

<210> 316
 <211> 381
 <212> DNA
 <213> Mus musculus
 <400> 316

atgaagtcac agaccaggt ctttgatatac atgttgctgt ggttgctctgg tgttgaagga 60
 gacattgtga tgaccagtc tcacaaattc atgtccacgt cagtaggaga cagggtcacc 120
 atcacctgca aggccagtc ggatgtcttt actgctgtag cctggatatca acagaaacca 180
 ggacaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtcctgat 240
 cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct 300
 gaagacttgg cagattattt ctgtcaacaa tatagcagct atcctctcac gttcgggtgct 360
 gggaccaagt tggagctgaa a 381

<210> 317
 <211> 138
 <212> PRT
 <213> Mus musculus
 <400> 317

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

Gly Gln Gly Thr Leu Val Thr Val ser ser
 130 135

<210> 318
 <211> 411

EP 2 251 351 B1

<212> DNA

<213> Mus musculus

<400> 318

```

5
    atgggatgga actggatcat cttcttctg atggcagtgg ttacaggggt caattcagag 60
    gticagctgc agcagtctgg ggctgagctt gtgaggccag gggccttagt caagttgtcc 120
    tgcaaagctt ctggcttcaa tattaagac tactatatgc actgggtgaa gcagaggcct 180
    gaacagggcc tggagtggat tggaaggatt gatcctgaga atggtgatat tatatatgac 240
    ccgaagticc agggcaaggc cagtataaca acagacacat cctccaacac agcctacctg 300
    cagctcagca gcctgacgtc tgaggacact gccgtctatt actgtgctta cgatgctggt 360
    gaccccgctt ggtttactta ctggggccaa gggactctgg tcaccgtctc g          411

```

<210> 319

15 <211> 130

<212> PRT

<213> Artificial sequence

<220>

20 <223> Humanized antibody sequence

<400> 319

```

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

```

40 <210> 320
<211> 390

<212> DNA

<213> Artificial Sequence

45 <220>
<223> Humanized antibody sequence

<400> 320

```

50
    atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gcgcggcgcg 60
    cgctgcgata tccagatgac ccagagcccg agcagcctga gcgcgagcgt gggcgatcgc 120
    gtgaccatta cctgcaaagc gagccaggat gtgtttaccg cggtggcgtg gtatcagcag 180
    aaaccgggca aagcgccgaa actgctgatt tattgggcga gcacccgcca taccggcgtg 240
    ccgagtcgct ttagcggcag cggcagcggc accgatttta ccctgaccat tagcagcctg 300
    cagccggaag attttgcgac ctattattgc cagcagtata gcagctatcc gctgaccttt 360
    ggcggcgcca ccaaagtgga aattaaactg

```

EP 2 251 351 B1

<210> 321
 <211> 138
 <212> PRT
 <213> Artificial Sequence

5

<220>
 <223> Humanized antibody sequence

10

<400> 321

15

20

25

```

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

```

30

<210> 322
 <211> 414
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Humanized antibody sequence

<400> 322

40

45

```

atggattgga cctggagcat tctgtttctg gtggcgggcg cgaccggcg gcatagcgaa 60
gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc 120
tgcaaagcga gcggctttaa cattaaagat tattatatgc attgggtgcg ccaggcgccg 180
ggccagggcc tggaatggat cggccgcatt gatccggaaa acggcgatat tatttatgat 240
ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg 300
gaactgcgca gcctgcgcag cgatgatacc gcggtgtatt attgcgcgta tgatgcgggc 360
gatccggcgt ggtttaccta ttggggccag ggcaccctgg tgaccgtctc gaggc 414

```

50

<210> 323
 <211> 106
 <212> PRT
 <213> Mus musculus

55

<400> 323

EP 2 251 351 B1

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

15 <210> 324
 <211> 324
 <212> PRT
 <213> Mus musculus

20 <400> 324

	Ala	Lys	Thr	Thr	Pro	Pro	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala
	1				5					10					15	
	Ala	Gln	Thr	Asn	Ser	Met	Val	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr
				20					25					30		
25	Phe	Pro	Glu	Pro	Val	Thr	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser
			35				40						45			
	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Asp	Leu	Tyr	Thr	Leu
		50					55					60				
	Ser	Ser	Ser	Val	Thr	Val	Pro	Ser	Ser	Thr	Trp	Pro	Ser	Glu	Thr	Val
	65				70					75						80
30	Thr	Cys	Asn	Val	Ala	His	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys
					85					90					95	
	Ile	Val	Pro	Arg	Asp	Cys	Gly	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Val	Pro
				100					105					110		
	Glu	Val	Ser	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu
			115					120					125			
35	Thr	Ile	Thr	Leu	Thr	Pro	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser
		130					135					140				
	Lys	Asp	Asp	Pro	Glu	Val	Gln	Phe	Ser	Trp	Phe	Val	Asp	Asp	Val	Glu
	145				150						155					160
	Val	His	Thr	Ala	Gln	Thr	Gln	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr
				165						170					175	
40	Phe	Arg	Ser	Val	Ser	Glu	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn
				180					185					190		
	Gly	Lys	Glu	Phe	Lys	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro
			195					200					205			
	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln
		210					215					220				
45	Val	Tyr	Thr	Ile	Pro	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val
	225				230						235					240
	Ser	Leu	Thr	Cys	Met	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val
				245						250					255	
	Glu	Trp	Gln	Trp	Asn	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln
				260					265					270		
50	Pro	Ile	Met	Asp	Thr	Asp	Gly	Ser	Tyr	Phe	Val	Tyr	Ser	Lys	Leu	Asn
			275					280					285			
	Val	Gln	Lys	Ser	Asn	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val
		290					295					300				
	Leu	His	Glu	Gly	Leu	His	Asn	His	His	Thr	Glu	Lys	Ser	Leu	Ser	His
	305					310					315					320
55	Ser	Pro	Gly	Lys												

<210> 325

EP 2 251 351 B1

<211> 106
 <212> PRT
 <213> Homo sapiens

5 <400> 325

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

20 <210> 326
 <211> 327
 <212> PRT
 <213> Homo sapiens

25 <400> 326

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EP 2 251 351 B1

	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
	1				5					10				15		
	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
				20					25					30		
5	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
			35		1			40					45			
	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
		50					55					60				
	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr
	65					70				75						80
10	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
				85						90					95	
	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro
				100					105					110		
	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
			115					120					125			
15	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val
		130					135					140				
	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp
	145					150					155					160
	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe
					165					170					175	
20	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp
				180					185					190		
	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu
			195					200					205			
	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
		210					215					220				
25	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys
						230					235					240
	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp
					245					250					255	
	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
				260					265					270		
30	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
			275					280					285			
	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser
		290					295					300				
	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
						310					315					320
35	Leu	Ser	Leu	Ser	Leu	Gly	Lys									
					325											

<210> 327

<211> 120

40 <212> PRT

<213> Mus musculus

<400> 327

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

EP 2 251 351 B1

Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser Ser
 100 105 110 115 120

<210> 328
 <211> 120
 <212> PRT
 <213> Mus musculus

<400> 328

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

<210> 329
 <211> 120
 <212> PRT
 <213> Mus musculus

<400> 329

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

<210> 330
 <211> 226
 <212> PRT
 <213> Mus musculus

<400> 330

EP 2 251 351 B1

1 Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 5 Ser Val Lys Met Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
 10 Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
 15 Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
 20 Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
 25 Met Asp Leu Ser Ser Leu Thr Ser Glu Gly Ser Ala Val Tyr Tyr Cys
 30 Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser Ser Thr Val Ala Ala Pro Ser Val Phe
 40 Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
 45 Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
 50 Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
 55 Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
 60 Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
 65 Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
 70 Glu Cys
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 105
 110
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30 <210> 331
 <211> 447
 <212> PRT
 <213> Mus musculus

35 <400> 331

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EP 2 251 351 B1

	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
	1				5					10					15	
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	Thr	Asp	Tyr
5				20					25					30		
	Ile	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Tyr	Ile	Asn	Pro	Tyr	Asn	Asp	Asp	Thr	Glu	Tyr	Asn	Glu	Lys	Phe
		50					55					60				
	Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
	65					70					75				80	
10	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Ser	Ile	Tyr	Tyr	Tyr	Asp	Ala	Pro	Phe	Ala	Tyr	Trp	Gly	Gln
				100					105					110		
	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
			115					120					125			
15	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala
		130					135					140				
	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
	145					150					155					160
	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
				165					170						175	
20	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
				180					185					190		
	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys
			195					200					205			
	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro
		210					215					220				
25	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val
						230					235					240
	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
				245					250						255	
	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu
				260					265					270		
30	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
			275					280					285			
	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser
		290					295					300				
35	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys
	305					310					315					320
	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile
					325					330					335	
40	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro
				340					345					350		
	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu
			355					360					365			
	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn
		370					375					380				
45	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser
					390						395					400
	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg
				405						410					415	
	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu
				420					425					430		
50	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys	
			435					440					445			

<210> 332

<211> 107

<212> PRT

55 <213> Mus musculus

<400> 332

EP 2 251 351 B1

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

15 <210> 333
 <211> 324
 <212> PRT
 <213> Mus musculus

20 <400> 333

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

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Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
 165 170 175
 Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
 180 185 190
 Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
 195 200 205
 Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
 210 215 220
 Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
 225 230 235 240
 Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
 245 250 255
 Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
 260 265 270
 Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
 275 280 285
 Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
 290 295 300
 Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
 305 310 315 320
 Ser Pro Gly Lys

<210> 334
 <211> 213
 <212> PRT
 <213> Mus musculus

<400> 334

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1 5 10 15
 Asp Arg Val Asn Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
 35 40 45
 Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Ala Gln
 65 70 75 80
 Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile Lys His Pro Thr
 85 90 95
 Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Thr Asp Ala Ala Pro
 100 105 110
 Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
 115 120 125
 Ala Ser Val val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
 130 135 140
 Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
 145 150 155 160
 Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
 165 170 175
 Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
 180 185 190
 Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
 195 200 205
 Asn Arg Asn Glu Cys
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<210> 335
 <211> 444
 <212> PRT
 <213> Mus musculus

<400> 335

EP 2 251 351 B1

	Glu 1	Val	Gln	Leu	Gln 5	Gln	Ser	Gly	Pro	Glu 10	Leu	Val	Lys	Pro	Gly 15	Ala
5	Ser	Val	Lys	Met 20	Ser	Cys	Lys	Ala	Ser 25	Gly	Phe	Thr	Phe	Thr 30	Asp	Tyr
	Ile	Met	His 35	Trp	Val	Lys	Gln	Lys 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Ile
10	Gly	Tyr 50	Ile	Asn	Pro	Tyr	Asn 55	Asp	Asp	Thr	Glu	Tyr 60	Asn	Glu	Lys	Phe
	Lys 65	Gly	Lys	Ala	Thr	Leu 70	Thr	Ser	Asp	Lys	Ser 75	Ser	Ser	Thr	Ala	Tyr 80
	Met	Asp	Leu	Ser	Ser 85	Leu	Thr	Ser	Glu	Gly 90	Ser	Ala	Val	Tyr	Tyr 95	Cys
15	Ala	Arg	Ser	Ile 100	Tyr	Tyr	Tyr	Asp	Ala 105	Pro	Phe	Ala	Tyr	Trp 110	Gly	Gln
	Gly	Thr	Leu 115	Val	Thr	Val	Ser	Ser 120	Ala	Lys	Thr	Thr	Pro 125	Pro	Ser	Val
	Tyr	Pro 130	Leu	Ala	Pro	Gly	Ser 135	Ala	Ala	Gln	Thr	Asn 140	Ser	Met	Val	Thr
20	Leu 145	Gly	Cys	Leu	Val	Lys 150	Gly	Tyr	Phe	Pro	Glu 155	Pro	Val	Thr	Val	Thr 160
	Trp	Asn	Ser	Gly	Ser 165	Leu	Ser	Ser	Gly	Val 170	His	Thr	Phe	Pro	Ala	Val 175
	Leu	Gln	Ser	Asp 180	Leu	Tyr	Thr	Leu	Ser 185	Ser	Ser	Val	Thr	Val 190	Pro	Ser
25	Ser	Thr	Trp 195	Pro	Ser	Glu	Thr	Val 200	Thr	Cys	Asn	Val	Ala 205	His	Pro	Ala
	Ser	Ser 210	Thr	Lys	Val	Asp	Lys 215	Lys	Ile	Val	Pro	Arg 220	Asp	Cys	Gly	Cys
	Lys 225	Pro	Cys	Ile	Cys	Thr 230	Val	Pro	Glu	Val	Ser 235	Ser	Val	Phe	Ile	Phe 240
30	Pro	Pro	Lys	Pro	Lys 245	Asp	Val	Leu	Thr	Ile 250	Thr	Leu	Thr	Pro	Lys 255	Val
	Thr	Cys	Val	Val 260	Val	Asp	Ile	Ser	Lys 265	Asp	Asp	Pro	Glu	Val 270	Gln	Phe
	Ser	Trp	Phe 275	Val	Asp	Asp	Val	Glu 280	Val	His	Thr	Ala	Gln 285	Thr	Gln	Pro
35	Arg	Glu 290	Glu	Gln	Phe	Asn	Ser 295	Thr	Phe	Arg	Ser	Val 300	Ser	Glu	Leu	Pro
	Ile 305	Met	His	Gln	Asp	Trp 310	Leu	Asn	Gly	Lys	Glu 315	Phe	Lys	Cys	Arg	Val 320
	Asn	Ser	Ala	Ala	Phe 325	Pro	Ala	Pro	Ile	Glu 330	Lys	Thr	Ile	Ser	Lys 335	Thr
40	Lys	Gly	Arg	Pro 340	Lys	Ala	Pro	Gln	Val 345	Tyr	Thr	Ile	Pro	Pro 350	Pro	Lys
	Glu	Gln	Met 355	Ala	Lys	Asp	Lys	Val 360	Ser	Leu	Thr	Cys	Met 365	Ile	Thr	Asp
	Phe	Phe 370	Pro	Glu	Asp	Ile	Thr 375	Val	Glu	Trp	Gln	Trp 380	Asn	Gly	Gln	Pro
45	Ala 385	Glu	Asn	Tyr	Lys	Asn 390	Thr	Gln	Pro	Ile	Met 395	Asp	Thr	Asp	Gly	Ser 400
	Tyr	Phe	Val	Tyr	Ser 405	Lys	Leu	Asn	Val	Gln 410	Lys	Ser	Asn	Trp	Glu 415	Ala
	Gly	Asn	Thr	Phe 420	Thr	Cys	Ser	Val	Leu 425	His	Glu	Gly	Leu	His 430	Asn	His
50	His	Thr	Glu 435	Lys	Ser	Leu	Ser	His 440	Ser	Pro	Gly	Lys				

<210> 336

<211> 108

<212> PRT

55 <213> Mus musculus

<400> 336

EP 2 251 351 B1

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 Lys Ala Ser Gln Asp Val Phe Thr Ala
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Trp Ala Ser Thr Arg His Thr 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 Tyr Ser Ser Tyr Pro Leu
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 337

<211> 324

<212> DNA

<213> Mus musculus

<400> 337

gatatccaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcca tcgcgtgacc 60
 attacctgca aagcgagcca ggatgtgttt accgcggtgg cgtggtatca gcagaaaccg 120
 ggcaaacgca cgaaactgct gatttattgg gcgagcacc gccataccgg cgtgccgagt 180
 cgcttttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240
 gaagattttg cgacctatta ttgccagcag tatagcagct atccgctgac ctttggcggc 300
 ggcaccaaag tggaaattaa acgt 324

<210> 338

<211> 119

<212> PRT

<213> Mus musculus

<400> 338

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

<210> 339

<211> 357

<212> DNA

<213> Mus musculus

<400> 339

EP 2 251 351 B1

	gaagtgcagc	tggtgcagag	cggcgcgga	gtgaaaaaac	cggcgcgag	cgtgaaagt	60
	agctgcaaag	cgagcggctt	taacattaaa	gattattata	tgcattgggt	gcgccaggcg	120
	ccgggccagg	gcctgggaatg	gatcggccgc	attgatccgg	aaaacggcga	tattatttat	180
	gatccgaaat	ttcagggccg	cgtgaccatg	accaccgata	ccagcaccag	caccgcgtat	240
5	atggaactgc	gcagcctgcg	cagcgatgat	accgcggtgt	attattgcgc	gtatgatgcg	300
	ggcgatccgg	cgtgggtttac	ctattggggc	cagggcaccc	tggtgaccgt	ctcagagc	357

<210> 340

<211> 1395

<212> DNA

<213> Mus musculus

<400> 340

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	gtgcagctgg	tgcagtctgg	ggctgaggtg	aagaagcctg	qgtcctcggt	gaaggtctcc	120

20	tgcaaggctt	ctggtttttac	cttcaccgac	tatattatgc	actgggtgcg	tcaggcccct	180
	ggcaagggc	ttgagtggat	gggctatatc	aacccttata	atgatgacac	cgaatacaac	240
	gagaagttca	agggccggtg	cacgattacc	gcggacaaat	ccacgagcac	agcctacatg	300
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<210> 341

<211> 213

<212> PRT

<213> Mus musculus

<400> 341

EP 2 251 351 B1

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 Tyr Ser Thr Ser Arg Leu Asn 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 Asp Ile Lys His Pro Thr
 85 90 95
 Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
 100 105 110
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
 115 120 125
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
 130 135 140
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
 145 150 155 160
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
 165 170 175
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
 180 185 190
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
 195 200 205
 Asn Arg Gly Glu Cys
 210

<210> 342
 <211> 639
 <212> DNA
 <213> Mus musculus

<400> 342

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<210> 343
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 <212> PRT
 <213> Mus musculus

<400> 343

EP 2 251 351 B1

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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
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Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60
Ala Pro Lys Leu Leu Ile Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val
65 70 75 80
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110
Asp Ile Lys His Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
115 120 125
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
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<210> 344

<211> 705

<212> DNA

<213> Mus musculus

<400> 344

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<211> 446

<212> PRT

<213> Mus musculus

<400> 345

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 35 40 45
 Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr 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 Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
 210 215 220
 Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 225 230 235 240
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 260 265 270
 Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285
 Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
 290 295 300
 Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320
 Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 325 330 335
 Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
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 Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
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 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380
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 385 390 395 400
 Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
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<210> 346
 <211> 1338
 <212> DNA
 <213> Mus musculus

<400> 346

EP 2 251 351 B1

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	atggagctga	gcagcctg	ctctgaggac	acggccgtgt	attactgtgc	gcgttcgatt	300
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<210> 347

<211> 465

<212> PRT

25 <213> Mus musculus

<400> 347

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EP 2 251 351 B1

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	Thr	Asp	Tyr	Ile	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu
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	Glu	Trp	Met	Gly	Tyr	Ile	Asn	Pro	Tyr	Asn	Asp	Asp	Thr	Glu	Tyr	Asn
10	65					70				75					80	
	Glu	Lys	Phe	Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser
				85					90					95		
	Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val
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20	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe
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	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val
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	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro
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	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
		290					295					300				
35	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val
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	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
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40	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys
				340					345					350		
	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
			355					360					365			
	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
		370					375					380				
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	385					390					395				400	
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu
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	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
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	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
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 <212> DNA
 <213> Mus musculus

<400> 348

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<400> 350

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EP 2 251 351 B1

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 Gly Thr Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
 Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Glu Ile Pro Ala
 Arg Phe Ser Gly Thr Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 10 Pro Val Glu Glu Glu Asp Ile Thr Thr Tyr Tyr Cys Gln Gln Ser Asn
 Glu Asp Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
 Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Glu Gln
 15 Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
 Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
 Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
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<210> 351
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<400> 351

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<210> 354
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EP 2 251 351 B1

<212> DNA

<213> Mus musculus

<400> 354

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<210> 355

<211> 238

<212> PRT

<213> Mus musculus

<400> 355

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35 40 45
Val Asp Tyr Asp Gly Thr Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
50 55 60
Gly Gln Pro Pro Lys Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
65 70 75 80
Glu Ile Pro Ala Arg Phe Ser Gly Thr Gly Ser Gly Thr Asp Phe Thr
85 90 95
Leu Asn Ile His Pro Val Glu Glu Glu Asp Ile Thr Thr Tyr Tyr Cys
100 105 110
Gln Gln Ser Asn Glu Asp Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu
115 120 125
Glu Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro
130 135 140
Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu
145 150 155 160
Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly
165 170 175
Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser
180 185 190
Lys Asp Ser Thr Tyr Ser Met Ser Thr Leu Thr Leu Thr Lys Asp
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<211> 717

<212> DNA

<213> Mus musculus

<400> 356

EP 2 251 351 B1

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20 <400> 357

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EP 2 251 351 B1

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				20					25					30		
5	Trp	Met	Asn	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Asp	Gln	Lys
			35					40					45			
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10	Met	His	Leu	Ser	Gly	Pro	Thr	Ser	Val	Asp	Ser	Ala	Val	Tyr	Tyr	Cys
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		210					215					220				
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	225					230					235					240
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	305					310					315					320
35	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly
					325					330					335	
	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	Thr	Ile	Pro	Pro	Pro	Lys	Glu	Gln
				340					345					350		
	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr	Cys	Met	Ile	Thr	Asp	Phe	Phe
			355					360					365			
40	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln	Trp	Asn	Gly	Gln	Pro	Ala	Glu
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	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	Met	Asp	Thr	Asp	Gly	Ser	Tyr	Phe
	385					390					395					400
	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys	Ser	Asn	Trp	Glu	Ala	Gly	Asn
					405					410					415	
45	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu	Gly	Leu	His	Asn	His	His	Thr
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 <213> Mus musculus

55 <400> 358

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EP 2 251 351 B1

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<400> 359

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<210> 360
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<400> 360

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<210> 361
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<400> 361

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cctggacaag	gccttgagtg	gattggcatg	attcatcctt	ccgcaagtga	aattagggtg	180
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 <212> PRT
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<400> 362

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				20				25						30		
5	Pro	Gly	Thr	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe
			35					40					45			
	Thr	Thr	Tyr	Trp	Met	Asn	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu
		50					55					60				
	Glu	Trp	Ile	Gly	Met	Ile	His	Pro	Ser	Ala	Ser	Glu	Ile	Arg	Leu	Asp
	65					70					75				80	
10	Gln	Lys	Phe	Lys	Asp	Lys	Ala	Thr	Leu	Thr	Leu	Asp	Lys	Ser	Ser	Ser
				85						90					95	
	Thr	Ala	Tyr	Met	His	Leu	Ser	Gly	Pro	Thr	Ser	Val	Asp	Ser	Ala	Val
				100					105					110		
	Tyr	Tyr	Cys	Ala	Arg	Ser	Gly	Glu	Trp	Gly	Ser	Met	Asp	Tyr	Trp	Gly
			115					120					125			
15	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Ala	Lys	Thr	Thr	Pro	Pro	Ser
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	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala	Ala	Gln	Thr	Asn	Ser	Met	Val
	145					150					155				160	
	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
				165						170					175	
20	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
				180					185					190		
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			195					200					205			
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		210					215					220				
25	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Val	Pro	Arg	Asp	Cys	Gly
	225					230					235					240
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	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile	Thr	Leu	Thr	Pro	Lys
				260					265					270		
30	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp	Asp	Pro	Glu	Val	Gln
			275					280					285			
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	305					310					315					320
35	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Phe	Lys	Cys	Arg
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				340					345					350		
	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	Thr	Ile	Pro	Pro	Pro
			355					360					365			
40	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr	Cys	Met	Ile	Thr
		370					375					380				
	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln	Trp	Asn	Gly	Gln
	385					390					395				400	
	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	Met	Asp	Thr	Asp	Gly
				405						410				415		
45	Ser	Tyr	Phe	Ile	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys	Ser	Asn	Trp	Glu
				420					425					430		
	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu	Gly	Leu	His	Asn
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<211> 1386

<212> DNA

55 <213> Mus musculus

<400> 363

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<211> 106

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 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ser Thr Ser Arg Leu Asn 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
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 Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
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<210> 365

<211> 318

<212> DNA

<213> Mus musculus

<400> 365

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EP 2 251 351 B1

<211> 120
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5 <400> 366

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      Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35          40          45
15      Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
      50          55          60
      Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr 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
20      Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
      100          105          110
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25 <210> 367
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30 <400> 367

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40 <210> 368
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<213> Mus musculus

45 <400> 368

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50      Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35          40          45
      Tyr Trp Ala Ser Thr Arg His Thr 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
55      Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Leu
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      Thr Phe Gly Gly Thr Lys Val Glu Ile Lys Arg
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EP 2 251 351 B1

<210> 369
<211> 324
<212> DNA
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cgcttttagcg gcagcggcag cggcaccgat ttaccctga ccattagcag cctgcagccg 240
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<210> 370
<211> 119
<212> PRT
<213> Mus musculus

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20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
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<210> 371
<211> 357
<212> DNA
<213> Mus musculus

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<213> Mus musculus

<400> 372

EP 2 251 351 B1

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

15 <210> 373
 <211> 324
 <212> DNA
 <213> Mus musculus

20 <400> 373

gatattcagc tgacccagag cccgagcttt ctgagcgcga gcgtgggcca tcgctgacc 60
 attacctgca gctgagcag cagcattagc agcagcaacc tgcattggta tcagcagaaa 120
 ccgggcaaag cgccgaaact gctgatttat ggcaccagca acctggcgag cggcgtgccg 180
 agccgcttta gcggcagcgg cagcggcacc gaatttacc tgaccattag cagcctgcag 240
 ccggaagatt ttgcgaccta ttattgccag cagtggacca ccacctatac ctttggccag 300
 ggcaccaaac tggaaattaa acgt 324

30 <210> 374
 <211> 122
 <212> PRT
 <213> Mus musculus

35 <400> 374

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

50 <210> 375
 <211> 366
 <212> DNA
 <213> Mus musculus

55 <400> 375

EP 2 251 351 B1

gaagtgcagc tgggtgcagag cggcgcgga gtgaaaaaac cgggcgcgag cgtgaaagtg 60
agctgcaaag cgagcggctt taacattaaa gattattata ttcatagggt gcgccaggcg 120
ccgggccagg gcctgggaat gatgggccc accaccgata ccagcaccag caccgcgtat 180
gtgccgaaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat 240
atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgctg gcgcgaaggc 300
ctggattatg gcgattatta tgcggtgatg tattggggcc agggcaccct ggtgaccgtc 360
tcgagc

<210> 376

<211> 107

<212> PRT

<213> Mus musculus

<400> 376

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 Asp Ile Ser Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile
35 40 45
Tyr Tyr Thr Ser Arg Leu Leu 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 Gly Asp Thr Leu Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 377

<211> 321

<212> DNA

<213> Mus musculus

<400> 377

gacatccaga tgacccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc 60

ataacatgta gagcatctca agatatttcc aactatttga attggtacca acaaaaaccc 120
ggcaaagcac ctaaactcct catttactat acatcaagac tcctctccgg cgttccatca 180
cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca 240
gaagattttg caacctatta ctgtcaacaa ggcgatacac tccatacac attcggcggc 300
ggcacaaaag ttgaaattaa a 321

<210> 378

<211> 123

<212> PRT

<213> Mus musculus

<400> 378

EP 2 251 351 B1

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

<210> 379
 <211> 369
 <212> DNA
 <213> Mus musculus
 <400> 379

gaggtgcagc tgggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgttaaagtt 60
 tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg 120
 ccaggacaag gattggaatg gatgggagaa attaacccta atagtggagg agcaggctac 180
 aatcaaaaat tcaaaaggag agttacaatg acaacagaca caagcacttc aacagcatat 240
 atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg 300
 tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc 360
 gtctctagtt 369

<210> 380
 <211> 108
 <212> PRT
 <213> Mus musculus
 <400> 380

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

<210> 381
 <211> 324
 <212> DNA
 <213> Mus musculus
 <400> 381

EP 2 251 351 B1

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gacatccagc tgacccagag cccagcttc ctttccgcat ccgttggtga ccgagtaaca 60
atcacatgcc gcgcctcatc ttcagttaca tcttcttata ttaattggta tcaacaaaaa 120
ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatac aggagttccc 180
tctcgatttt caggatctgg atcaggcaca gaatttacac ttactataac atcactccaa 240
ccagaagact tcgccactta ttactgccaa caatacgatt tttttccaag cacattcgga 300
ggaggtacaa aagtagaaat caag                                     324

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<210> 382

<211> 121

<212> PRT

<213> Mus musculus

<400> 382

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Glu 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 Asp Tyr
20      25      30
Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35      40      45
Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
50      55      60
Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala 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 Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
100      105      110
Gln Gly Thr Thr Val Thr Val Ser Ser
115      120

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<210> 383

<211> 363

<212> DNA

<213> Mus musculus

<400> 383

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gaggtgcagc tggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaagggt 60
agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc 120
cctggacaaa gacttgaatg gatgggagac attaacccctt ataacgacga cactacatac 180
aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatac aaccgcctat 240
atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact 300
gccgttatta ctactaacgc tatggattac tgggggtcaag gaaccactgt taccgtctct 360
agt                                     363

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<210> 384

<211> 108

<212> PRT

<213> Mus musculus

<400> 384

EP 2 251 351 B1

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

15 100 105

<210> 385
 <211> 324
 <212> DNA
 <213> Mus musculus

<400> 385

gacatccaga tgacccagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca 60
 ataacatgca gcgtatcatc aactatatca tcaaatacatc ttcattgggt ccaacagaaa 120
 cccggcaaag cacctaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct 180
 tcaagatttt caggctctgg ctcaggcacc gactttactc ttacaatatc ctccctccaa 240
 cccgaagact tcgcaaccta ttactgtcaa caatgggtcct catatccact cacatttggc 300
 ggcggcacaa aagtagaaat taaa 324

<210> 386
 <211> 125
 <212> PRT
 <213> Mus musculus

<400> 386

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

<210> 387
 <211> 375
 <212> DNA
 <213> Mus musculus

<400> 387

EP 2 251 351 B1

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gaggtgcagc  tgggtgcagtc  tggggctgag  gtgaagaagc  ctggggcctc  agtgaaggtc  60
tcctgcaagg  cttctgactt  caacattaa  gacttctatc  tacactgggt  gcgacaggcc  120
cctggacaag  ggcttgagtg  gattggaagg  attgatcctg  agaatgggtg  tactttatat  180
gacccgaagt  tccaggacaa  ggtcaccatg  accacagaca  cgtccaccag  cacagcctac  240
atggagctga  ggagcctgag  atctgacgac  acggccgtgt  attactgtgc  gagagaggcg  300
gattatttcc  acgatggtag  ctccctactg  tacttcgatg  tctggggccg  tggcacccctg  360
gtcacccgtct  ctagt

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<210> 388

<211> 106

<212> PRT

<213> Mus musculus

<400> 388

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

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
 65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
 85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100           105

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<210> 389

<211> 318

<212> DNA

<213> Mus musculus

<400> 389

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gacatccagt  tgaccagtc  tccatccttc  ctgtctgcat  ctgtaggaga  cagagtcacc  60
atcacttgca  gggccagctc  aagtataagt  tacatacact  ggtatcagca  aaaaccaggg  120
aaagccccta  agctcctgat  ctatgccaca  tccaacctgg  cttctggggg  cccatcaagg  180
ttcagcggca  gtggatctgg  gacagaattc  actctcaca  tcagcagcct  gcagcctgaa  240
gattttgcaa  cttattactg  tcagcagtgg  agtagtgacc  cactcacgtt  cggcggaggg  300
accaaggtgg  agatcaaa

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<210> 390

<211> 121

<212> PRT

<213> Mus musculus

<400> 390

Glu 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 Phe Asp Ile Lys Asp Tyr
 20 25 30
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
 50 55 60
 Pro Gly Lys Val Thr Met Thr Thr 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 Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 391
 <211> 363
 <212> DNA
 <213> Mus musculus

<400> 391

gaggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggctc 60
 tcctgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc 120
 cctggacaag ggcttgagtg gatcgggaagg gttgacacctg acaatgggtga gactgaattt 180
 gccccgaagt tcccgggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac 240
 atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac 300
 tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct 360
 agt 363

<210> 392
 <211> 448
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Humanized antibody sequence

<400> 392

EP 2 251 351 B1

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

50 <210> 393
 <211> 446
 <212> PRT
 <213> Artificial Sequence

55 <220>
 <223> Humanized antibody sequence

<400> 393

EP 2 251 351 B1

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

50 <210> 394
 <211> 450
 <212> PRT
 <213> Artificial Sequence

55 <220>
 <223> Humanized antibody sequence

<400> 394

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

<210> 395

<211> 446

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 395

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

<210> 396

<211> 445

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 396

5 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
 20 25 30
 Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
 50 55 60
 10 Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr 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 Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
 100 105 110
 15 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140
 20 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 25 Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
 210 215 220
 30 Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 225 230 235 240
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255
 35 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 260 265 270
 Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285
 Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
 290 295 300
 40 Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320
 Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 325 330 335
 Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350
 45 Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 355 360 365
 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380
 50 Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
 385 390 395 400
 Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 405 410 415
 Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 420 425 430
 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440 445

Claims

- 55 1. A polypeptide consisting of the amino acid sequences SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5, wherein SEQ ID NO: 2 and 4 are joined by a disulfide bond at amino acid positions 57 and 111 with reference to SEQ ID NO: 1, and SEQ ID NO: 3 and 5 are joined by (a) a disulfide bond at amino acid positions 82 and 142 with reference to SEQ ID NO: 1, and (b) a disulfide bond at amino acid positions 86 and 144 with reference to SEQ

ID NO: 1.

2. A polypeptide consisting of the amino acid sequences of SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72 and SEQ ID NO: 73, wherein SEQ ID NO: 72 and 73 are joined by a disulfide bond at amino acid positions 57 and 111 with reference to SEQ ID NO: 1, and SEQ ID NO: 70 and 71 are joined by (a) a disulfide bond at amino acid positions 82 and 142 with reference to SEQ ID NO: 1, and (b) a disulfide bond at amino acid positions 86 and 144 with reference to SEQ ID NO: 1.
3. A polypeptide consisting of a multiply truncated human sclerostin protein of SEQ ID NO: 1, wherein amino acids 1-50, 65-72, 91-100, 118-137, and 150-190 of SEQ ID NO: 1 are absent from said polypeptide, and wherein said polypeptide is obtained by tryptic digestion of human sclerostin.
4. A polypeptide consisting of a multiply truncated human sclerostin protein of SEQ ID NO: 1, wherein amino acids 1-56, 65-72, 87-110, 118-137, and 145-190 of SEQ ID NO: 1 are absent from said polypeptide, and wherein said polypeptide is obtained by tryptic digestion of human sclerostin.
5. The polypeptide of claim 3 or 4, wherein said human sclerostin is treated with trypsin to achieve complete trypsin digestion and said polypeptide is isolated by HPLC.
6. A portion of human sclerostin consisting of amino acids 51-64, 73-90, 101-117, and 138-149 of SEQ ID NO: 1, wherein said portion has all three of:
 - (a) a disulfide bond between amino acids 57 and 111;
 - (b) a disulfide bond between amino acids 82 and 142; and
 - (c) a disulfide bond between amino acids 86 and 144.
7. A portion of human sclerostin consisting of amino acids 57-64, 73-86, 111-117, and 138-144 of SEQ ID NO: 1, wherein said portion has all three of:
 - (a) a disulfide bond between amino acids 57 and 111;
 - (b) a disulfide bond between amino acids 82 and 142; and
 - (c) a disulfide bond between amino acids 86 and 144.
8. A method of producing a portion of human sclerostin, comprising the steps of:
 - (a) treating human sclerostin with trypsin to achieve complete tryptic digestion;
 - (b) collecting the tryptic digest sample having average molecular mass of 7122.0D (theoretical mass 7121.5D) or retention time of about 20.6 minutes as determined by elution from a reverse-phase HPLC column with linear gradient from 0.05% trifluoroacetic acid to 90% acetonitrile in 0.05% TFA at a flow rate of 0.2ml/min; and
 - (c) purifying said portion.
9. A non-therapeutic method of generating an antibody, comprising administering to a non-human mammal a polypeptide as defined in any one of claims 1 to 5.
10. A monoclonal antibody that binds to the polypeptide of any one of claims 1 to 5 or to a portion of human sclerostin of claim 6 or 7 and has a binding affinity for human sclerostin of less than or equal to 1×10^{-10} M.
11. The monoclonal antibody of claim 10 that is a $F(ab')_2$, Fab, Fab' or Fv fragment.
12. The monoclonal antibody of claim 10 or 11, which is a humanized antibody or a human antibody.
13. The monoclonal antibody of any one of claims 10 to 12, which binds to human sclerostin with a binding affinity less than or equal to 1×10^{-11} M or less than or equal to 1×10^{-12} M.
14. The monoclonal antibody of any one of claims 10 to 12, which binds to human sclerostin with an affinity that is at least 50, 100, 250, 500, 1000 or 10,000 times greater than the affinity for hen egg white lysozyme.
15. The monoclonal antibody of any one of claims 10 to 14, which also binds to a loop 2 epitope of SEQ ID NO: 6.

16. The monoclonal antibody of claim 10 that comprises the following set of CDR sequences:

CDR-L1 of SEQ ID NO: 284
 CDR-L2 of SEQ ID NO: 285
 CDR-L3 of SEQ ID NO: 286
 CDR-H1 of SEQ ID NO: 296
 CDR-H2 of SEQ ID NO: 297
 CDR-H3 of SEQ ID NO: 298.

17. The monoclonal antibody of any one of claims 10 to 16, which increases at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength in a mammal, or which blocks the inhibitory effect of sclerostin in a cell-based mineralization assay.

18. The monoclonal antibody of any one of claims 10 to 17 for use in a method of treating osteopenia, osteoporosis or bone loss caused by achondroplasia, cleidocranial dysostosis, enchondromatosis, fibrous dysplasia, Gaucher's Disease, hypophosphatemic rickets, Marfan's syndrome, multiple hereditary exostoses, neurofibromatosis, osteogenesis imperfecta, osteopoikilosis, sclerotic lesions, pseudoarthrosis, pyogenic osteomyelitis, periodontal disease, anti-epileptic drug induced bone loss, primary and secondary hyperparathyroidism, familial hyperparathyroidism syndromes, weightlessness induced bone loss, osteoporosis in men, postmenopausal bone loss, osteoarthritis, renal osteodystrophy, infiltrative disorders of bone, oral bone loss, osteonecrosis of the jaw, juvenile Paget's disease, melorheostosis, metabolic bone diseases, mastocytosis, sickle cell anemia/disease, organ transplant related bone loss, kidney transplant related bone loss, systemic lupus erythematosus, ankylosing spondylitis, epilepsy, juvenile arthritides, thalassemia, mucopolysaccharidoses, fabry disease, turner syndrome, Down Syndrome, Klinefelter Syndrome, leprosy, Perthes' Disease, adolescent idiopathic scoliosis, infantile onset multi-system inflammatory disease, Winchester Syndrome, Menkes Disease, Wilson's Disease, ischemic bone disease (such as Legg-Calve-Perthes disease, regional migratory osteoporosis), anemic states, conditions caused by steroids, glucocorticoid-induced bone loss, heparin-induced bone loss, bone marrow disorders, scurvy, malnutrition, calcium deficiency, idiopathic osteopenia or osteoporosis, congenital osteopenia or osteoporosis, alcoholism, chronic liver disease, postmenopausal state, chronic inflammatory conditions, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, inflammatory colitis, Crohn's disease, oligomenorrhea, amenorrhea, pregnancy, diabetes mellitus, hyperthyroidism, thyroid disorders, parathyroid disorders, Cushing's disease, acromegaly, hypogonadism, immobilization or disuse, reflex sympathetic dystrophy syndrome, regional osteoporosis, osteomalacia, bone loss associated with joint replacement, HIV-associated bone loss, bone loss associated with loss of growth hormone, bone loss associated with cystic fibrosis, fibrous dysplasia, chemotherapy-associated bone loss, tumor induced bone loss, cancer-related bone loss, hormone-ablative bone loss, multiple myeloma, drug-induced bone loss, anorexia nervosa, disease associated facial bone loss, disease associated cranial bone loss, disease associated bone loss of the jaw, disease associated bone loss of the skull, or bone loss associated with space travel.

19. The monoclonal antibody of any one of claims 10 to 17 for use in treating osteoporosis or osteopenia.

20. The monoclonal antibody of any one of claims 10 to 17, for use in a method of improving outcomes in orthopedic procedures, dental procedures, implant surgery, joint replacement, bone grafting, bone cosmetic surgery or bone repair such as fracture healing, nonunion healing, delayed union healing or facial reconstruction.

Patentansprüche

1. Polypeptid bestehend aus den Aminosäuresequenzen SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 und SEQ ID NO: 5, wobei SEQ ID NO: 2 und 4 durch eine Disulfidbindung an Aminosäurepositionen 57 und 111 in Bezug auf SEQ ID NO: 1 verbunden sind und SEQ ID: 3 und 5 durch (a) eine Disulfidbindung an Aminosäurepositionen 82 und 142 in Bezug auf SEQ ID NO: 1 und (b) eine Disulfidbindung an Aminosäurepositionen 86 und 144 in Bezug auf SEQ ID NO: 1 verbunden sind.

2. Polypeptid bestehend aus den Aminosäuresequenzen SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72 und SEQ ID NO: 73, wobei SEQ ID NO: 72 und 73 durch eine Disulfidbindung an Aminosäurepositionen 57 und 111 in Bezug auf SEQ ID NO: 1 verbunden sind und SEQ ID: 70 und 71 durch (a) eine Disulfidbindung an Aminosäurepositionen 82 und 142 in Bezug auf SEQ ID NO: 1 und (b) eine Disulfidbindung an Aminosäurepositionen 86 und 144 in Bezug auf SEQ ID NO: 1 verbunden sind.

EP 2 251 351 B1

3. Polypeptid bestehend aus einem mehrfach verkürzten humanen Sclerostinprotein von SEQ ID NO: 1, wobei Aminosäuren 1-50, 65-72, 91-100, 118-137 und 150-190 von SEQ ID NO: 1 an dem Polypeptid fehlen und wobei das Polypeptid durch tryptischen Verdau von humanem Sclerostin erhalten wird.
- 5 4. Polypeptid bestehend aus einem mehrfach verkürzten humanen Sclerostinprotein von SEQ ID NO: 1, wobei Aminosäuren 1-56, 65-72, 87-110, 118-137 und 145-190 von SEQ ID NO: 1 an dem Polypeptid fehlen und wobei das Polypeptid durch tryptischen Verdau von humanem Sclerostin erhalten wird.
- 10 5. Polypeptid nach Anspruch 3 oder 4, wobei das humane Sclerostin mit Trypsin behandelt wird, um einen vollständigen Trypsinverdau zu erreichen, und das Polypeptid durch Hochleistungsflüssigkeitschromatographie (HPLC) isoliert wird.
- 15 6. Abschnitt von humanem Sclerostin bestehend aus Aminosäuren 51-64, 73-90, 101-117 und 138-149 von SEQ ID NO: 1, wobei der Abschnitt alle folgenden drei aufweist:
- (a) eine Disulfidbindung zwischen Aminosäuren 57 und 111;
(b) eine Disulfidbindung zwischen Aminosäuren 82 und 142; und
(c) eine Disulfidbindung zwischen Aminosäuren 86 und 144.
- 20 7. Abschnitt von humanem Sclerostin bestehend aus Aminosäuren 57-64, 73-86, 111-117 und 138-144 von SEQ ID NO: 1, wobei der Abschnitt alle folgenden drei aufweist:
- (a) eine Disulfidbindung zwischen Aminosäuren 57 und 111;
(b) eine Disulfidbindung zwischen Aminosäuren 82 und 142; und
25 (c) eine Disulfidbindung zwischen Aminosäuren 86 und 144.
8. Verfahren zum Herstellen eines Abschnitts von humanem Sclerostin, welches die folgenden Schritte umfasst:
- (a) Behandeln von humanem Sclerostin mit Trypsin, um vollständigen tryptischen Verdau zu erreichen;
30 (b) Entnahme der Probe tryptischen Verdaust mit einer mittleren Molekülmasse von 7122,0 D (theoretische Masse 7121,5 D) oder Verweilzeit von etwa 20,6 Minuten, bestimmt durch Elektrophorese aus einer Umkehrphase-HPLC-Säule mit linearem Gradienten von 0,05% Trifluoressigsäure zu 90% Acetonitril in 0,05% TFA bei einem Durchsatz von 0,2 ml/min; und
(c) Reinigen des Abschnitts.
- 35 9. Nichttherapeutisches Verfahren zum Erzeugen eines Antikörpers, welches das Verabreichen eines Polypeptids nach einem der Ansprüche 1 bis 5 an einen nichthumanen Säuger umfasst.
- 40 10. Monoklonaler Antikörper, der an das Polypeptid nach einem der Ansprüche 1 bis 5 oder an einen Abschnitt von humanem Sclerostin nach Anspruch 6 oder 7 bindet und eine Bindungsaffinität für humanes Sclerostin von kleiner oder gleich 1×10^{-10} M aufweist.
11. Monoklonaler Antikörper nach Anspruch 1, der ein $F(ab')_2$ -, Fab-, Fab'- oder Fv-Fragment ist.
- 45 12. Monoklonaler Antikörper nach Anspruch 10 oder 11, der ein humanisierter Antikörper oder ein humaner Antikörper ist.
13. Monoklonaler Antikörper nach einem der Ansprüche 10 bis 12, welcher mit einer Bindungsaffinität von kleiner oder gleich 1×10^{-11} M oder kleiner oder gleich 1×10^{-12} M an humanes Sclerostin bindet.
- 50 14. Monoklonaler Antikörper nach einem der Ansprüche 10 bis 12, welcher an humanes Sclerostin mit einer Affinität bindet, die mindestens um das 50-, 100-, 250-, 500-, 1000- oder 10.000-fache größer als die Affinität für Hühner-eiweiß-Lysozym ist.
- 55 15. Monoklonaler Antikörper nach einem der Ansprüche 10 bis 14, welcher auch an ein Loop-2-Epitop von SEQ ID NO: 6 bindet.
16. Monoklonaler Antikörper nach Anspruch 10, welcher den folgenden Satz von CDR-Sequenzen umfasst:

CDR-L1 von SEQ ID NO: 284
 CDR-L2 von SEQ ID NO: 285
 CDR-L3 von SEQ ID NO: 286
 CDR-H1 von SEQ ID NO: 296
 CDR-H2 von SEQ ID NO: 297
 CDR-H3 von SEQ ID NO: 298.

17. Monoklonaler Antikörper nach einem der Ansprüche 10 bis 16, welcher mindestens eines von Knochenbildung, Knochenmineraldichte, Knochenmineralgehalt, Knochenmasse, Knochenqualität und Knochenfestigkeit in einem Säuger steigert oder welcher die hemmende Wirkung von Sclerostin in einem zellbasierten Mineralisierungsassay blockiert.
18. Monoklonaler Antikörper nach einem der Ansprüche 10 bis 17 zur Verwendung bei einem Verfahren zum Behandeln von Osteopenie, Osteoporose oder Knochenverlust verursacht durch Achondroplasie, kleidokranialer Dysostose, Enchondromatose, fibröser Dysplasie, Morbus Gaucher, hypophosphatämischer Rachitis, Marfan-Syndrom, multiplen hereditären Exostosen, Neurofibromatose, Osteogenesis imperfecta, Osteopoikilose, sklerotischen Läsionen, Pseudoarthrose, pyogener Osteomyelitis, Parodontose, durch Antiepileptika induziertem Knochenverlust, primärem und sekundärem Hyperparathyreoidismus, familiären Hyperparathyreoidismussyndromen, durch Schwerelosigkeit induziertem Knochenverlust, Osteoporose bei Männern, postmenopausalem Knochenverlust, Osteoarthritis, renaler Osteodystrophy, infiltrativen Knochenkrankungen, oralem Knochenverlust, Osteonekrose des Kieferknochens, jugendlicher Paget-Erkrankung, Melorheostose, metabolischen Knochenkrankungen, Mastozytose, Sichelzellenanämie/-erkrankung, organtransplantationsbedingtem Knochenverlust, nierentransplantationsbedingtem Knochenverlust, systemischem Lupus erythematosus, ankylosierender Spondylitis, Epilepsie, juvenilen Arthritiden, Thalassemie, Mucopolysaccharidosen, Morbus Fabry, Turner-Syndrom, Down-Syndrom, Klinefelter-Syndrom, Lepra, Morbus Perthes, adoleszenter idiopathischer Skoliose, frühkindlich einsetzender entzündlicher Multi-System-Erkrankung, Winchester-Syndrom, Morbus Menkes, Morbus Wilson, ischämischer Knochenkrankung (wie etwa Morbus Legg-Calve-Perthes, regionaler migratorischer Osteoporose), anämischen Zuständen, durch Steroide bedingten Zuständen, glucocorticoid-induziertem Knochenverlust, heparin-induziertem Knochenverlust, Knochenmarkserkrankungen, Skorbut, Fehlernährung, Calciummangel, ideopathischer Osteopenie oder Osteoporose, kongenitaler Osteopenie oder Osteoporose, Alkoholismus, chronischer Lebererkrankung, postmenopausalem Zustand, chronischen Entzündungszuständen, rheumatoider Arthritis, entzündlicher Darmerkrankung, Colitis ulcerosa, entzündlicher Colitis, Morbus Crohn, Oligomenorrhoe, Amenorrhoe, Schwangerschaft, Diabetes mellitus, Schilddrüsenüberfunktion, Schilddrüsenkrankungen, Nebenschilddrüsenkrankungen, Morbus Cushing, Akromegalie, Hypogonadismus, Immobilisierung oder Inaktivität, reflex-sympathetischem Dystrophiesyndrom, regionaler Osteoporose, Osteomalazie, Knochenverlust in Verbindung mit Gelenkersatz, HIV-bedingtem Knochenverlust, Knochenverlust bedingt durch Verlust von Wachstumshormon, Knochenverlust bedingt durch zystische Fibrose, fibröser Dysplasie, chemotherapie-bedingtem Knochenverlust, tumor-induziertem Knochenverlust, krebsbedingtem Knochenverlust, hormon-ablativem Knochenverlust, multiplen Myelom, arzneimittel-induziertem Knochenverlust, Anorexia nervosa, Erkrankung in Verbindung mit Verlust von facialem Knochen, Erkrankung in Verbindung mit cranialem Knochenverlust, Erkrankung in Verbindung mit Knochenverlust des Kieferknochens, Erkrankung in Verbindung mit Knochenverlust des Schädels oder Knochenverlust bedingt durch Raumfahrt.
19. Monoklonaler Antikörper nach einem der Ansprüche 10 bis 17 zur Verwendung beim Behandeln von Osteoporose oder Osteopenie.
20. Monoklonaler Antikörper nach einem der Ansprüche 10 bis 17 zur Verwendung beim Verbessern der Ergebnisse bei orthopädischen Eingriffen, zahnmedizinischen Eingriffen, Implantatoperation, Gelenkersatz, Knochentransplantation, kosmetischer Knochenchirurgie oder Knochenreparatur wie etwa Frakturheilung, Pseudoarthrose-Heilung, verlangsamter Knochenheilung oder Gesichtsrekonstruktion.

Revendications

1. Polypeptide constitué des séquences d'acides aminés SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, et SEQ ID NO: 5, SEQ ID NO: 2 et 4 étant reliées par un pont disulfure aux positions des acides aminés 57 et 111 en référence à SEQ ID NO: 1, et SEQ ID NO: 3 et 5 étant reliées par (a) un pont disulfure aux positions des acides aminés 82 et 142 en référence à SEQ ID NO: 1, et (b) un pont disulfure aux positions des acides aminés 86 et 144 en référence à SEQ ID NO: 1.

EP 2 251 351 B1

- 5 2. Polypeptide constitué des séquences d'acides aminés de SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72 et SEQ ID NO: 73, SEQ ID NO: 72 et 73 étant reliées par un pont disulfure aux positions des acides aminés 57 et 111 en référence à SEQ ID NO: 1, et SEQ ID NO: 70 et 71 étant reliées par (a) un pont disulfure aux positions des acides aminés 82 et 142 en référence à SEQ ID NO: 1, et (b) un pont disulfure aux positions des acides aminés 86 et 144 en référence à SEQ ID NO: 1.
- 10 3. Polypeptide constitué d'une multiplicité de protéines de sclérostine humaine tronquées de SEQ ID NO: 1, les acides aminés 1-50, 65-72, 91-100, 118-137, et 150-190 de SEQ ID NO: 1 étant absents dudit polypeptide, et ledit polypeptide étant obtenu par digestion trypsique de la sclérostine humaine.
- 15 4. Polypeptide constitué d'une multiplicité de protéines de sclérostine humaine tronquées de SEQ ID NO: 1, les acides aminés 1-56, 65-72, 87-110, 118-137, et 145-190 de SEQ ID NO: 1 étant absents dudit polypeptide, et ledit polypeptide étant obtenu par digestion trypsique de la sclérostine humaine.
- 20 5. Polypeptide de la revendication 3 ou 4, ladite sclérostine humaine étant traitée avec la trypsine pour obtenir une digestion complète par la trypsine et ledit peptide étant isolé par HPLC.
6. Portion de sclérostine humaine constituée des acides aminés 51-64, 73-90, 101-117, et 138-149 de SEQ ID NO: 1, ladite portion possédant l'ensemble des trois éléments suivants :
- (a) un pont disulfure entre les acides aminés 57 et 111 ;
(b) un pont disulfure entre les acides aminés 82 et 142 ; et
(c) un pont disulfure entre les acides aminés 86 et 144.
- 25 7. Portion de sclérostine humaine constituée des acides aminés 57-64, 73-86, 111-117, et 138-144 de SEQ ID NO: 1, ladite portion possédant l'ensemble des trois éléments suivants :
- (a) un pont disulfure entre les acides aminés 57 et 111 ;
(b) un pont disulfure entre les acides aminés 82 et 142 ; et
(c) un pont disulfure entre les acides aminés 86 et 144.
- 30 8. Procédé de production d'une portion de sclérostine humaine, comprenant les étapes consistant à :
- (a) traiter la sclérostine humaine avec la trypsine pour obtenir une digestion trypsique complète ;
(b) collecter l'échantillon de digestat trypsique ayant une masse moléculaire moyenne de 7122,0 D (masse théorique 7121,5 D) ou un temps de rétention d'environ 20,6 minutes tel que déterminé par élution à partir d'une colonne HPLC en phase inverse avec un gradient linéaire d'acide trifluoroacétique 0,05 % - acétonitrile 90 % dans ATF 0,05 % avec un débit de 0,2 ml/min ; et
(c) purifier ladite portion.
- 35 9. Procédé non thérapeutique pour générer un anticorps, comprenant l'administration à un mammifère non humain d'un polypeptide tel que défini dans l'une quelconque des revendications 1 à 5.
- 40 10. Anticorps monoclonal qui se lie au polypeptide de l'une quelconque des revendications 1 à 5 ou à une portion de sclérostine humaine de la revendication 6 ou 7 et a une affinité de liaison pour la sclérostine humaine inférieure ou égale à 1×10^{-10} M.
- 45 11. Anticorps monoclonal selon la revendication 10 qui est un fragment $F(ab')_2$, Fab, Fab' ou Fv.
- 50 12. Anticorps monoclonal selon la revendication 10 ou 11, qui est un anticorps humanisé ou un anticorps humain.
13. Anticorps monoclonal selon l'une quelconque des revendications 10 à 12, qui se lie à la sclérostine humaine avec une affinité de liaison inférieure ou égale à 1×10^{-11} M ou inférieure ou égale à 1×10^{-12} M.
- 55 14. Anticorps monoclonal selon l'une quelconque des revendications 10 à 12, qui se lie à la sclérostine humaine avec une affinité qui est au moins 50, 100, 250, 500, 1000 ou 10 000 fois supérieure à l'affinité pour le lysozyme de blanc d'oeuf de poule.

15. Anticorps monoclonal selon l'une quelconque des revendications 10 à 14, qui se lie également à un épitope de la boucle 2 de SEQ ID NO: 6.

16. Anticorps monoclonal selon la revendication 10 comprenant l'ensemble suivant de séquences de CDR :

CDR-L1 de SEQ ID NO: 284
 CDR-L2 de SEQ ID NO: 285
 CDR-L3 de SEQ ID NO: 286
 CDR-H1 de SEQ ID NO: 296
 CDR-H2 de SEQ ID NO: 297
 CDR-H3 de SEQ ID NO: 298.

17. Anticorps monoclonal selon l'une quelconque des revendications 10 à 16, qui augmente au moins l'un parmi la formation osseuse, la densité minérale osseuse, le contenu minéral osseux, la masse osseuse, la qualité osseuse et la résistance osseuse chez un mammifère, ou qui bloque l'effet inhibiteur de la sclérostine dans un essai de minéralisation sur cellules.

18. Anticorps monoclonal selon l'une quelconque des revendications 10 à 17 pour utilisation dans un procédé de traitement de l'ostéopénie, ostéoporose ou perte osseuse dont les causes sont les suivantes : achondroplasie, dysostose cléidocrânienne, enchondromatose, dysplasie fibreuse, maladie de Gaucher, rachitisme hypophosphatémique, syndrome de Marfan, maladie héréditaire des exostoses multiples, neurofibromatose, ostéogénèse imparfaite, ostéopoïkilose, lésions sclérotiques, pseudoarthrose, ostéomyélite à pyogène, maladie périodontique, pertes osseuses induites par un médicament anti-épileptique, hyperparathyroïdie primaire ou secondaire, syndromes d'hyperparathyroïdie familiale, pertes osseuses induites par l'apésanteur, ostéoporose masculine, pertes osseuses post-ménopause, arthrose, ostéodystrophie rénale, troubles infiltrants des os, pertes osseuses buccales, ostéonécrose de la mâchoire, maladie de Paget juvénile, mélorhéostose, maladies osseuses métaboliques, mastocytose, drépanocytose/anémie à hématies falciformes, pertes osseuses liées à une transplantation d'organe, pertes osseuses liées à une transplantation de rein, lupus érythémateux aigu disséminé, spondylarthrite ankylosante, épilepsie, arthrite juvénile, thalassémie, mucopolysaccharidoses, maladie de Fabry, syndrome de Turner, syndrome de Down, syndrome de Klinefelter, lèpre, maladie de Perthes, scoliose idiopathique de l'adolescent, maladie inflammatoire multisystémique néonatale, syndrome de Winchester, maladie de Menkes, maladie de Wilson, maladie osseuse ischémique (telle que la maladie de Legg-Calvé-Perthes, l'ostéoporose migratoire régionale), états anémiques, états provoqués par les stéroïdes, pertes osseuses induites par des glucocorticoïdes, pertes osseuses induites par l'héparine, troubles de la moelle osseuse, scorbut, malnutrition, déficit en calcium, ostéopénie ou ostéoporose idiopathique, ostéopénie ou ostéoporose congénitale, alcoolisme, maladie chronique du foie, état de post-ménopause, états inflammatoires chroniques, polyarthrite rhumatoïde, affections intestinales inflammatoires, colite ulcéreuse, colite inflammatoire, maladie de Crohn, oligoménorrhée, aménorrhée, grossesse, diabète sucré, hyperthyroïdie, troubles thyroïdiens, troubles parathyroïdiens, maladie de Cushing, acromégalie, hypogonadisme, immobilisation ou inactivité, syndrome de dystrophie sympathique réflexe, ostéoporose régionale, ostéomalacie, pertes osseuses associées à la pose d'une prothèse articulaire, pertes osseuses associées au VIH, pertes osseuses associées à un déficit en hormone de croissance, pertes osseuses associées à la mucoviscidose, dysplasie fibreuse, pertes osseuses associées à une chimiothérapie, pertes osseuses induites par une tumeur, pertes osseuses liées à un cancer, pertes osseuses liées à l'ablation d'un organe sécréteur d'hormones, myélome multiple, pertes osseuses induites par un médicament, anorexie mentale, pertes osseuses faciales associées à une maladie, pertes osseuses crâniennes associées à une maladie, pertes osseuses de la mâchoire associées à une maladie, pertes osseuses du crâne associées à une maladie, ou pertes osseuses associées à un voyage spatial.

19. Anticorps monoclonal selon l'une quelconque des revendications 10 à 17 pour utilisation dans le traitement de l'ostéoporose ou de l'ostéopénie.

20. Anticorps monoclonal selon l'une quelconque des revendications 10 à 17, pour utilisation dans un procédé d'amélioration des résultats d'interventions orthopédiques, d'interventions dentaires, de chirurgie d'implantation, de pose de prothèse articulaire, de greffes osseuses, de chirurgie osseuse cosmétique ou de réparation osseuse telle que guérison de fracture, guérison d'une absence de soudure osseuse, guérison d'un retard de soudure osseuse ou reconstruction faciale.

A.

1 AQVLTQTPAS VSAAVGGTVT INCQSSQSVY DNNWLAWFQQ KPGQPPKLLI
 51 YDASDLASGV PSRFSGSG TQFTLTISGV QCADAATYYC QGAYNDVIYA
 101 FGGGTEVVVK RTDAAPTISI FPPSSEQLTS GGASVVCFLN NFYPKDINVK
 151 WKIDGSERON GVLNSWTDQD SKDSTYSMSS TLLTLTKDEYE RHNSYTCEAT
 201 HKTSTSPIVK SFNRNEC

B.

1 QSLEESGGRL VTPGTPLTLT CTASGFSLS YMNWVRQAP GEGLEWIGTI
 51 DSGGRTDYAS WAKGRFTISR TSTTMDLKMT SLTTGDTARY FCARNWNLMG
 101 QGTLVTVSSA STKGPSVYPL APGSAAQTNM MVTLGCLVKG YFPEPVTVTW
 151 NSGSLSSGVH TFPVVLQSDI YTLSSSVTVP SSTWPSETVT CNVAHPASST
 201 KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLITIT LTPKVTVCVV
 251 DISKDDPEVQ FSWFVDDVEV HTAQTPREE QFNSTFRSVS ELPIMHQDWL
 301 NGKEFKCRVN SAAFPAPTEK TISKTKGRPK APQVYTIPPP KEQMAKDKVS
 351 LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMNTNGSY FVYSKLNQVK
 401 SNWEAGNTFT CSVLHEGLHN HHTKSLSHS PGK

Figure 1

A.

1 QIVLTQSPTI VSASGGEKVT LICSASSSVS FVDWFQOKPG TSPKRWIYRT
 51 SNLGFVGPAP FSGGGSGTSH SLTISRMEAE DAATYYCQQR STYPTTFGAG
 101 TKLELKRA DA APTVSIFFPS SEQLTSGGAS VVCFLNFFYP KDINVVKWKID
 151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
 201 TSPIVKSFNR NEC

B.

1 QVTLKESGPG ILQPSQTLISL TCSFSGFSL TSGMGVGVWIR HPSGKNLEWL
 51 AHIWWDVKKR YNPVLKSRLT ISKDTSNSQV FLKIANVDTA DTATYYCARI
 101 EDFDYDEEYY AMDYWGQGT S VIVSSAKTTP PSVYPLAPGS AAQTNSMVTLL
 151 GCLVKGYFPE PVTVTWNSSGS LSSGVHTFPA VLQSDLYTLL SSVTVPSSTW
 201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
 251 DVLTTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
 301 TFRSVSELP I MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
 351 YTIPTPEQOM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIIM
 401 DTDGSYFVYS KLNVOQSNWE AGNTFTCSVL HEGLHNHHTTE KSLSHSPGK

Figure 2

A.

```

1 DIVLTQSPAS LTVSLGLRAT ISCKASQSD YDGDSYMNY QQKPGQPPKL
51 LIYAASNLES GIPARFSGNG SGTDFTLNIH PVEEEDAVTY YCQQSNEDPW
101 TFGGGTKLEI KRADAAPTYS IFPPSSEQLT SGASVVCFL NNFYPKDINV
151 KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS STLTLTKEY ERHNSYTCEA
201 THKTSTSPIV KSFNRNEC

```

B.

```

1 EVQLQQSGPE LVKPGTSVKM SCKASGYTFT DCYMNWVKQS HGKSLEWIGD
51 INPFNGGTTY NQFKGKATL TVDKSSSTAY MQLNSLTSDS SAVYYCARSH
101 YYFDGRVPWD AMDYWGQGS VTVSSAKTTP PSVYPLAPGS AAQTNSMVTL
151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
251 DVLITITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQENS
301 TFRSVSELPV MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIIM
401 DTDGSYFIYS KLVNQKSNWE AGNTFTCSVL HEGLHNHHTTE KSLSHSPGK

```

Figure 3

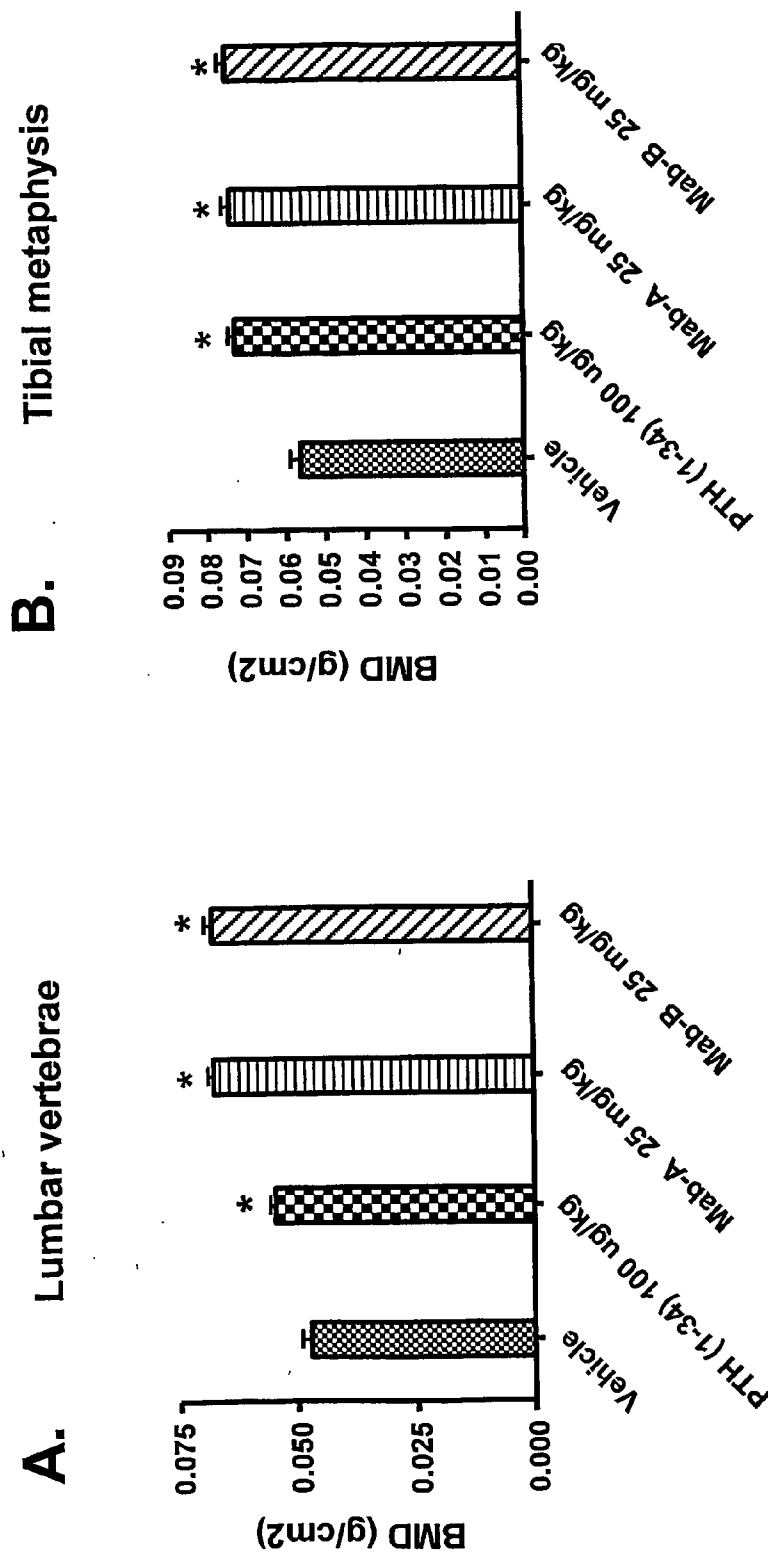
A.

1 DVQMIQSPSS LSASLGDIVT MTCQASQGTS INLNWFQQKP GKAPKLLIYG
 51 SSNLEDGVPS RFSGSRYGTD FTLTISSELED EDLATYFCLQ HSYLPYTFGG
 101 GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFNNFY PKDINVKWKI
 151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC

B.

1 EVQLQQSGPE LVTPGASVKI SCKASGYTFT DHYMSWVKQS HGKSLEWIGD
 51 INPYSGETTY NQKFKGTATL TVDKSSSIAY MEIRGLTSED SAVYYCARD
 101 YDASPFAYWG QGTLVTVSAA KTTPPSVYPL AFGSAAQNTS MVTLGCLVKG
 151 YFPEPVTVTW NSGSLSSGVH TFPVAVLQSDL YTLSSSVTVP SSTWPSETVT
 201 CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLITIT
 251 LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQIQPREE QFNSTFRSVS
 301 ELPIMHQDWL NGKEFKCRVN SPAFFAPIEK TISKTKGRP KAPQVYTIPPP
 351 KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY
 401 FIYSKLNQVK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK

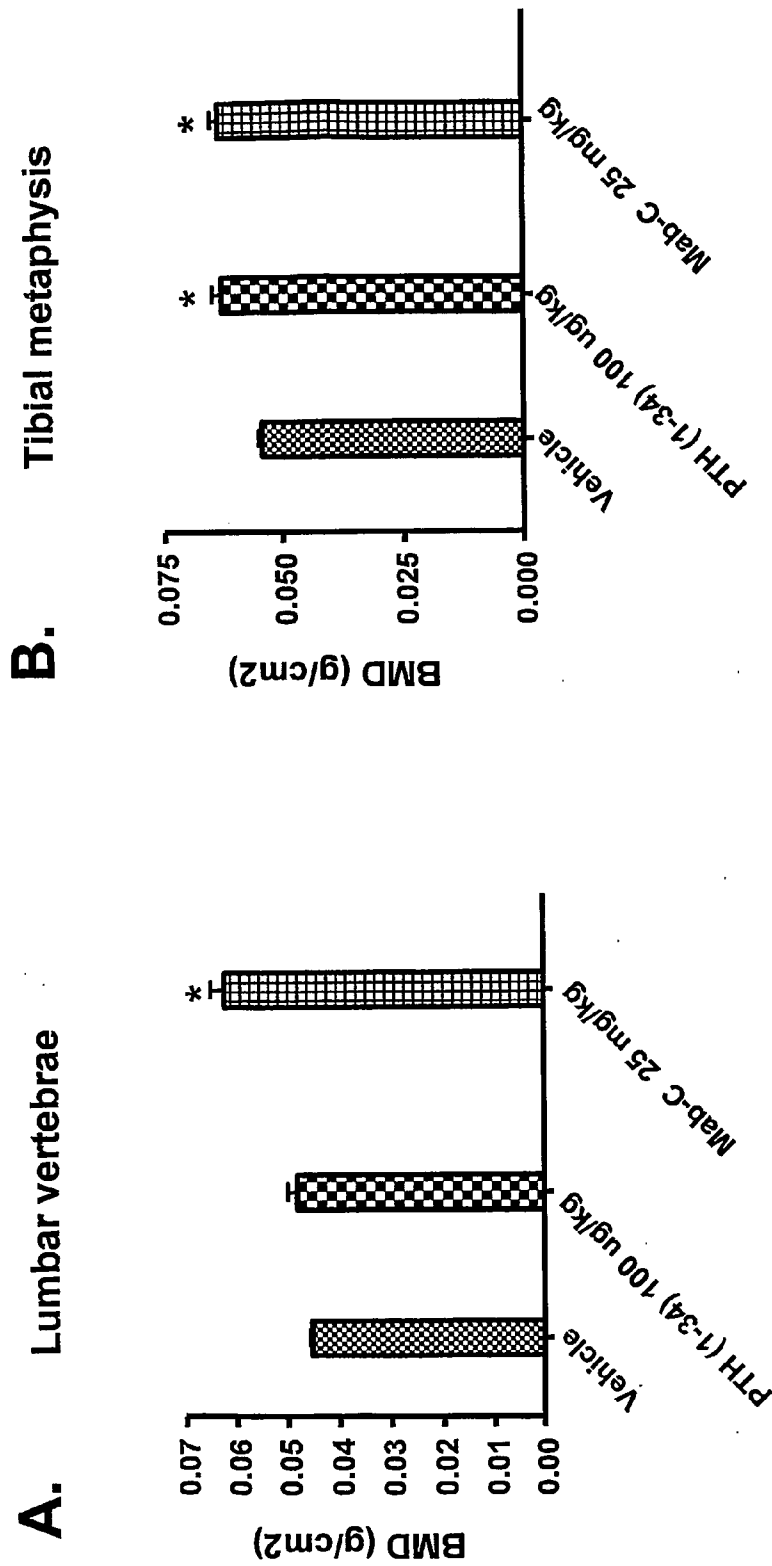
Figure 4



* = statistically significantly different from Vehicle

Error bars = Mean $\pm$ standard deviation

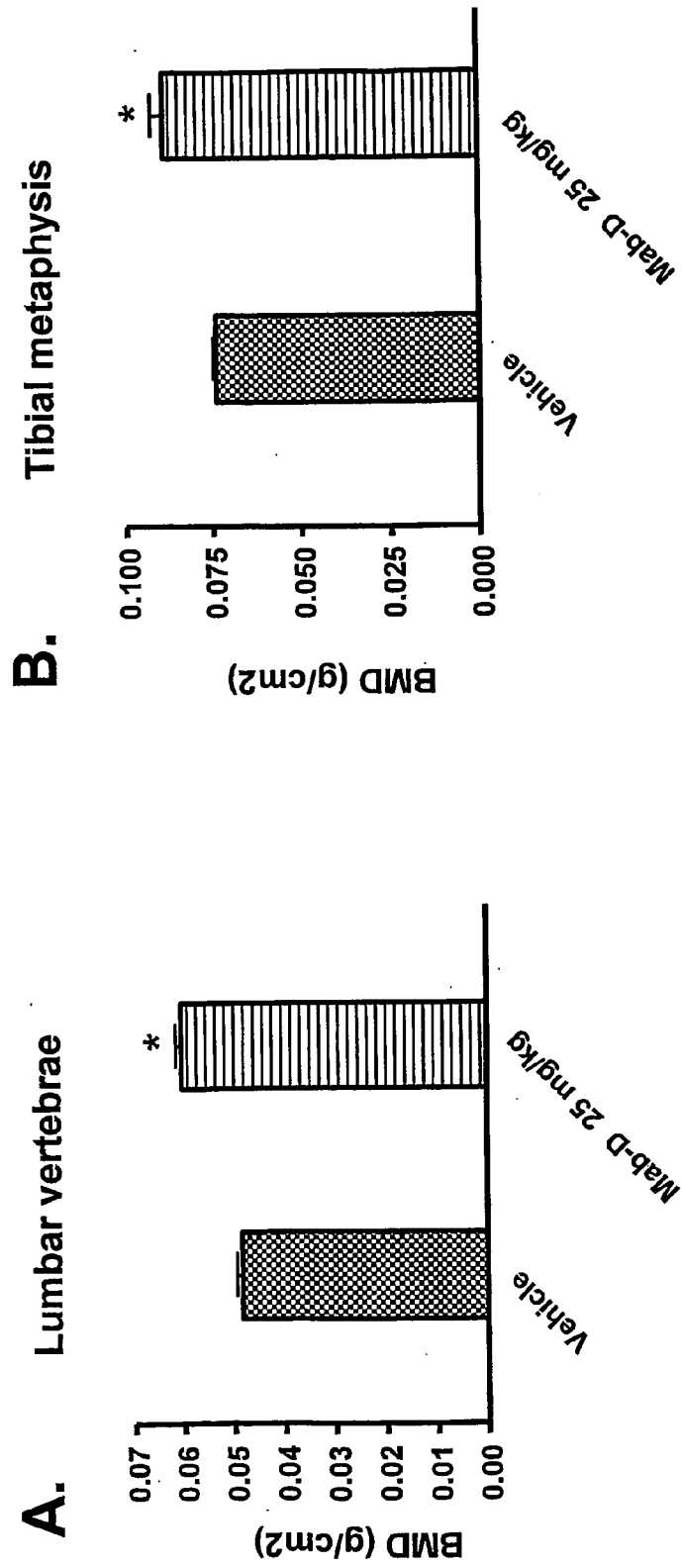
Figure 5



* = statistically significantly different from Vehicle

Error bars = Mean +/- standard deviation

Figure 6



* = statistically significantly different from Vehicle
 Error bars = Mean +/- standard deviation

Figure 7

1 QGWQAFKND A TEIIPELGEY PEPPELENN KTMNRAENG RPPHHPFETK
 51 DVSEYSCREL HFTRYVTDGP CRSKPVTEL VCSGQCGPAR LLPNAIGRGK
 101 WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF
 151 HNQSELKDFG TEAARPQKGR KPRPRARSAK ANQAELENAY

EP 2 251 351 B1

1 CAGGGGTGGC AGCGTTCAA GAATGATGCC ACGAAATCA TCCCCGAGCT
 51 CGGAGAGTAC CCGAGCCTC CACCGGAGCT GGAGAACAA AGACCATGA
 101 ACCGGCGGA GAACGGAGG CGGCTCCCC ACCACCCCTT TGAGACCAAA
 151 GACGTGTCCG AGTACAGCTG CCGGAGCTG CACTTCACCC GCTACGTGAC
 201 CGATGGGCCG TGCCGCAGCG CCAAGCCGGT CACCGAGCTG GTGTGCTCCG
 251 GCCAGTGCGG CCGGCGCGC CTGCTGCCCCA ACGCCATCGG CCGCGGCAAG
 301 TGGTGGCGAC CTAGTGGGC CCACTTCCGC TGCATCCCCG ACCGCTACCG
 351 CGCGCAGCGC GTGCAGCTGC TGTGTCCCGG TGGTGAGGCG CCGCGCGCGC
 401 GCAAGGTGCG CCTGGTGGCC TCGTGCAAGT GCAAGCGCCT CACCCGCTTC
 451 CACAACCACT CGGAGCTCAA GGAATTGGG ACCGAGGCGG CTCGGCCGCA
 501 GAAGGGCCCG AAGCCGCGG CCGCGCCCCG GAGCGCCAAA GCCAACCAAG
 551 CCGAGCTGGA GAACGCCTAC

Figure 8

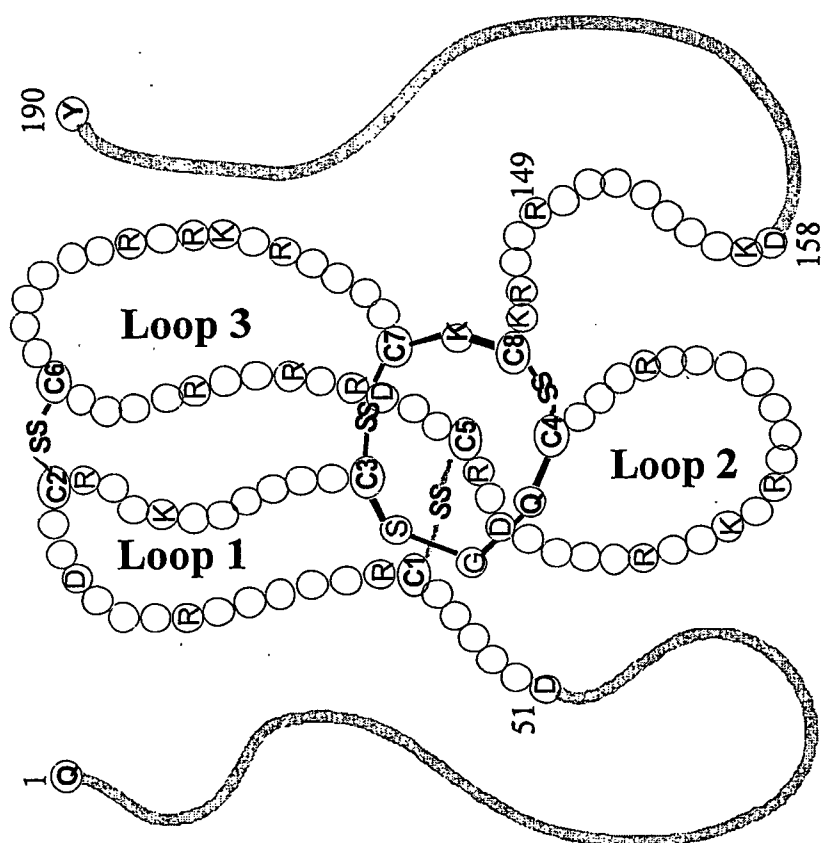


Figure 9

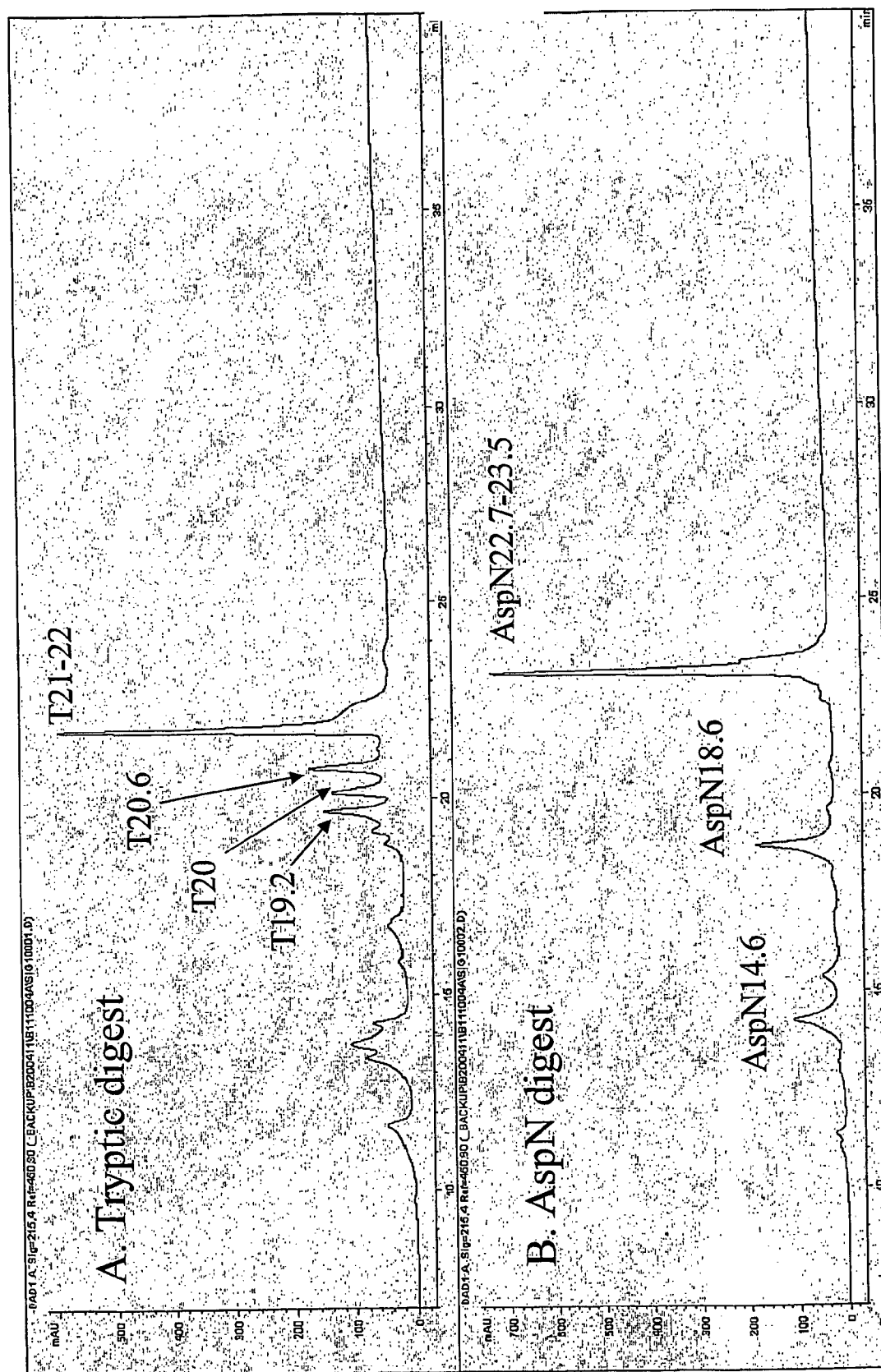


Figure 10

Peptides	Seq.pos.	Obs. Mass	Sequence
T19.2	65-72	2146.34	1. YVTDGP CR (910) <u>C2</u>
	121-132	(2145.8)	2. VQLLCPGGEA PR (1239) <u>C6</u>
T20	51-90	9620.8 (MALDI); 9638.41 (ESI-MS)	1. DVSEYSCREL HFTRYVTDGP CRSAKPVTEL
		(4419.1)	VCSGQCGPAR
T20.6	104-149	(5226.2)	2. PSGPDR CIPDRYRAQR VQLLCPGGEA
			PRARKVRLVA SCKCKRLT R
T20.6		7105.7 (MALDI); 7122.0 (ESI-MS)	
	51-64	3944.5	1. DVSEYSCREL HFTR (1740.9) <u>C1</u>
	101-117		2. WWRPSGPPFR CIPDRYR (2206.6) <u>C5</u>
	73-90	3177.0	3. SAKPVTELVC SGQCGPAR (1802.2) <u>C3, C4</u>
	138-149		4. LVASCKCKRL TR (1378.5) <u>C7, C8</u>
T21-22	51-90	10,147 (MALDI); 10170.3 (ESI-MS)	1. DVSEYSCREL HFTRYVTDGP CRSAKPVTEL
		(4419.1)	VCSGQCGPAR
	101-149	(5754.8)	2. WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA
			PRARKVRLVA SCKCKRLTR

Figure 11

Peptides	Seq.pos.	Obs.Mass	Sequence
AspN14.6	34-47	1245.5	ENGGRPPHHPF
	12-25	1585.4	EIIPELGFYP EPPP
	158-184	2964.5	DFGTEAARPQ KGRKPRPRAR SAKANQA
AspN18.6	9-50		DATEIIPELG EYPEPPPELE NNKTMNRAEN
			GGRPPHHPFE TK (Glycopeptide)
AspN22.7-23.5	51-154	11,740	DVSEYSCREL HFTRYVTDGP CRSAKPVTEL
			VCSGQCGPAR LLPNAIGRGK WWRPSGPDFR
			CIPDRYRAQR VQLLCPGGEA PRARKVRLVA
			SCKCKRLTRF HNQS

Figure 12

1 QGWQAFKND A TEIIPELGEY PEPPPELENN KTMNRAENGG RPPHHPFETK
51 DVSEYSCREL HFTRYVTDGP **CRSAKPVT**EL **VCSGQCGPAR** LLPNAIGRGK
101 WWRPSGPDER **CIPDRYRAQR** VQLLCPGGEA PRARKVRLVA **SCCKRLTRF**
151 HNOSELKDFG TEAARPQKGR KPRPRARS AK ANQAELENAY

Diagram illustrating the domain architecture of the protein, showing the arrangement of loops and transmembrane domains (T20, T20.6, T21-22) across the sequence. The protein is divided into three main regions: Loop 1 (residues 1-50), Loop 2 (residues 51-100), and Loop 3 (residues 101-150). The transmembrane domains are labeled T20, T20.6, and T21-22. The sequence is shown with the corresponding domain boundaries indicated by vertical lines and labels (C1, C2, C3, C4, C5, C6, C7, C8).

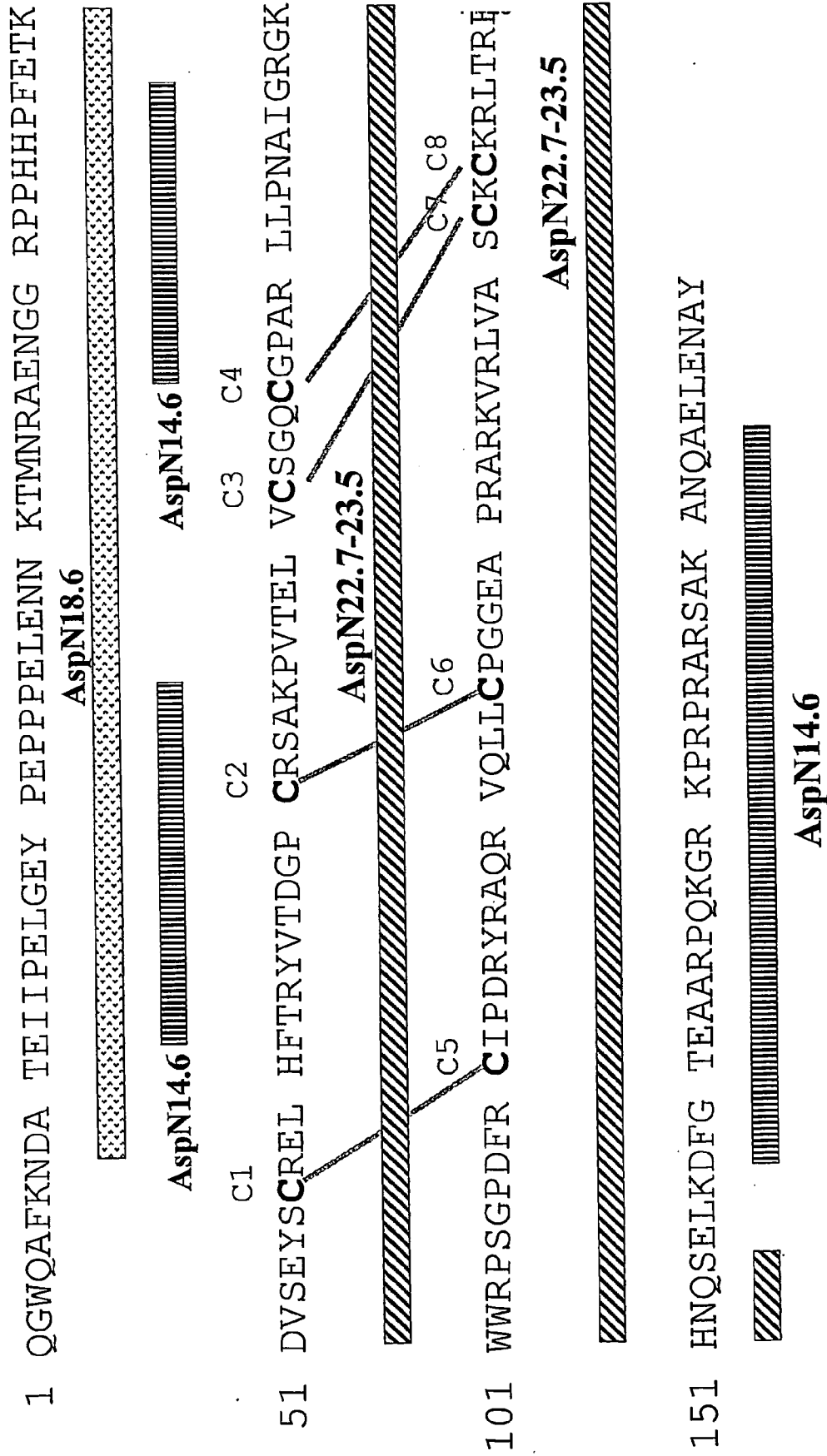


Figure 14

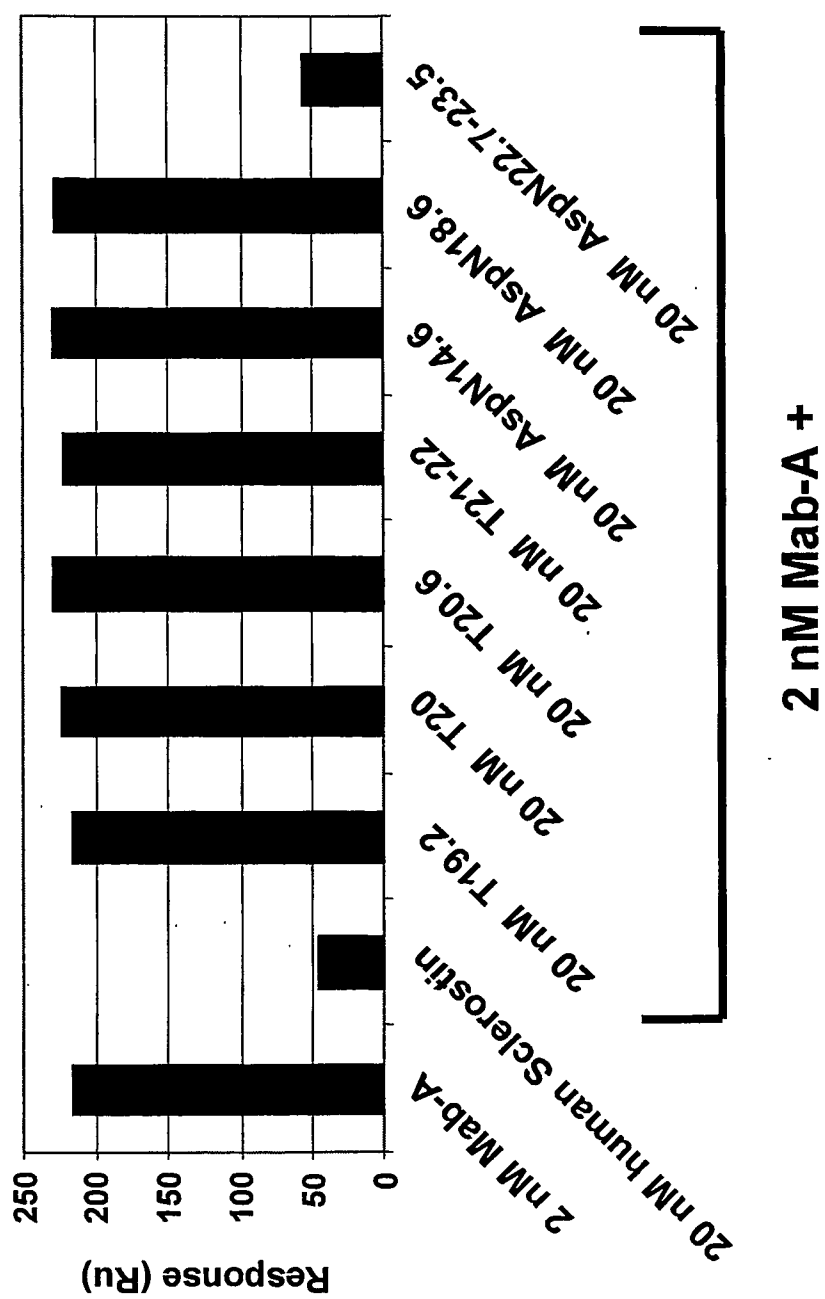


Figure 15

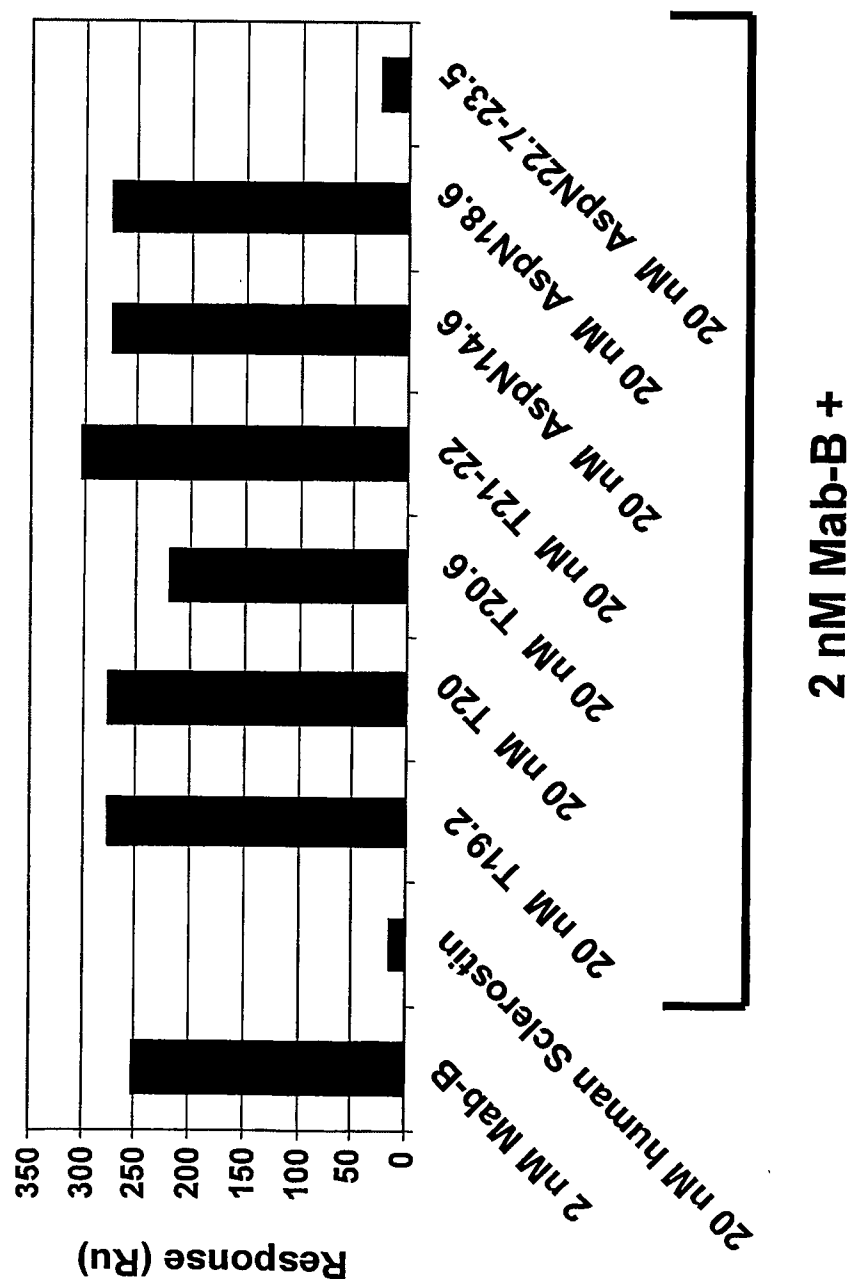


Figure 16

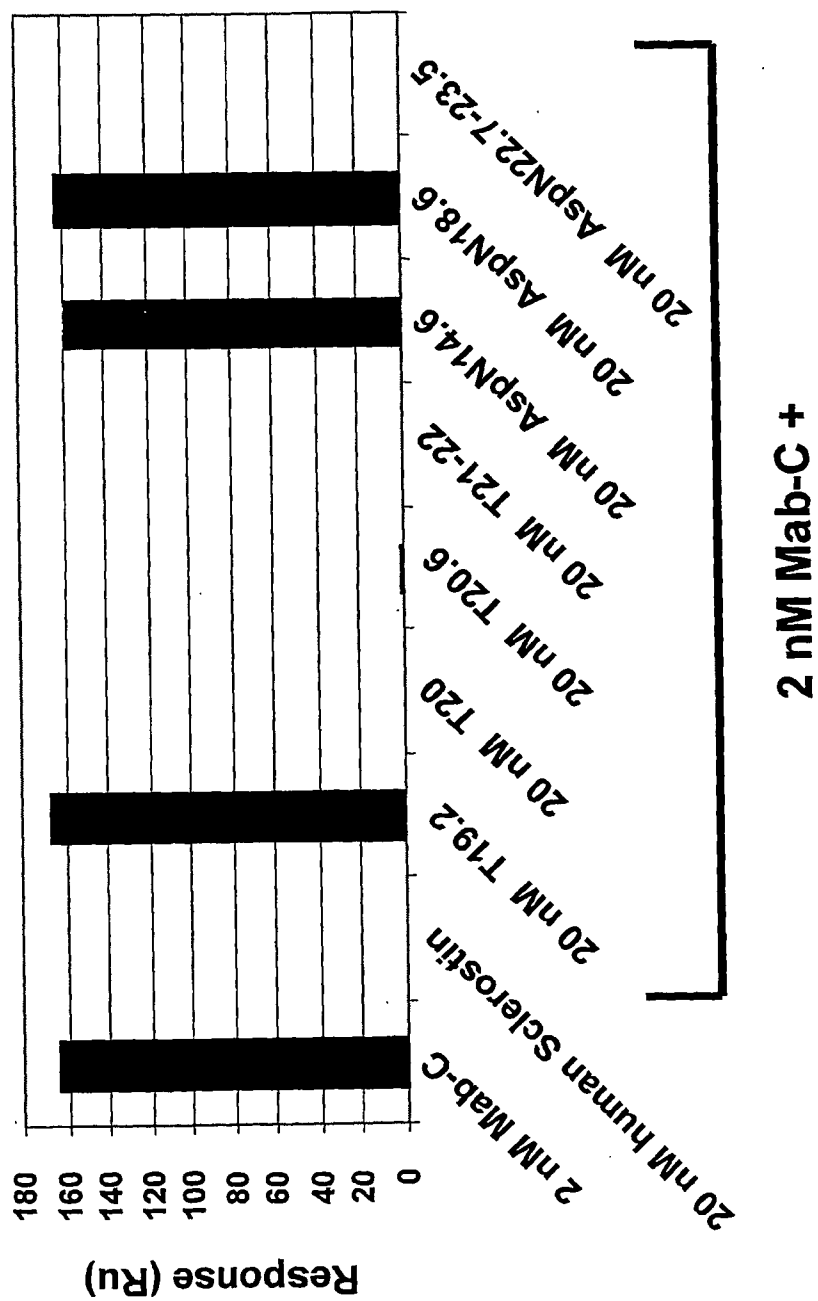


Figure 17

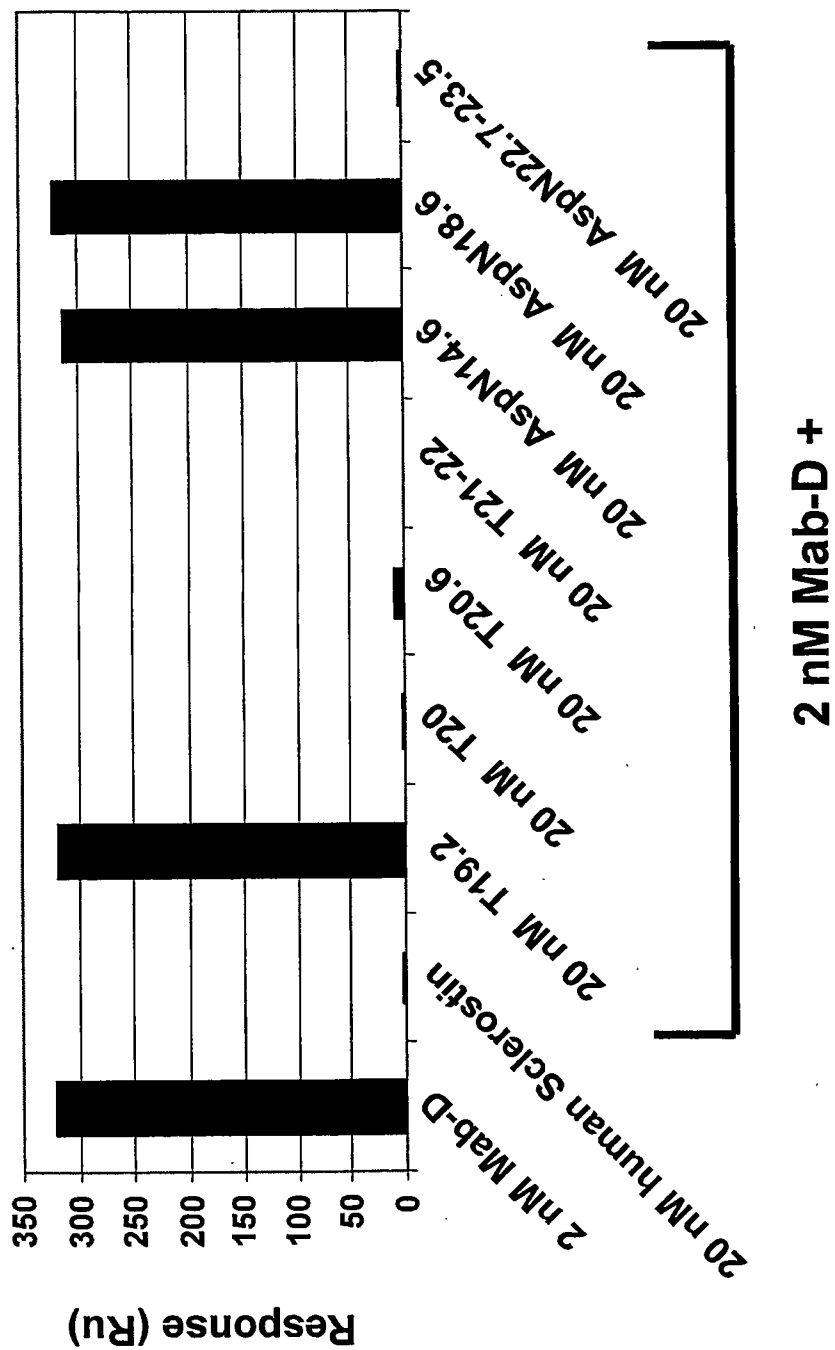


Figure 18

A. Loop 2 epitope for Mab-A and Mab-B

C4GPARLLPNAIGRGKWWRPSPGPDFRC5
└──────────┘

B. T20.6 epitope for Mab-C and Mab-D

DVSEYSC1RELHFTR SAKPVTLC3SGQC4GPAR
WWRPSPGDFRC5IPDRYR LVASC7KC8KRLTR

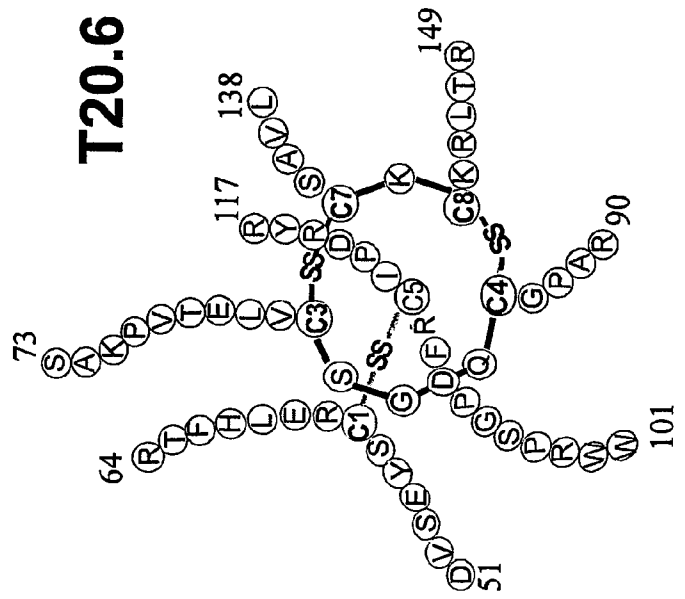


Figure 19

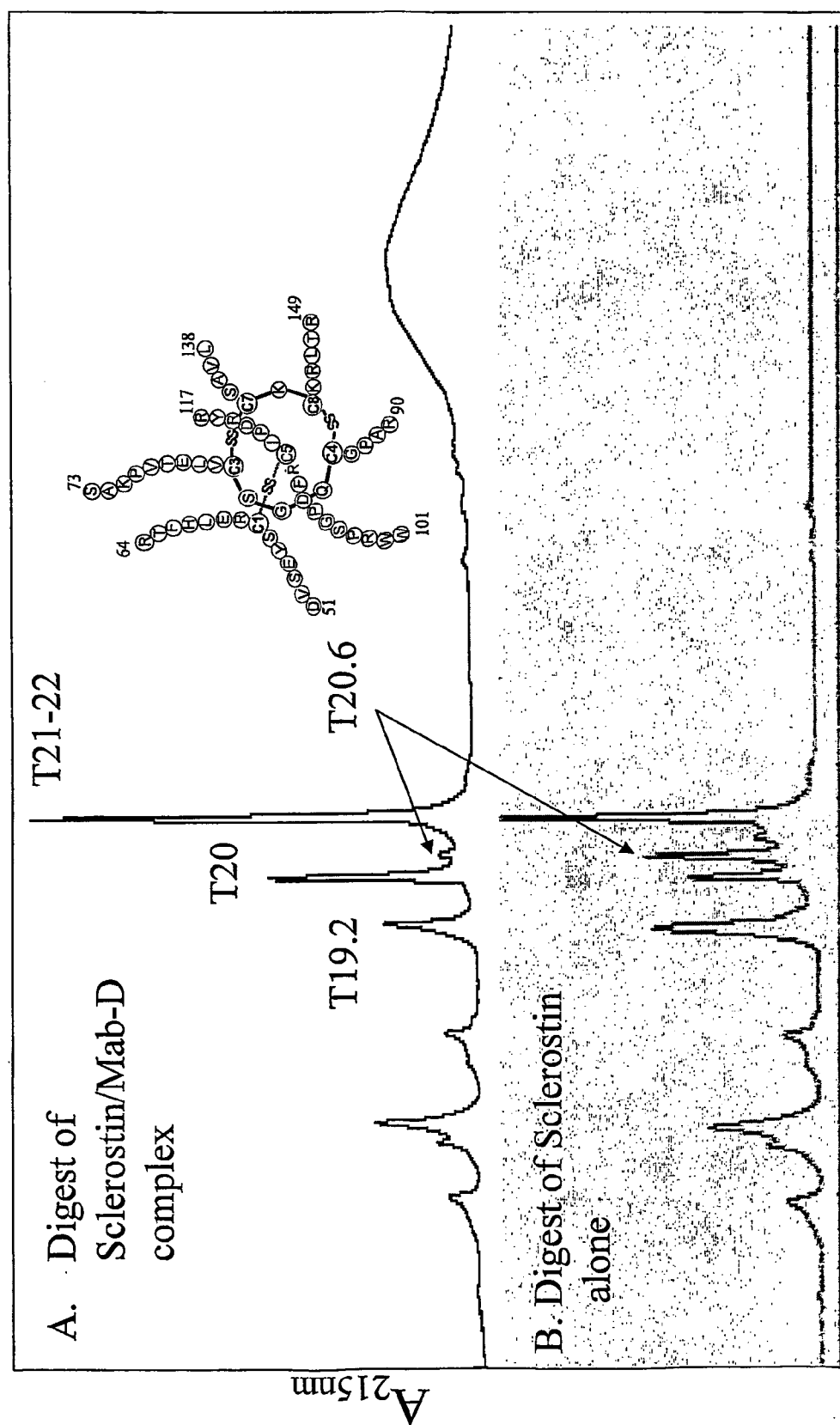


Figure 20

“T20.6 derivative 1 (cystine-knot + 4 arms)” epitope for Mab-D

C1RELHFTR SAKPVT~~EL~~VC3SGQC4
C5IPDRYR LVASC7KC8

“T20.6 derivative 1
(cystine-knot + 4 arms)”

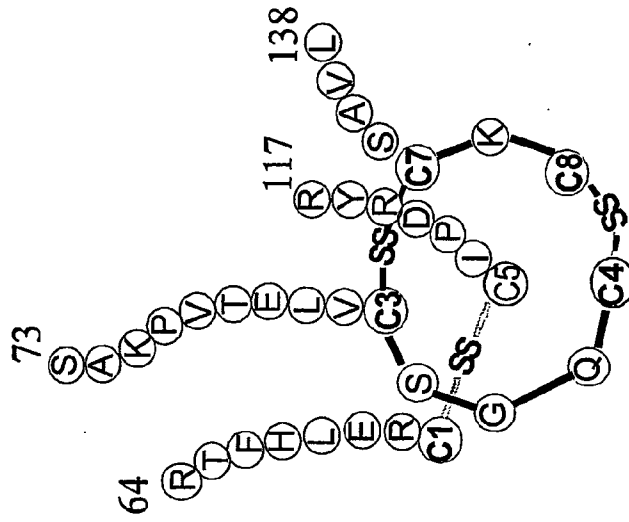
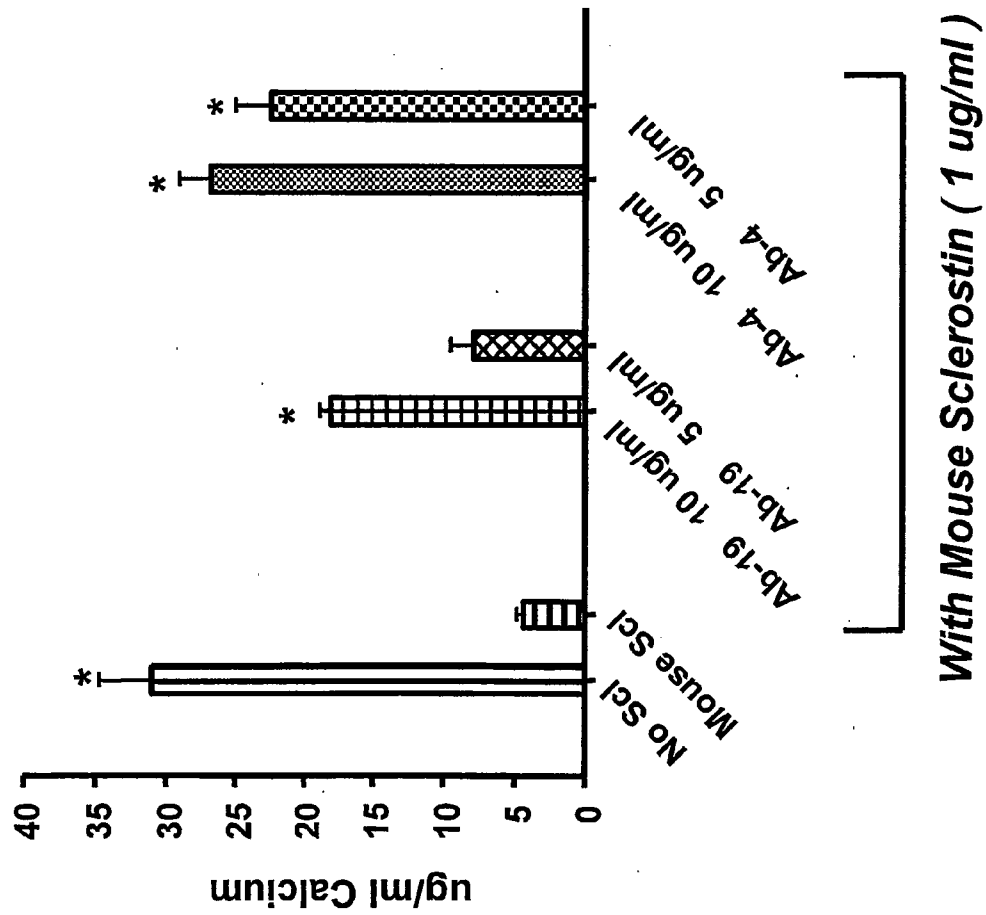


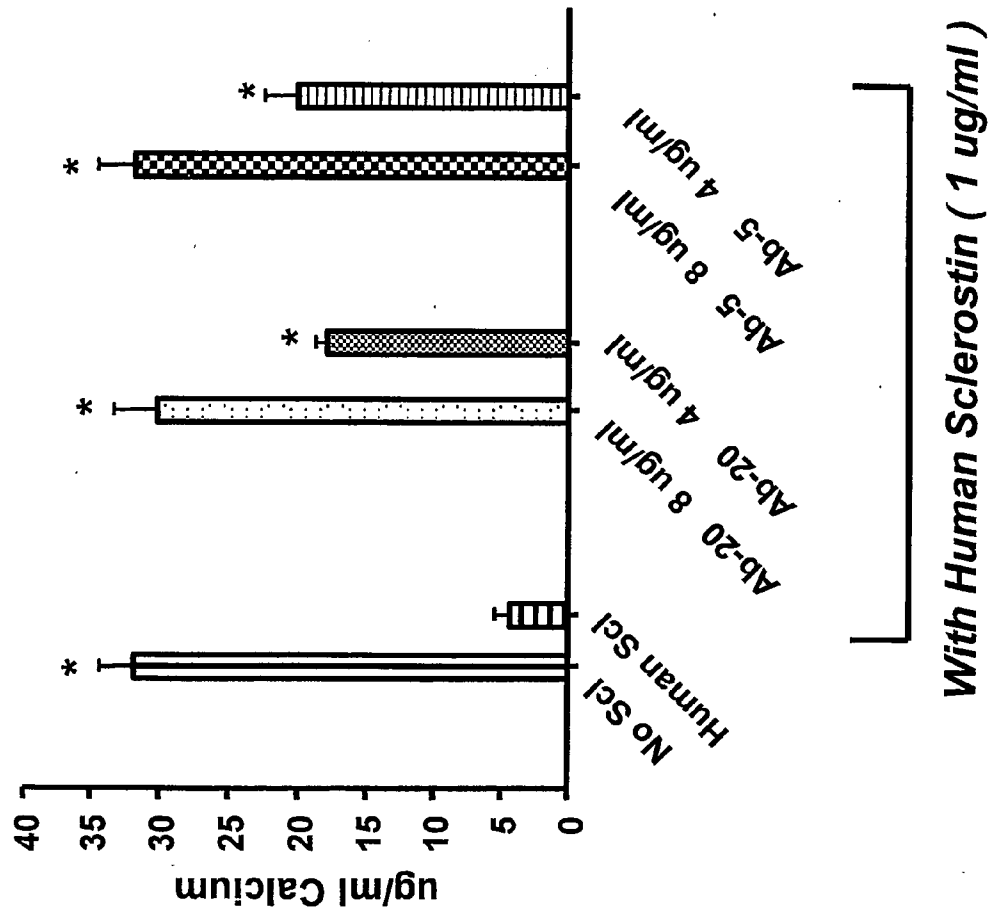
Figure 21



* = statistically significantly different from Mouse Scl group.

Error bars = Mean +/- SEM

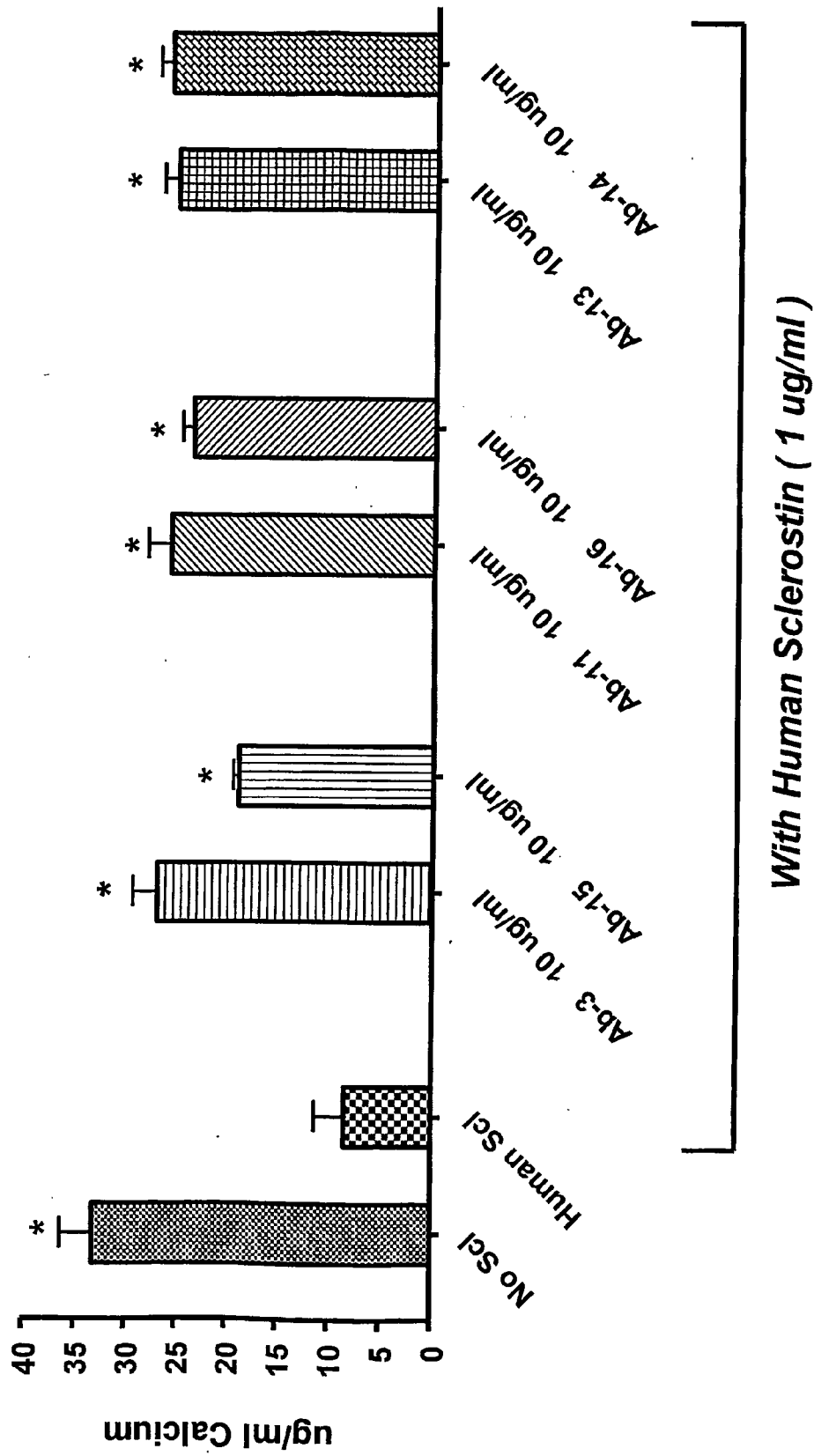
Figure 22



* = statistically significantly different from Human Scl group.

Error bars = Mean +/- SEM

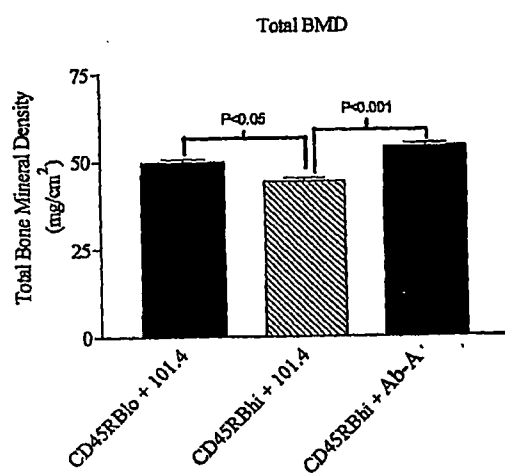
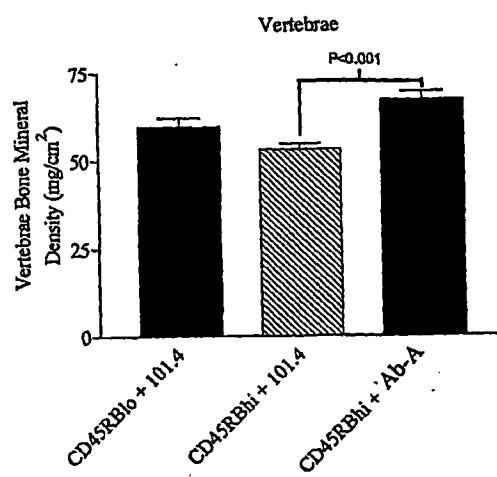
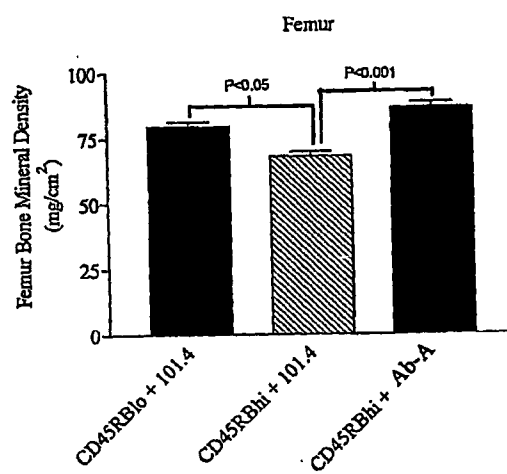
Figure 23



* = statistically significantly different from Human Scl group.

Error bars = Mean +/- SEM

Figure 24

**A****B****C**

REFERENCES CITED IN THE DESCRIPTION

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Szklerosztin építópok

Szabadalmi igénypontok

1. Egy 2. számú szekvenciájú, 3. számú szekvenciájú, 4. számú szekvenciájú, és 5. számú szekvenciájú aminosavszekvenciából álló polipeptid, ahol a 2. és 4. számú szekvencia egy diszulfidkötéssel kapcsolódik az 1. számú szekvencia szerinti 57. és 111. aminosav-helyzetek között, és a 3. és 5. számú szekvencia (a) egy diszulfidkötéssel kapcsolódik az 1. számú szekvencia szerinti 82. és 142. aminosav-helyzetek között, és (b) egy diszulfidkötéssel kapcsolódik az 1. számú szekvencia szerinti 86. és 144. aminosav-helyzetek között.

2. Egy 70. számú szekvenciájú, 71. számú szekvenciájú, 72. számú szekvenciájú, és 73. számú szekvenciájú aminosavszekvenciából álló polipeptid, ahol a 72. és 73. számú szekvencia egy diszulfidkötéssel kapcsolódik az 1. számú szekvencia szerinti 57. és 111. aminosav-helyzetek között, és a 70. és 71. számú szekvencia (a) egy diszulfidkötéssel kapcsolódik az 1. számú szekvencia szerinti 82. és 142. aminosav-helyzetek között, és (b) egy diszulfidkötéssel kapcsolódik az 1. számú szekvencia szerinti 86. és 144. aminosav-helyzetek között.

3. Egy 1. számú szekvenciájú többszörösen csonkolt humán szklerosztin proteinből álló polipeptid, ahol az 1. számú szekvencia 1-50, 65-72, 91-100, 118-137, és 150-190. aminosavai hiányoznak a polipeptidből, és ahol a polipeptid a humán szklerosztin tripszines emésztése útján előállított.

4. Egy 1. számú szekvenciájú többszörösen csonkolt humán szklerosztin proteinből álló polipeptid, ahol az 1. számú szekvencia 1-56, 65-72, 87-110, 118-137, és 145-190. aminosavai hiányoznak a polipeptidből, és ahol a polipeptid a humán szklerosztin tripszines emésztése útján előállított.

5. A 3. vagy 4. igénypont szerinti polipeptid, ahol a humán szklerosztin tripszinnel kezelt, teljes tripszines emésztés elérésére, és a polipeptid HPLC-vel izolált.

6. Az 1. számú szekvencia 51-64, 73-90, 101-117, és 138-149. aminosavaiból álló humán szklerosztin egy része, ahol a rész:

- (a) az 57. és 111. aminosavak között egy diszulfidkötést;
- (b) a 82. és 142. aminosavak között egy diszulfidkötést; és
- (c) a 86. és 144. aminosavak között egy diszulfidkötést egyaránt tartalmaz.

7. Az 1. számú szekvencia 57-64, 73-86, 111-117, és 138-144. aminosavaiból álló humán szklerosztin egy része, ahol a rész:

- (a) az 57. és 111. aminosavak között egy diszulfidkötést;
- (b) a 82. és 142. aminosavak között egy diszulfidkötést; és
- (c) a 86. és 144. aminosavak között egy diszulfidkötést egyaránt tartalmaz.

8. Eljárás a humán szklerosztin egy részének előállítására, melynek során:

- (a) humán szklerosztint tripszinnel kezelünk, teljes tripszines emésztés eléréséig;
- (b) a 7122.0 D (elméleti tömeg 7121.5 D) átlagos molekulatömegű vagy reverz-fázisú HPLC oszlopkromatográfiában 0,05% trifluorecetsav - 90 % acetonitril 0,05 %-os TFA-ban rendszerben 0,2 ml/perc sebességű elúció során körülbelül 20,6 perc retenció idejű tripszines emésztési mintát összegyűjtjük; és
- (c) a részt tisztítjuk.

9. Nem-terápiás módszer egy antitest létrehozására, melynek során egy nem-humán emlősnek egy 1-5. igénypontok bármelyike szerinti polipeptidet adagolunk.

10. Egy monoklonális antitest, mely kötődik az 1-5. igénypontok bármelyike szerinti polipeptidhez vagy a 6. vagy 7. igénypont szerinti humán szklerosztin részhez, és a humán szklerosztin elleni kötődési affinitása 1×10^{-10} M vagy annál kisebb.

11. A 10. igénypont szerinti monoklonális antitest, mely egy $F(ab')_2$, Fab, Fab' vagy Fv fragmens.

12. A 10. vagy 11. igénypont szerinti monoklonális antitest, mely egy humanizált antitest vagy egy humán antitest.

13. A 10-12. igénypontok bármelyike szerinti monoklonális antitest, mely a humán szklerosztinhoz 1×10^{-11} M vagy annál kisebb vagy 1×10^{-12} M vagy annál kisebb kötődési affinitással kötődik.

14. A 10-12. igénypontok bármelyike szerinti monoklonális antitest, mely a humán szklerosztinhoz legalább 50-, 100-, 250-, 500-, 1000- vagy 10,000-szeresen nagyobb kötődési affinitással kötődik a tyúktöjás fehérje lizozimhoz

15. A 10-14. igénypontok bármelyike szerinti monoklonális antitest, mely ugyancsak kötődik a 6. számú szekvencia egy loop 2 epitópjához.

16. A 10. igénypont szerinti monoklonális antitest mely magába foglalja a következő CDR szekvenciákat:

284. számú szekvenciájú CDR-L1

285. számú szekvenciájú CDR-L2

286. számú szekvenciájú CDR-L3

296. számú szekvenciájú CDR-H1

297. számú szekvenciájú CDR-H2

298. számú szekvenciájú CDR-H3.

17. A 10-16. igénypontok bármelyike szerinti monoklonális antitest, mely a csontképződés, csont ásványi anyag sűrűsége, csont ásványi anyag tartalma, csonttömeg, csontminőség és csontszilárdság legalább egyikét fokozza emlősbén, vagy gátolja a szklerosztin gátló hatását egy sejt-alapú mineralizációs meghatározásban.

18. A 10-17. igénypontok bármelyike szerinti monoklonális antitest chondroplasia, cleidocranialis dysostosis, enchondromatosis, rostos dysplasia, Gaucher-kór, hypophosphatemiás angolkór, Marfan-szindróma, többszörös öröklődő exostosisok, neurofibromatosis, osteogenesis imperfecta, osteopoikilosis, szklerotikus leziók, pseudoarthrosis, pyogen osteomyelitis, periodontális betegség legalább egyike által okozott abnormális növekedése vagy fejlődése, antiepileptikus drug által kiváltott csontvesztés, primer és szekunder hyperparathyroidismus, familiális hyperparathyroidismus szindrómák, súlytalanság által kiváltott csontvesztés, osteo-porosis férfiakban, postmenopausális csontvesztés, osteoarthritis, renális osteo-dystrophia, a csont infiltratív rendellenességei, orális csont-

vesztés, az állkapocs osteo-necrosis, juvenilis Paget-kór, melorheostosis, metabolikus csontrendellenességek, mastocytosis, sarlósejtes vérszegénység/betegség, szervátültetéssel kapcsolatos csont-vesztés, veseátültetéssel kapcsolatos csontvesztés, systematicus lupus erythematosus, ankylosisos spondylitis, epilepszia, juvenilis arthritidek, thalassemia, mucopolysaccharidosisok, Fabry-szindróma, Turner-szindróma, Down-szindróma, Klinefelter-szindróma, lepra, Perthes-szindróma, serdülőkori idiopathias scoliosis, csecsemőkorban fellépő multi-system gyulladásos betegség, Winchester-szindróma, Menkes-szindróma, Wilson-kór, ischemiás csontbetegés (így Legg-Calve-Perthes-kór, regionalis migratio osteoporosis), anemiás állapotok, szteroidok által kiváltott állapotok, glükokortikoid által kiváltott csontvesztés, heparin-indukált csontvesztés, csontvelő betegségek, skorbut, alultápláltság, kalciumhiány, alkoholizmus, krónikus májbetegség, postmenopausalis állapot, krónikus gyulladásos állapotok, rheumatoid arthritis, gyulladásos bélbetegség, ulceratív colitis, gyulladásos colitis, Crohn-betegség, oligomenorrhea, amenorrhea, terhesség, diabetes mellitus, hyperthyroidismus, pajzsmirigy rendellenességek, parathyroid rendellenességek, Cushing-kór, acromegalia, hypogonadismus, immobilizáció vagy mozgáshiány, reflex sympathetic dystrophia szindróma, regionalis osteo-porosis, osteomalácia, ízület-pótlással kapcsolatos csontvesztés, HIV-vel társult csontvesztés, növekedési hormon vesztéssel kapcsolatos csontvesztés, cisztikus fibrózissal kapcsolatos csontvesztés, kemoterápiával kapcsolatos csontvesztés, daganat által kiváltott csontvesztés, rákkal kapcsolatos csontvesztés, hormon ablatív csontvesztés, multiple myeloma, drug által kiváltott csontvesztés, anorexia nervosa, facialis csontvesztéssel társult betegség, koponyacsont vesztéssel társult betegség, az állkapocs csontvesztésével társult betegség, a koponya csontvesztésével társult betegség, öregedéssel járó csontvesztés, öregedéssel járó facialis csontvesztés, öregedéssel járó koponyacsontvesztés, a koponya öregedéssel járó csontvesztése és úrutazással járó csontvesztés által okozott osteopenia, osteoporosis vagy csontvesztés kezelése során történő alkalmazásra.

19. A 10-17. igénypontok bármelyike szerinti monoklonális antitest osteoporosis vagy osteopenia kezelésében történő alkalmazásra.

20. A 10-17. igénypontok bármelyike szerinti monoklonális antitest ortopéd beavatkozás, fogászati beavatkozás, sebészeti implantálás, ízületi pótlás, csontátültetés, kozmetikai csontsebészet és csonthelyreállítás, így törés gyógyítás, összeforrás hiánya miatti kezelés, késlekedő összeforrás miatti kezelés és arcreekonstrukció kimenetelének javítási eljárásában történő alkalmazásra.