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Fortsættes ...

DESCRIPTION

TECHNICAL FIELD

[0001] The present invention relates generally to antibodies capable of binding to sclerostin.

BACKGROUND OF THE INVENTION

[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. 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.

[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. 70:978-982, 1995).

[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*).

[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. WO 2005/014650 discloses antibodies specific for sclerostin and methods for increasing bone mineralization.

BRIEF SUMMARY

[0007] 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 advantages described herein.

[0008] The disclosure relates to regions (epitopes) of human sclerostin recognized by the binding agents disclosed herein, methods of using these epitopes, and methods of making such epitopes.

[0009] The disclosure also relates to epitopes specific to the region of sclerostin identified as Loop 2, and binding agents which specifically bind to that region.

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

[0011] The disclosure relates to binding agents, such as antibodies, that specifically bind to sclerostin. The binding agents can be characterized by their ability to cross-block the binding of at least one antibody disclosed herein to sclerostin and/or to be cross-blocked from binding sclerostin by at least one antibody disclosed herein. The antibodies and other binding agents 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 disclosure relates to binding agents, such as antibodies, 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.

[0013] The disclosure relates to binding agents, such as antibodies, that can block the inhibitory effect of sclerostin in a cell based mineralization assay.

[0014] The disclosure further relates to polypeptide constructs comprising two, three, or four polypeptide fragments linked by at least one disulfide bond, representing a core region of the cystine-knot of sclerostin, and antibodies capable of specifically binding thereto.

[0015] The disclosure relates to methods of obtaining epitopes suitable for use as immunogens for generating, in mammals, binding agents, such as antibodies capable of binding specifically to sclerostin; in certain embodiments the binding agents generated are capable of neutralizing sclerostin activity *in vivo*.

[0016] The disclosure relates to a composition for eliciting an antibody specific for sclerostin when the composition is administered to an animal, the composition comprising a polypeptide having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, or SEQ ID NO:69.

[0017] The disclosure also relates to a composition for eliciting an antibody specific for sclerostin when the composition is administered to an animal, the composition comprising at least one polypeptide consisting essentially of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5; the composition may comprise at least two or at least three of the amino acid sequences of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5, and the composition may comprise all four of the amino acid sequences of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5.

[0018] The disclosure 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 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; the polypeptide may retain the tertiary structure of the corresponding polypeptide region of human sclerostin of SEQ ID NO:1.

[0019] The disclosure also relates to polypeptide T20.6 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 the polypeptide; this polypeptide may be obtained by tryptic digestion of human sclerostin, and the protein may be isolated by HPLC fractionation.

[0020] 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 at least one of:

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

the immunogenic portion may have at least two of these disulfide bonds; and the immunogenic portion may have all three disulfide bonds.

[0021] 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 at least one of:

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

the immunogenic portion may have at least two of these disulfide bonds; and the immunogenic portion may have all three disulfide bonds.

[0022] 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.

[0023] 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).

[0024] 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 PNAIGRVKWWRPNGPDFR (SEQ ID NO:96).

[0025] 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 KWWRPNGPDFRCIPDRYRAQRV (SEQ ID NO:97).

[0026] The disclosure relates to a method of producing an immunogenic portion of human sclerostin, comprising the steps of:

1. (a) treating human sclerostin to achieve complete tryptic digestion;
2. (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
3. (c) purifying the immunogenic portion.

[0027] The disclosure relates to a method of generating an antibody capable of specifically binding to sclerostin, comprising:

1. (a) immunizing an animal with a composition comprising a polypeptide of SEQ ID NO:6, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:96, or SEQ ID NO:97;
2. (b) collecting sera from the animal; and
3. (c) isolating from the sera an antibody capable of specifically binding to sclerostin.

[0028] The disclosure also relates to a method of generating an antibody capable of specifically binding to sclerostin, the method comprising:

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

[0029] The disclosure further relates to a method of detecting an anti-sclerostin antibody in a biological sample, comprising the steps of

1. (a) contacting the biological sample with a polypeptide consisting essentially of SEQ ID NO:6, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:96, or SEQ ID NO:97 under conditions allowing a complex to form between the antibody and the polypeptide; and
2. (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.

[0030] The disclosure also relates to a method of detecting an anti-sclerostin antibody in a biological sample, comprising the steps of

1. (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
2. (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.

[0031] The disclosure further relates to a sclerostin binding agent, such as an 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 sclerostin binding agent 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.

[0032] The disclosure further relates to a sclerostin binding agent, such as an 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.

[0033] The disclosure further relates to a sclerostin binding agent, such as 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 sclerostin binding agent 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.

[0034] The disclosure further relates to a sclerostin binding agent, such as 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.

[0035] The disclosure further relates to a binding agent, such as 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.

[0036] 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 by providing to a subject in need of such treatment an amount of an anti-sclerostin binding agent sufficient to increase at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength wherein the anti-sclerostin binding agent comprises an antibody, or sclerostin-binding fragment thereof.

[0037] 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.

[0038] Provided herein are antibodies that specifically bind to human sclerostin. The antibodies are characterized by their ability

to cross-block the binding of at least one antibody disclosed herein to human sclerostin and/or to be cross-blocked from binding human sclerostin by at least one antibody disclosed herein.

[0039] Also provided 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.

[0040] Also provided in an isolated antibody, or an antigen-binding fragment thereof, that can block the inhibitory effect of sclerostin in a cell based mineralization assay.

[0041] Also provided is a binding agent, such as 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, wherein the antibody or antigen-binding fragment thereof neutralizes sclerostin.

[0042] Also provided is a binding agent, such as 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.

[0043] Also provided are regions of human sclerostin which are important for the *in vivo* activity of the protein.

[0044] The invention provides a monoclonal antibody for use in a method of increasing at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength in a mammal and thereby treating a condition 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, wherein the monoclonal antibody (a) binds to human sclerostin with a binding affinity of less than or equal to 1×10^{-10} M and (b) cross-blocks the binding of antibody Ab-13 or Ab-14 to sclerostin and/or is cross-blocked from binding to sclerostin by antibody Ab-13 or Ab-14, wherein antibody Ab-13 has light chains of SEQ ID NO: 205 and heavy chains of SEQ ID NO: 209 and antibody Ab-14 has light chains of SEQ ID NO: 213 and heavy chains of SEQ ID NO: 217 or 393.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045]

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 µg/ml. Monoclonal antibodies were used at 10 and 5 µg/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 µg/ml. Monoclonal antibodies were used at 8 and 4 µg/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 µg/ml. Monoclonal antibodies were used at 10 µg/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

[0046] The present disclosure 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 disclosure also provides binding agents (such as antibodies) that specifically bind to sclerostin or portions of sclerostin, and uses for such binding agents. The binding agents are useful to block or impair binding of human sclerostin to one or more ligand.

[0047] 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.

[0048] 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.

[0049] Binding agents are preferably 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.

[0050] 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.

[0051] 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).

[0052] 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)).

[0053] Thus, the binding agent may comprise 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).

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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, which is hereby incorporated by reference for any purpose.

[0058] It will be appreciated that a binding agent 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 disclosure. 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.

[0059] 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.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] A number of scientific publications have been devoted to the prediction of secondary structure. See Moulton J., *Curr. Op. in Biotech.*, 7(4):422-427 (1996); Chou et al., *Biochemistry*, 13(2):222-245 (1974); Chou et al., *Biochemistry*, 11(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.

[0065] 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)).

[0066] 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.

[0067] 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.

[0068] 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. Single or multiple amino acid substitutions (e.g. conservative amino acid substitutions) may be made in the naturally-occurring sequence (e.g. in the portion of the polypeptide outside the domain(s) forming intermolecular contacts). 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).

[0069] Binding agents may be chemically bonded with polymers, lipids, or other moieties.

[0070] 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.

[0071] 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).

[0072] Binding agents 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).

[0073] 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-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 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-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 neutralizes sclerostin.

[0074] 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).

[0075] Once synthesized, the DNA encoding an antibody 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, 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). 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.

[0076] 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).

[0077] Where it is desired to improve the affinity of antibodies containing one or more of the above-mentioned CDRs, such antibodies 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., Bio/Technology, 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).

[0078] Other antibodies may be obtained by conventional immunization and cell fusion procedures as described herein and known in the art. Monoclonal antibodies 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); Picksley 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.

[0079] 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 or 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 29.1-2.9.3; 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.

[0080] 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 hypennutation 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.

[0081] 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.

[0082] 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.

[0083] 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); Altling-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).

[0084] 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*.

[0085] In a hybridoma, the variable regions of a gene expressing a monoclonal antibody of interest may be 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).

[0086] 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.

[0087] 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.

[0088] 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.

[0089] Sclerostin binding agents 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.

[0090] Binding agents may be 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 are antibodies as defined herein.

[0091] 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).

[0092] 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

[0093] 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.

[0094] The amino acid sequence of the mature form (signal peptide removed) of Ab-D light chain:

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1 DVQMISQSPSS LSASLGDIVT MTCQASOGTS INLNWFQOKP GKAPKLLIYG
51 SSNLEDGVPS RFSGSRYGTD FTLTISSLED EDLATYFCLO HSYLPYTFGG
101 GTKLEIKRAD AAPTYSIFPP SSEQLTSGGA SVYCFLNNFY PKDINVKWKI
151 DGSEKQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:7)

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[0095] Nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-D LC is as follows:

1 GATGTCCAGA TGATTCAAGTC TCCATCCTCC CTGTCTGCAT CTTTGGGAGA
 51 CATAGTCACC ATGACTTGCC AGGCAAGTCA GGGCACTAGC ATTAATTTAA
 101 ACTGGTTTCA GCAAAAACCA GGGAAAGGCTC CTAAGCTCCT GATCTATGGT
 151 TCAAGCAACT TGGAAGATGG GGTCCTCATCA AGGTTCAGTG GCAGTAGATA
 201 TGGGACAGAT TTCACTCTCA CCATCAGCAG CCTGGAGGAT GAAGATCTGG
 251 CAACCTATTT CTGTCTACAA CATAGTTATC TCCCGTACAC GTTCGGAGGG
 301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACAA CTGTATCCAT
 351 CTTCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACCTCTAC CCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCAG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID NO:8)

[0096] 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 TDFLTISL
 101 EDEDLATYFC LQHSYLPYTF GGGTKLEIKR ADAAPTYSIF PPSSEQLTSG
 151 GASVVCFLNN FYPKDNVW KIDGSEKQNG VLNSWIDQDS KDSYMSMSST
 201 LTLTKDEYER HNSYTCEATH KTSTSPIVKS FNRNEC (SEQ ID NO:9)

[0097] Nucleic acid sequence of Ab-D LC including signal peptide encoding sequence:

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

151 ACTAGCATTATTTAACTG GTTTCAGCAA AAACCAGGGA AGGCTCCTAA
 201 GCTCCTGATC TATGGTTCAA GCAACTTGGA AGATGGGGTC CCATCAAGGT
 251 TCAGTGGCAG TAGATATGGG ACAGATTICA CTCTACCAT CAGCAGCCTG
 301 GAGGATGAAG ATCTGGCAAC TTATTCTGT CTACAACATA GTTATCTCCC
 351 GTACACGTTT GGAGGGGGGA CCAAGCTGGA AATAAACGG GCTGATGCTG
 401 CACCAACTGT ATCCATCTTC CCACCATCCA GTGAGCAGTT AACATCTGGA
 451 GGTGCTCAG TCGTGTGCTT CTTGAACAAC TTCTACCCCA AAGACATCAA
 501 TGTCAGTGG AAGATTGATG GCAGTGAACG ACAAATGGC GTCCTGAACA
 551 GTTGGACTGA TCAGGACAGC AAAGACAGCA CCTACAGCAT GAGCAGCACC
 601 CTCACGTTGA CCAAGGACGA GTATGAACGA CATAACAGCT ATACCTGTGA
 651 GGCCACTCAC AAGACATCAA CTTACCCAT TGTCAGAGC TTCAACAGGA
 701 ATGAGTGTTA G (SEQ ID NO:10)

[0098] The amino acid sequence of the mature form (signal peptide removed) of Ab-D HC heavy chain is as follows:

1 EVQLQDSGPE LVTPGASVKI SCKASGYTFT ~~DHYMSWVKQS~~ HGKSLEWIGD
 51 ~~INPYSGEFTY~~ ~~NQKFKGTATL~~ TVDKSSSLAY MEIRGLTSED SAVYYCARD
 101 ~~NDASPEAYWG~~ QGILVTVSAA ~~KTPPSVYPL~~ ~~APGSAAQTN~~ ~~MVTLGCLVKG~~
 151 ~~YFPEPVTVTW~~ NSGSLSSGVH ~~TFPAVLQSDL~~ ~~YTLSSSVTVF~~ ~~SSTWPSETVT~~
 201 ~~CNVAHPASST~~ ~~KVDEKIVPRD~~ ~~CGCKPCICTV~~ ~~PEVSSVFIFP~~ ~~PKPKDVLIT~~
 251 ~~LTPKVTCTVVV~~ ~~DISKDDPEVQ~~ ~~FSWFVDDVEV~~ ~~HTAQTPREE~~ ~~QFNSTFRSVS~~
 301 ~~ELPIMHQDWL~~ ~~NGKEFKCRVN~~ ~~SPAPPAPIEK~~ ~~TISKTEGRPK~~ ~~APQVYTHPPP~~
 351 ~~KEQMAKDKVS~~ ~~LTCMITDFFP~~ ~~EDITVEWQWN~~ ~~GQPAENYKNT~~ ~~QPMMDTDGSY~~
 401 ~~FIYSKLVNQK~~ ~~SNWEAGNTFT~~ ~~CSVLHBEGLHN~~ ~~HHTEKSLSHS~~ ~~PGK~~ (SEQ ID NO:11)

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

1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTGGTGACGC CTGGGGCTTC
 51 AGTGAAGATA TCCTGTAAAG CTCTGGATA CACATTCAC TACCACACTACA
 101 TGAGCTGGGT GAAGCAGAGT CATGGAAAAA GCCTTGAGTG GATTGGAGAT
 151 ATTAATCCCT ATTCTGGTGA AACTACCTAC AACCAGAAAGT TCAAGGGCAC
 201 GGCCACATTG ACTGTAGACA AGTCTTCCAG TATAGCCTAC ATGGAGATCC
 251 GCGGCCCTGAC ATCTGAGGAC TCTGCAGTCT ATTAAGTGTG AAGAGATGAT
 301 TACGACGCCT CTCCGTTTGC TTAAGTGGGC 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 TACACTCTGA
 551 CGACGTCAGT GACTGTCCCC TCCAGCACCT GGCCAGCGA GACCGTCACC
 601 TGCAACGTTG CCCACCCGGC CAGCAGCACC AAGGTGGACA AGAAAATTGT
 651 GCCCAGGAGT TGTGGTTGTA AGCCTTGCA TGTACAGTC CCAGAAATAT
 701 CATCTGTCTT CATTTCCCC CCAAAGCCCC AGGATGTGCT CACCATTACT
 751 CTGACTCTTA AGGTACAGTG TGTGTGGTA GACATCAGCA AGGATGATCC
 801 CGAGGTCCAG TTCAGCTGGT TTGTAGATGA TGTGGAGGTG CACACAGCTC
 851 AGAGCGCAAC CCGGGAGGAG CAGTTCAACA GCACTTCCG 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 CAAGAACACT CAGCCCATCA TGGACACAGA TGGCTTTAC
 1201 TTCTCTACA GAAAGCTCAA TGTGCAGAA AGCAACTGGG AGGCAGGAAA
 1251 TACTTTACAC TGCTCTGTGT TACATGAGGG CCTGCACAAC CACCATACTG
 1301 AGAAGAGCCT CTCCACTCT CCTGGTAAAT GA (SEQ ID NO:12)

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

1 MRCRWIFL LSGTAGVLS VQLQSGPEL VTPGASVKIS CKASGYTFD
 51 HYMSVWKQSH GKSLEWIGDI NPYSGETTYN QKFKGTATLT VDKSSSIAYM
 101 EIRGLTSBDS AVYYCARDY DASPFAYWGQ GILVTVSAK TTPSVYPLA
 151 PGSAQAQNSM YTLGCLVKGY FPEFVTVWN SGLSSGVHT FPAVLQSDLY
 201 TLSSSVTVPS STWPSSETVTC NVAHPASSIK VDKKIVPRDC GCKPCICTVP
 251 EVSSVFIFFP KPKDVLITL TPKVTCVVD ISKDDPEVQF SWFVDDVEVH
 301 TAQTQPREBQ FNTFRSVSE LPMHQDWLN GKEFKCRVNS PAFPAIEKT
 351 ISKTKGRPKA PQVYTIPPK EQMAKDKVSL TCMITDFFPB DITVEWQWNG
 401 QPAENYKNTQ PIMDTDGSYF IYSLNVQKS NWEAGNTFTC SVLHEGLHNN
 451 HTEKSLSHSP GK (SEQ ID NO:13)

[0100] The nucleic acid sequence of Ab-D HC including signal peptide encoding sequence is:

1 ATGAGATGCA GGTGGATCTT TCTCTTCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGAACTG GTGACGCCTG
 101 GGGCTTCAGT GAAGATATCT TGTAAAGCTT CTGGATACAC ATTAAGTAC
 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 TCACGTGCTC TGCAGCCAAA ACGACACCCC CATCTGTCTA TCCACTGGCC
 451 CCTGGATCTG CTGCCCCAAC TAACTCCATG GTGACCCTGG GATGCCTGGT
 501 CAAGGGCTAT TTCCCTGAGC CAGTGACAGT GACCTGGAAC TCTGGATCCC
 551 TGTCAGCGCG TGTGCACACC TTCCAGCTG TCTGCAGTC TGACCTTAC
 601 ACTCTGAGCA GCTCAGTGAC TGTCCCTCC AGCACCTGGC CCAGCGAGAC
 651 CGTCACCTGC AACGTTGCC ACCCGGCCAG CAGCACCAAG GTGACAAGA
 701 AAATTGTGCC CAGGATTGT GGTGTAAGC CTGTCATATG TACAGTCCCA
 751 GAAGTATCAT CTGTCTTCAT CTCCCCCA AAGCCCAAGG ATGTGCTCAC
 801 CATTACTCTG ACTCCTAAGG TCACGTGTGT TGTGGTAGAC ATCAGCAAGG
 851 ATGATCCCGA GGTCCAGTTC AGCTGGTTG TAGATGATGT GGAGGTGCAC
 901 ACAGCTCAGA CGCAACCCCG GGAGGAGCAG TTCAACAGCA CTTTCCGCTC
 951 AGTCAAGTGA CTCCCATCA TGCACAGGA CTGGCTCAAT GGCAAGGAGT
 1001 TCAAATGCAG GGTCAACAGT CCAGCTTTCC CTGCCCCCAT CGAGAAAACC
 1051 ATCTCCAAAA CCAAAGGCAG ACCGAAGGCT CCACAGGTGT ACACATTCC
 1101 ACCTCCCAAG GAGCAGATGG CCAAGGATAA AGTCAGTCTG ACCTGCATGA
 1151 TAACAGACTT CTCCCTGAA GACATTACTG TGGAGTGGCA GTGGAATGGG
 1201 CAGCCAGCGG AGAACTACAA GAACACTCAG CCCATCATGG ACACAGATGG
 1251 CTCTTACTTC ATCTACAGCA AGCTCAATGT GCAGAAGAGC AACTGGGAGG
 1301 CAGGAAATAC TTTACCTGC TCTGTGTAC ATGAGGGCCT GCACAACCAC
 1351 CATACTGAGA AGAGCCTCTC CCACTCTCTT GGTAATGA (SEQ ID NO:14)

[0101] 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)
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[0102] The light chain variable region CDR sequences of Ab-D are:

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

Ab-C

[0103] 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 ISCKASQSV DYGDSYMNWY QOKPGQPPKL
 51 LYAASNLES GIPARFSGNG SGTDFILNIH PVEEEDAVTY YCQQSNEDEW
 101 TFGGGTKLEI KRADAAPTYS IFPPSSEQLT SGGASVVCFL NNFYPKDINV
 151 KWKIDGSE RQ NGVLNSWTDQ DSKDSTYSMS STLTLTKDEY ERHNSYTCEA
 201 THKTSTSPIV KSFNRNEC (SEQ ID NO:15)

[0104] 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 ACTTCACCTT CAACATCCAT CCTGTGGAGG
 251 AGGAGGATGC TGTAACCTAT TACTGTCAAC AAAGTAATGA GGATCCGTGG
 301 ACGTTCGGTG GAGGCACCAA GCTGGAAATC AAACGGGCTG ATGCTGCACC
 351 AACTGTATCC ATCTTCCAC CATCCAGTGA GCAGTTAACA TCTGGAGGTG
 401 CCTCAGTCGT GTGCTTCTTG ACAACTTCT ACCCAAAGA CATCAATGTC
 451 AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC TGAACAGTTG
 501 GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC AGCACCTCA
 551 CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC CTGTGAGGCC
 601 ACTACAAGA CATCAACTTC ACCCATTTGC AAGAGCTTCA ACAGGAATGA
 651 GTGTTAG (SEQ ID NO:16)

[0105] The amino acid sequence of Ab-C LC including signal peptide is:

1 METDTILLWV LLLWVPGSTG DIVLTQSPAS LTVSLGLRAT ISCKASQSV D
 51 YDGDSYMNWY QOKPGQPPKL LYAASNLES GIPARFSGNG SGTDFILNIH
 101 PVEEEDAVTY YCQQSNEDEW TFGGGTKLEI KRADAAPTYS IFPPSSEQLT

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

[0106] The nucleic acid sequence of Ab-C LC including signal peptide encoding sequence is:

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

Ab-C Heavy Chain

[0107] The amino acid sequence of the mature form (signal peptide removed) of Ab-C HC is:

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1 EVQLQDSGPELVKPGTSVKMSCKASGYTFTDCYMNWVKQSHGKSLEWIGDI
51 NPFNGGTTYNQKFKGKATLTVDKSSSTAYMQLNSLTSDDSAVYYCARSH
101 YFDGRVPWDAMDYWGQGTSTVTVSSAKTTPPSVYPLAPGSAQTNSMVL
151 GCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTW
201 PSETVTCNVAPHASSTKVDKIVPRDCGCKPCICTVPEVSVFIFFPKPK
251 DVLITITLTPKVTCTVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNS
301 TFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQV
351 YTIPTPKQMAKDKVSLTCMIIDFFPEDITVEWQWNGQPAENYKNTQPIIM
401 DTDGSYFIYSKLNQVQKSNWEAGNTFTCSVLHEGLNHHTTEKSLSHSPGK (SEQ
ID NO:19)

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[0108] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-C HC is as follows:

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1 GAGGTCCAGCTGCAACAATCTGGACCTGAGCTGGTGAAGCTGGGACTTC
51 AGTGAAGATGTCTCTGAAGCTTCTGGATACACATTCACCTGACTGCTACA
101 TGAACCTGGGTGAAGCAGAGCATGGGAAGA GCCTTGAATGATTGGAGAT
151 ATTAATCCTTCAACGGTGGTACTACCTAC AACCAGAACTCAAGGGCAA
201 GGCCACATTGACTGTAGACA AATCTCCAGCACAGCCTACATGCAGCTCA
251 ACAGCCTGACATCTGACGACTCTGCACTCTATTACTGTGC AAGATCCCAT
301 TATTACTTCGATGGTAGAGTCCCTGGGATGCTATGGA CTGAGGCTCA
351 AGGAACCTCA GTCACCGTCTCTCAGCCAA AACGACACCCCATCTGTCT
401 ATCCAATGGC CCCTGGATCTGCTGCCAAA CTAATCCATGGTGACCCCTG
451 GGATGCCTGGTCAAGGGCTA TTTCCCTGAGCAGTGACAGTGACCTGGAA
501 CTCTGGATCCCTGTCCAGCGGTGTGCACACCTTCCAGCTGTCCTGCAGT
551 CTGACCTCTA CACTCTGAGCAGCTCAGTGA CTGTCCCTC CAGCACCTGG
601 CCCAGCGAGA CCGTCACCTGCAACGTTGCC CACCCGGCCA GCAGACCAA
651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTGTGAAG CTTGTCATAT
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 ACTTTCCGCT CAGTCAGTGA ACTTCCATC ATGCACAGG ACTGGCTCAA
951 TGGCAAGGAG TTCAAATGCA GGTCAACAG TGCAGCTTTC CTTGCCCCCA
1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGCA GACCGAAGGC TCACAGGTG
1051 TACACCATTC CACCTCCCAA GGAGCAGATG GCCAAGGATA AAGTCAGTCT
1101 GACCTGCATG ATAACAGACT TCTTCCCTGA AGACATTACT GTGGAGTGGC
1151 AGTGGAAATG GCAGCCAGCG GAGAACTACA AGAACA CTCA GCCCATCATG
1201 GACACAGATG GCTCTTACT CATCTACAGC AAGCTCAATG TGCAGAAAGAG
1251 CAACTGGGAG GCAGGAAATA CTTTACCTG CTCTGTGTTA CATGAGGGCC
1301 TGCAACAACA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA
(SAQ ID NO:20)

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[0109] The amino acid sequence of Ab-C HC including signal peptide is:

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1 MGWNWIFLFLSGTAGVYSEVLQDSGPFLVKPGTSVKMSCKASGYTFTD
51 CYMNWVKQSHGKSLEWIGDINPFNGGTTYNQKFKGKATLTVDKSSSTAYM
101 QLNLSLTSDDSAVYYCARSHYFDGRVPWDA MDYWGQGTSTVTVSSAKTTPP
151 SVYPLAPGSAQTNSMVLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAV
201 LQSDLYTLSSSVTVPSSTWPSETVTCNVAPHASSTKVDKIVPRDCGCKP
251 CICTVPEVSVFIFFPKPKDVLITITLTPKVTCVVDISKDDPEVQFSWFV
301 DDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAF
351 APIEKTISKTKGRPKAPQVYTIPTPKQMAKDKVSLTCMIIDFFPEDITV
401 EWQWNGQPAENYKNTQPIIMDTDGSYFIYSKLNQVQKSNWEAGNTFTCSVLH
451 EGLNHHTTEKSLSHSPGK (SEQ ID NO:21)

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[0110] The nucleic acid sequence of Ab-C HC including signal peptide encoding sequence is:

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1 ATGGGATGGA ACTGGATCTT TCTCTTCTC TTGTCAGGAA CTGACGGTGT
51 CTAATCTGAG GTCCAGCTGC AACAATCTGG ACCTGAGCTG GTGAAGCCTG
101 GGACTTCACT GAAGATGTCC TGTAAAGCTT CTGGATACAC ATTCACTGAC
151 TGCTACATGA ACTGGGTGAA GCAGAGCCAT GGGAAAGAGCC TTGAATGGAT
201 TGGAGATATT AATCCTTCA ACGGTGGTAC TACCTACAAC CAGAAGTTCA
251 AGGGCAAGGC CACATTGACT GTAGACAAAT CCTCCAGCAC AGCCTACATG
301 CAGCTCAACA GCCTGACATC TGACGACTCT GCAGTCTATT ACTGTGCAAG
351 ATCCCATATT TACTTCGATG GTAGAGTCCC TTGGGATGCT ATGGACTACT
401 GGGGTCAAGG AACCTCAGT ACCGTCTCCT CAGCCAAAAC GACACCCCA
451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAAC TA CTCCATGGT
501 GACCCTGGGA TGCTGTGTC AGGGCTATTT CCTGAGCCA GTGACAGTGA
551 CCTGGAACT TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
601 CTGCACTGTC ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCTCCAG
651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCAC CCGGCCAGCA
701 GCACCAAGGT GGACAAGAAA ATTGTGCCA GGGATTGTGG TTGTAAGCCT
751 TGCAATATGA CAGTCCCAAG AGTATCATCT GTCTTCATCT TCCCCCAAAA
801 GCCCAAGGAT GTGCTACCA TTAATCTGAC TCCTAAGGTC ACGTGTGTTG

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851 TGGTAGACAT CAGCAAGGAT GATCCCGAGG TCCAGTTCAG CTGGTTTGTA
 901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
 951 CAACAGCACT TTCCGCTCAG TCAGTGAAGT TCCATCATG CACCAGGACT
 1001 GGCTCAATGG CAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCCT
 1051 GCCCCCATCG 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 GGAAATACIT TCACCTGCTC TGTGTTACAT
 1351 GAGGGCCTGC ACAACCACCA TACTGAGAAG AGCCTCTCCC ACTCTCCTGG
 1401 TAAATGA (SEQ ID NO:22)

[0111] The CDR (complementarity determining region) sequences in the variable region of the heavy chain of Ab-C are as follows:

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

[0112] The light chain variable region CDR sequences of Ab-C are:

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

Ab-A

[0113] Antibody A (also referred to herein as Ab-A and Mab-A) is a rabbit-mouse chimeric antibody which exhibits high affinity binding to sclerostin. The BIAcore binding pattern of Ab-A is shown in Figure 15.

Ab-A Light Chain

[0114] The amino acid sequence of the mature form (signal peptide removed) of Ab-A LC:

1 AQLVTQTPAS VSAAVGGTVT INCQSSQSVY DNNWLA WFOQ KPGQPPKLLI
 51 YDASDLASGV PSRFSGSGSG TQFTLITSGV QCADAATYYC QGAYNDVIYA
 101 FGGGTEVVVK RTDAAPTYSI FPPSSEQLTS GGASVVCFLN NFYPKDINVK
 151 WKIDGSEKQN GVLNSWTDQD SKDSTYSMSS TLTLTKDEYE RHNSYTCEAT
 201 HKTSTSPIVK SFNRNEC (SEQ ID NO:23)

[0115] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-A LC:

1 GCGCAAGTGC TGACCCAGAC TCCAGCCTCC GTGTCTGCAG CTGTGGGAGG

51 CACAGTCACC ATCAATTGCC AGTCCAGTCA GAGTGTTTAT GATAACAACT
 101 GGTTAGCCTG GTTTCAGCAG AAACCAAGGC AGCCTCCCAA GCTCCTGATT
 151 TATGATGCAT CCGATCTGGC ATCTGGGGTC CCATCGCGGT TCAGTGGCAG
 201 TGGATCTGGG ACACAGTTCA CTCTACCAT CAGCGGCGTG CAGTGTGCCG
 251 ATGCTGCCAC TTAATACTGT CAAGGCGCTT ATAATGATGT TATTATGCT
 301 TTCGGCGGAG GGACCGAGGT GGTGGTCAAA CGTACGGATG CTGCACCAAC
 351 TGTATCCATC TTCCACCAT CCAGTGAGCA GTTAACATCT GGAGGTGCCT
 401 CAGTCGTGTG CTCTTGAAC AACTTCTACC CCAAAGACAT CAATGTCAAG
 451 TGGAAAGATTG ATGGCAGTGA ACGACAAAAT GGCGTCCTGA ACAGTTGGAC
 501 TGATCAGGAC AGCAAAGACA GCACCTACAG CATGAGCAGC ACCCTACGT
 551 TGACCAAGGA CGAGTATGAA CGACATAACA GCTATACCTG TGAGGCCACT
 601 CACAAGACAT CAATTCACC CATTGTCAAG AGCTTCAACA GGAATGAGTG
 651 TTAG (SEQ ID NO:24)

[0116] The amino acid sequence of Ab-A LC including signal peptide is:

1 MDTRAPTQLL GLLLLWLPGA TFAQVLTQTP ASVSAAVGGT VTINCQSSQS
 51 VYDNNWLAWF QQKPGQPPKL LIYDASDLAS GVPSRFSGSG SGTQFTLITIS
 101 GVQCADAATY YCQGAYNDAVI YAFGGGTEVV VKRTDAAPT V SIFPPSSEQL
 151 TSGGASVYCF LNNFYPKDIN VKWKIDGSR QNGVLNSWTD QDSKDYSTM
 201 SSTLTLTKE YERHNSYTCE ATHKTSTSPI VKSFNRNEC (SEQ ID NO:25)

[0117] The nucleic acid sequence of Ab-A LC including signal peptide encoding sequence is:

1 ATGGACACGA GGGCCCCAC TCAGCTGCTG GGGCTCCTGC TGCTCTGGCT
 51 CCCAGGTGCC ACATTGCGC AAGTGCTGAC CCAGACTCCA GCCTCCGTGT
 101 CTGCAGCTGT GGGAGGCACA GTCACCATCA ATTGCCAGTC CAGTCAGAGT
 151 GTTATGATA ACAACTGGTT AGCCTGGTTT CAGCAGAAAC CAGGGCAGCC
 201 TCCCAAGCTC CTGATTATG ATGCATCCGA TCTGGCATCT GGGGTCCCAT
 251 CGCGGTTCAG TGGCAGTGGA TCTGGGACAC AGTTCACTCT CACCATCAGC
 301 GGCCTGCAGT GTGCCGATGC TGCCACTTAC TACTGTCAAG GCGCTTATAA
 351 TGATGTTATT TATGCTTTTC GCGGAGGGAC CGAGGTGGTG GTCAAACGTA
 401 CGGATGCTGC ACCAACTGTA TCCATCTTCC CACCATCCAG TGAGCAGTTA
 451 ACATCTGGAG GTGCCTCAGT CGTGTGCTTC TTGAACAACT TCTACCCCAA
 501 AGACATCAAT GTCAAGTGGA AGATTGATGG CAGTGAACGA CAAAATGGCG
 551 TCCTGAACAG TTGGACTGAT CAGGACAGCA AAGACAGCAC CTACAGCATG
 601 AGCAGCACCC TCACGTTGAC CAAGGACGAG TATGAACGAC ATAACAGCTA
 651 TACCTGTGAG GCCACTACA AGACATCAAC TTCACCCATT GTCAAGAGCT
 701 TCAACAGGAA TGAGTGTTAG (SEQ ID NO:26)

[0118] The amino acid sequence of the mature form (signal peptide removed) of Ab-A HC is:

1 QSLEESGGRL VTPGTPLTLT CTASGFSLS YWMNVVRQAP GEGLEWIGIT
 51 DSGGRIDYAS WAKGRFTISR TSTMDLKM TSLTGDTRY FCARNWNLWG
 101 QGTLVTVSSA STKGPSVYPL APGSAAQINS MYLGCLVEG YFPEPVTYTW
 151 NSGSLSSGVH TFAVLQSDL YTLSSSVTVP SSTWPSSETV CNVAHPASST
 201 KYDEKIVPRD CGKPCICTV PEVSVVFLP PKPDVLTIT LTPKVTCTVV
 251 DISKDDPEVQ FSWFVDDVEV HTAQTPREE QFNSTFRSVS ELPIMHQDWL
 301 NGKEFKCRVN SAAPPAIEK TSKTKGRPK APQVYTPPP KEQMAKDKVS
 351 LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMNINGSY FVYSKLVQK

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

[0119] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-A HC:

1 CAGTCGCTGG AGGAGTCCGG GGGTCGCCCTG GTCACGCCTG GGACACCCCT
 51 GACACTCACC TGCACAGCCT CTGGATTCTC CCTCAGTAGT TATTGGATGA
 101 ACTGGGTCCG CCAGGCTCCA GGGGAGGGGC TGGAAATGGAT CGGAACCAT
 151 GATTCTGGTG GTAGGACGGA CTACGCGAGC TGGGCAAAAG GCCGATTCAC
 201 CATCTCCAGA ACCTCGACTA CGATGGATCT GAAAATGACC AGTCTGACGA
 251 CCGGGGACAC GGCCCGTTAT TTCTGTGCCA GAAATTGGAA CTGTGGGGC
 301 CAAGGCACCC TCGTACCCGT CTCGAGCGCT TCTACAAAGG GCCCATCTGT
 351 CTATCCACTG GCCCTGGAT CTGCTGCCCA AACTAACTCC ATGGTGACCC
 401 TGGGATGCCCT GGTCAAAGGC TATTTCCCTG AGCCAGTGAC AGTGACCTGG
 451 AACTCTGGAT CCTGTCCAG CGGTGTGCAC ACCTTCCAG CTGTCCTGCA
 501 GTCTGACCTC TACACTCTGA GCAGCTCAGT GACTGTCCC TCCAGCACCT
 551 GGCCAGCGA GACCGTCACC TGCAACGTTG CCCACCCGGC CAGCAGCACC
 601 AAGGTGGACA AGAAAATTGT GCCCAGGGAT TGTGGTTGTA AGCCTTGCAT
 651 ATGTACAGTC CCAGAAGTAT CATCTGTCTT CATCTTCCCC CCAAAGCCCA
 701 AGGATGTGCT CACCATTACT CTGACTCCTA AGGTACAGTG TGTGTGGTA
 751 GACATCAGCA AGGATGATCC CGAGGTCCAG TTCAGTGGT TGTAGATGA
 801 TGTGGAGGTG CACACAGCTC AGACGCAACC CCGGGAGGAG CAGTTCAACA
 851 GCACTTTCCG CTCAGTCAGT GAACTTCCCA TCATGCACCA GGACTGGCTC
 901 AATGGCAAGG AGTTCAAATG CAGGGTCAAC AGTGCAGCTT TCCCTGCCCC
 951 CATCGAGAAA ACCATCTCCA AAACCAAAGG CAGACCGAAG GCTCCACAGG
 1001 TGTACACCAT TCCACCTCCC AAGGAGCAGA TGGCCAAGGA TAAAGTCAGT
 1051 CTGACCTGCA TGATAACAGA CTCTTCCCT GAAGACATTA CTGTGGAGTG
 1101 GCAGTGAAT GGGCAGCCAG CGGAGAACTA CAAGAACACT CAGCCCATCA
 1151 TGGACACAGA TGGCTCTTAC TTCGTCTACA GCAAGCTCAA TGTGCAGAAG
 1201 AGCAACTGGG AGGCAGGAAA TACTTTCACC TGCTCTGTGT TACATGAGGG
 1251 CCTGCACAAC CACCATACTG AGAAGAGCCT CTCCACTCT CTGGTAAAT
 1301 GA (SEQ ID NO:28)

[0120] The amino acid sequence of the Ab-A HC including signal peptide is:

1 METGLRWLL VAVLKGVHCQ SLBESGGRLV TPGTPLTLTC TASGFSLSY
 51 WMNWVRQAPG EGLEWIGTID SGGRTDYASW AKGRFTISRT STTMDLKMTS
 101 LTGDTARYF CARNWNLWGO GLVTVSSAS TKGFSVYPLA PGSAQAQNSM
 151 VTGLCLVKGY FPEPVTVTWN SGLSSGVHT FPAVLQSDLY TLSSSVTVPS
 201 STWPSETVTC NVAHPASSIK VDKKIVPRDC GCKPCICTVP EVSSVFIFP
 251 KPKDVLITL TPKVTCVVVD ISKDDPEVQF SWFVDDVEVH TAQTPFREEQ
 301 FNSTFRSVSE LPIMHQDWLN GKEFKCRVNS AAFPAPIEKT ISKTKGRPKA
 351 PQVYTPPPK EQMAKDKVSL TCMITDFFPE DITVEWQWNG QPAENYKNTQ
 401 PIMNTNGSYF VYSKLNQKS NWEAGNTFTC SVLHEGLHNH HTEKSLSHSP
 451 GK (SEQ ID NO:29)

[0121] The nucleic acid sequence of Ab-A HC including signal peptide encoding sequence:

1 ATGGAGACTG GGCTGCGCTG GCTTCTCTG GTCGCTGTGC TCAAAGGTGT
 51 CCACTGTCAG TCGCTGGAGG AGTCCGGGGG TCGCCTGGTC ACGCTGGGA
 101 CACCCCTGAC ACTCACCTGC ACAGCCTCTG GATTCTCCCT CAGTAGTTAT

151 TGGATGAACT GGGTCGCCA GGCTCCAGGG GAGGGGCTGG AATGGATCGG
 201 AACCATTGAT TCTGGTGTA GGACGGACTA CGCGAGCTGG GCAAAAAGGCC
 251 GATTCACCAT CTCAGAAACC TCGACTACGA TGGATCTGAA AATGACCACT
 301 CTGACGACCG GGGACACGGC CCGTTATTTT TGTGCCAGAA ATTGGAACCT
 351 GTGGGGCCAA GGCACCTCG TCACCGTCTC GAGCGCTTCT ACAAAGGGCC
 401 CATCTGTCTA TCCACTGGCC CTTGGATCTG CTGCCCAAAC TAACTCCATG
 451 GTGACCTGGG GATGCTGGT CAAGGGCTAT TTCCCTGAGC CAGTGACAGT
 501 GACCTGGAAC TCTGGATCCC TGTCCAGCGG TGTGCACACC TTCCAGCTG
 551 TCTGTCAGTC TGACCTCTAC ACTCTGAGCA GCTCAGTGAC TGTCCCTCC
 601 AGCACCTGGC CCAGCGAGAC CGTCACCTGC AACGTTGCC ACCCGGCCAG
 651 CAGCAACAAG GTGGAACAAGA AAATTGTGCC CAGGGATTGT GGTGTGAAGC
 701 CTTCATATG TACAGTCCCA GAAGTATCAT CTGTCTTCAT CTTCCCCCA
 751 AAGCCCAAGG ATGTGCTCAC CATTACTCTG ACTCCTAAGG TCACGTGTGT
 801 TGTGGTAGAC ATCAGCAAGG ATGATCCCGA GGTCCAGTTC AGCTGTTTG
 851 TAGATGATGT GGAGGTGCAC ACAGCTCAGA CGCAACCCCG GGAGGAGCAG
 901 TTCAACAGCA CTTCCGCTC AGTCAGTGAA CTTCCCATCA TGCACCAGGA
 951 CTGGCTCAAT GGCAAGGAGT TCAAATGCAG GGTCAACAGT GCAGCTTTC
 1001 CTGCCCCCAT CGAGAAAACC ATCTCCAAA CCAAAGGCAG ACCGAAGGCT
 1051 CCACAGGTGT ACACCATTC ACCTCCCAAG GAGCAGATGG CCAAGGATAA
 1101 AGTCAGTCTG ACCTGCATGA TAACAGACTT CTTCCCTGAA GACATTACTG
 1151 TGGAGTGGCA GTGGAATGGG CAGCCAGCGG AGAATACAA GAACACTCAG
 1201 CCCATCATGG ACACAGATGG CTCTTACTTC GTCTACAGCA AGCTCAATGT
 1251 GCAGAAGAGC AACTGGGAGG CAGGAAATAC TTTACCTGC TCTGTGTAC
 1301 ATGAGGGCCT GCACAACCAC CATACTGAGA AGAGCCTCTC CCACTCTCT
 1351 GGTAATGA (SEQ ID NO:30)

[0122] 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:	TIDSGGRTDYASWAKG (SEQ ID NO:52)
CDR-H3:	NWNL (SEQ ID NO:53)

[0123] 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:	QGAYNDAIYA (SEQ ID NO:56)

[0124] 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

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCTGCTGCTCTGGCTCCAGGT
 GCCACATTGCTCAAGTCTGACCCAGAGTCCAAGCAGTCTCTCCGCCAGCGTAGGC

GATCGTGTGACTATTACCTGTCAATCTAGTCAGAGCGTGTATGATAACAATTGGCTG
 GCGTGGTACCAGCAAAAACCGGGCAAGGCCCGAAGCTGCTCATCTATGACGCGTC
 CGATCTGGCTAGCGGTGTGCCAAGCCGTTTCAAGTGGCAGTGGCAGCGGTACTGACT
 TTACCCTACAATTTCTGCTCTCCAGCCGGAAGATTTGCCCACTTACTATTGTCAAG
 GTGCTTACAACGATGTGATTTATGCCTTCGGTCAGGGCACTAAAGTAGAAATCAAA
 CGT (SEQ ID NO:74)

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

MDTRAPTQLLGLLLWLPGA~~T~~FAQVLTQSPSSLSASVGDRTITCQSSQSVYDNNWLA

WYQQKPGKAPKLLIYDASDLASGVPSRFGSGSGSDFTLTISLQPEDFATYYCQGAYN DVIYAFGQGTKVEIKR (SEQ ID NO:75)

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

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCACTGT
GAGGTGCAGCTGTTGGAGTCTGGAGGCGGGCTTGTCAGCCTGGAGGGAGCCTGCG
TCTCTCTTGTGCAGCAAGCGGCTTCAGCTTATCCTCTTACTGGATGAATTGGGTGCG
GCAGGCACCTGGGAAGGGCCTGGAGTGGGTGGGCACCATTTGATTCCGGAGGCCGTA
CAGACTACGCTCTTGGGCAAAGGGCGTTTCACCATTTCCGCGACAACCTCCAAA
AATACCATGTACCTCCAGATGAACCTCTCTCCGCGCAGAGGACACAGCACGTTATTA
CTGTGCACGCAACTGGAATCTGTGGGGTCAAGGTA~~CTTGTAA~~CAGTCTCGAGC
(SEQ ID NO:76)

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

[0125]

METGLRWLLVAVLKGVHCEVOLLESGGGLVQPGGSLRLSCAASGFSLSYWMN~~WVR~~
QAPGKGLEWVGITDSGGRTDYASWAKG~~GRFTISRDNSKNTMYLQMNSLRAEDTARYYC~~
ARNWNLWGQGITLVTVSS (SEQ ID NO:77)

[0126] 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:	TIDSGGRTDYASWAKG (SEQ ID NO:52)
CDR-H3:	NWNL (SEQ ID NO:53)

[0127] 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

[0128] 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

[0129] The amino acid sequence of the mature form (signal peptide removed) of the Ab-B LC is:

1 QIVLTQSPTI VSASPGKVT LICSA~~SSVS~~ FVDWFOOKPG TSPKRWIYRT
51 ~~SNL~~GEV~~PAR~~ FSGGSGTSH SLTISRM~~EAE~~ DAATYYCQQR STYPP~~TF~~GAG
101 TKLELKRADA APTVSI~~FPPS~~ SEQLTSGGAS VVCF~~LNNFYP~~ KDINVKWKID
151 GSERQNGVLN SWTDQDSKDS TYSMS~~STLTL~~ TKDEYERHNS YTCEATHKTS
201 TSPIVKSFNR NEC (SEQ ID NO:31)

[0130] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-B LC is:

```

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

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[0131] The amino acid sequence of Ab-B LC including signal peptide is:

```

1 MHFQVQIFSF LLISASVIVS RQIVLTQSP TIVSASPGEK VTILCSASSS
51 VSFVDWFQQK PGTSFKRWIY RTSNLGFGVP ARFSGGSGST SHSLTISRME
101 AEDAATYYCQ QRSTYPPTFG AGTKLELKRA DAAPTVISIFP PSSEQLTSGG
151 ASVVCFLNNF YPKDINVKWK IDGSRQNGV LNSWTDQDSK DSTYSMSSTL
201 TLTKDEYERH NSYTCEATHK TSTSPIVKSF NRNEC (SEQ ID NO:33)

```

[0132] The nucleic acid sequence of Ab-B LC including signal peptide encoding sequence is:

```

1 ATGCATTTTC AAGTGAGAT TTTCAGCTTC CTGCTAATCA GTGCCTCAGT
51 CATAGTGTCG AGAGGGCAAA TTGTTCTCAC CCAGTCTCCA ACAATCGTGT
101 CTGCATCTCC AGGGGAGAAG GTCACCCATA TCTGCAGTGC CAGTTCAAGT
151 GTAAGTTTCG TGGACTGGTT CCAGCAGAAG CCAGGCACCT CTCCAAAACG
201 CTGGATTTAC AGAACATCCA ACCTGGGTTT TGGAGTCCCT GCTCGCTTCA
251 GTGGCGGTGG ATCTGGGACC TCTCACTCTC TCACAATCAG CCGAATGGAG
301 GCTGAAGATG CTGCCACTTA TTACTGCCAG CAAAGGAGTA CTTACCCACC
351 CACGTTCCGT GCTGGGACCA AGCTGGAAC TAAACGGGCT GATGCTGCAC
401 CAACTGTATC CATCTTCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
451 GCCTCAGTCG TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT
501 CAAGTGGGAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
551 GGAAGTATCA GGACAGCAA GACAGCACCT ACAGCATGAG CAGCACCTTC
601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
651 CACTCACAAG ACATCAACTT CACCCATTGT CAGAGCTTC AACAGGAATG
701 AGTGTTAG (SEQ ID NO:34)

```

Ab-B Heavy Chain

[0133] The amino acid sequence of the mature form (signal peptide removed) of Ab-B HC:

```

1 QVTLKESGPG ILQPSQTLST TCSFSGFSLT TSGMGVGNIR HPSGKNLEWL
51 AHIWDDVKKR YNPVLKSRIT ISKDTNSQV FLKIANVDTA DTATYYCARI
101 EDFDYDEERY AMDYWGQGT VIVSSAKTTP PSVYPLAPGS AAQNSMVTIL
151 GCLVKGYPFE PVTVTWNSGS LSSGVHTFPA VLQSDLYTSL SSVTVPSSTW
201 PSETVTTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIPTPKPK
251 DVLITITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
301 TFRSVSELPY MQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
351 YTIPTPPKEQM AKDKVSLTCM ITDFEPEDIT VEWQWNGQPA ENYKNTQPID
401 DTDGSYFVYS KLVNQKSNWE AGNTFTCSVL HEGLNHHTE KSLSHSPGK (SEQ
ID NO:35)

```

[0134] The nucleic acid sequence encoding the mature form (signal peptide removed) of Ab-B HC:

```

1 CAGGTTACTC TGAAGAGTC TGGCCCTGGG ATATTGCAGC CCTCCCAGAC
51 CCTCAGTCTG ACTTGTCTT TCTCTGGGTT TTCCTGAGC ACTTCTGGTA
101 TGGGTGTAGG CTGGATTCTT CACCCATCAG GGAAGAATCT GGAGTGGCTG
151 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
401 ATCCACTGGC CCCTGGATCT GCTGCCCAA CTAATCCAT GGTGACCCCTG
451 GGATGCCCTG TCAAGGGCTA TTTCCCTGAG CCAGTGACAG TGACCTGGAA
501 CTCTGGATCC CTGTCCAGCG GTGTGCACAC CTTCCAGCT GTCCTGCAGT
551 CTGACCTCTA CACTCTGAGC AGCTCAGTGA CTGTCCCTC CAGCACCTGG
601 CCCAGCGAGA CCGTCACCTG CAACGTTGCC CACCCGCCA GCAGACCCAA
651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTTGTAAG CCTTGCATAT
701 GTACAGTCCC AGAAGTATCA TCTGTCTTCA TCTTCCCCC AAAGCCCCAAG
751 GATGTGCTCA CCATTACTCT GACTCCTAAG GTCACGTGTG TTGTGGTAGA
801 CATCAGCAAG GATGATCCCG AGGTCCAGTT CAGCTGGTTT GTAGATGATG
851 TGGAGGTGCA CACAGCTCAG ACGCAACCCC GGGAGGAGCA GTTCAACACG
901 ACTTTCGCTC 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 AGTGGAAATG GCAGCCAGCG GAGAACTACA AGAACACTCA GCCCATCATG

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1201 GACACAGATG GCTCTTACTT CGTCTACAGC AAGCTCAATG TGCAGAAGAG
1251 CAACTGGGAG GCAGGAAATA CTTTACCTG CTCTGTGTTA CATGAGGGCC
1301 TGCACAACCA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA
(SEQ ID NO:36)

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[0135] The amino acid sequence of Ab-B HC including signal peptide:

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1 MGRLTSSFLI LIVPAYVLSQ VTLKESGPGI LQPSQTLSLT CSFSGFSLST
51 SGMGVGWIRH PSQKNLEWLA HIWDDVKRY NPVLKSLRTI SKDTSNSQVF
101 LKIANVDTAD TATYYCARIE DFYDEEYYA MDYWGQTSV IVSSAKTTPP
151 SVYPLAPGSA AQTNMVTLLG CLVKGYFPEP VTVWNSGSL SSGVHTFFAV
201 LQSDLYTLSS SVTVPSSTWP SETVTCNVAH PASSTKVDKK IVPKDCCKPK
251 CICTVPEVSS VFIFPPKPKD VLTITLTPKV TCVVVDISKD DPEVQFSWV
301 DDVEVHTAQT QPREEQFNST FRVSSELPIM HQDWLNGKEF KCRVNSAAFP
351 APIEKTISKI KGRPKAPQVY TIFPPKEQMA KDKVSLTCMI TDFPFEDITV
401 EWQWNQPAE NYKNTQFIMD TDGSYFVYSK LNVQKSNWEA GNTFTCSVLH
451 EGLHNRHTEK SLSHSPGK (SEQ ID NO:37)

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[0136] The nucleic acid sequence of Ab-B HC including signal peptide encoding sequence:

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1 ATGGGCAGGC TTACTTCTTC ATTCCTGCTA CTGATTGTCC CTGCATATGT
51 CCTGTCCAGG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT
101 CCCAGACCTC CAGTCTGACT TGTTCTTTCT CTGGGTTTTC ACTGAGCACT
151 TCTGGTATGG GTGTAGGCTG GATTCTGCAC CCATCAGGGA AGAATCTGGA
201 GTGGCTGGCA CACATTTGGT GGGATGATGT CAAGCGCTAT AACCCAGTCC
251 TGAAGAGCCG ACTGACTATC TCCAAGGATA CCTCCAACAG CCAGGTATTC
301 CTCAGATCGC CCAATGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGC
351 TCGAATAGAG GACTTTGATT ACGACGAGGA GTATTATGCT ATGGACTACT
401 GGGGTCAAGG AACCTCAGTC ATCGTCTCCT CAGCCAAAAC GACACCCCA
451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAACCT ACTCCATGGT
501 GACCCCTGGG TGCCCTGGTCA AGGGCTATTT CCCTGAGCCA GTGACAGTGA
551 CCTGGAATCG TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
601 CTGCAGTCTG ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCTCCAG
651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCAC CCGGCCAGCA
701 GCACCAAGGT GGACAAGAAA ATTGTGCCCA GGGATTGTGG TTGTAAGCCT
751 TGCATATGTA CAGTCCGAGA AGTATCATCT GTCTTCATCT TCCCCCAAAA
801 GCCCAAGGAT GTGCTCACCA TTACTCTGAC TCCTAAGGTC ACGTGTGTTG
851 TGGTAGACAT CAGCAAGGAT GATCCCGAGG TCCAGTTCAG CTGGTTTGTA
901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
951 CAACAGCACT TTCGCTCAG TCAGTGAATC TCCATCATG CACCAGGACT
1001 GGCTCAATGG CAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCCT
1051 GCCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGCAGAC CGAAGGCTCC
1101 ACAGGTGTAC ACCATTCCAC CTCCAAGGA GCAGATGGCC AAGGATAAAG
1151 TCAGTCTGAC CTGCATGATA ACAGACTTCT TCCCTGAAGA CATTACTGTG
1201 GAGTGGCAGT GGAATGGGCA GCCAGCGGAG AACTACAAGA ACACCTAGCC
1251 CATCATGGAC ACAGATGGCT CTTACTTCGT CTACAGCAAG CTCAATGTGC
1301 AGAAGAGCAA CTGGGAGGCA GGAAATACTT TCACCTGCTC TGTGTTACAT
1351 GAGGGCCTGC ACAACACCA TACTGAGAAG AGCCTCTCCC ACTCTCTG
1401 TAAATGA (SEQ ID NO:38)

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[0137] 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)
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CDR-H2:	HWWDVVKRYNPVLKS (SEQ ID NO:58)
CDR-H3:	EDFDYDEEYYAMDY (SEQ ID NO:59)

[0138] The light chain variable region CDR sequences of Ab-B are:

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

[0139] 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 disclosure are known to those of skill in the art.

[0140] The present disclosure therefore relates in part to 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.

[0141] 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.

[0142] 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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.

[0147] 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.

[0148] 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

[0149] The sequences of the Antibody 2 (also referred to as Ab-2) LC and HC are as follows:

Ab-2 Light Chain:

[0150] Amino acid sequence of the mature form (signal peptide removed) of the Ab-2 LC:

1 QIVLSQSPAI LSTSPGEKVT MTCRASSSVY YMHWYQKPG SSPKPWIYAT
51 SNLASGVPVR FSGSGSGTSY SLTITRVEAE DAATYYCQOW SSDPLTFGAG
101 TKLELKRA DA APTVSIFPPS SEQLTSGGAS VVCFLNFPY KDINVKWKID
151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
201 TSPIVKSFNR NEC (SEQ ID NO:117)

[0151] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-2 LC:

1 CAAATTGTTTCTCCAGTC TCCAGCAATC CTGTCTACAT CTCCAGGGGA
51 GAAGGTCACA ATGACTTGCA GGGCCAGCTC AAGTGATAT TACATGCACT
101 GGTACCAGCA GAAGCCAGGA TCCTCCCCA AACCTGGAT TTATGCCACA
151 TCCAACCTGG CTTCTGGAGT CCCTGTTCCG TTCAGTGGCA GTGGGTCTGG
201 GACCTCTTAC TCTCTACAA 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 CGTCTGAAC AGTTGGACTG ATCAGGACAG
501 CAAAGACAGC ACCTACAGCA TGAGCAGCAC CCTACGTTG ACCAAGGACG
551 AGTATGAACG ACATAACAGC TATACCTGTG AGGCCACTCA CAAGACATCA
601 ACTTCAACCA TTGTCAAGAG CTTCAACAGG AATGAGTGTT AG (SEQ ID
NO:118)

[0152] Amino acid sequence of the Ab-2 LC including signal peptide:

1 MDFQVQIFSF LLISASVIMS RGQIVLSQSP AILSTSPGEK VITMTCRASSS
51 VYYMHWYQK PGSSPKPWIY ATSNLASGVP VRFSGSGSGT SYSLTITRVE
101 AEDAATYYCQ QWSSDPLTFG AGTKLELKRA DAAPTVSIFP PSSEQLTSGG
151 ASVVCFLNFP YPKDINVKWK IDGSRQNGV LNSWTDQDSK DSTYSMSSTL
201 TLTKDEYERH NSYTCEATHK TSTSPIVKSF NRNEC (SEQ ID NO:119)

[0153] 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 AGGGGAGAAAG GTCACAATGA CTTGCAGGGC CAGCTCAAGT
 151 GTATATTACA TGCACCTGGTA CCAGCAGAAAG CCAGGATCCT CCCCCAAACC
 201 CTGGATTATG GCCACATCCA ACCTGGCTTC TGGAGTCCCT GTTCGCTTCA
 251 GTGGCAGTGG GTCTGGGACC TCTTACTCTC TCACAATCAC CAGAGTGGAG
 301 GCTGAAGATG CTGCCACTTA TTA CTGCCAG CAGTGGAGTA GTGACCCACT
 351 CACGTTCCGT GCTGGGACCA AGCTGGAGCT GAAACGGGCT GATGCTGCAC
 401 CAACTGTATC CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
 451 GCCTCAGTCG TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT
 501 CAAGTGAAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
 551 GGACTGATCA GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCCTC
 601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
 651 CACTCACAAG ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG
 701 AGTGTTAG (SEQ ID NO:120)

Ab-2 Heavy Chain

[0154] Amino acid sequence of the mature form (signal peptide removed) of the Ab-2 HC:

1 EVQVQSGPE LVKPGASVKL SCTASGFNIK ~~DYFIHWVKQR~~ PEQGLEWIGR
 51 ~~LDPEDGESDY~~ ~~APKFDKAIM~~ TADTSSNTAY LQLRLTSED TAIYYCERED
 101 ~~YDGLTYTFPY~~ WGQGLVTVS AAKTTPSVY PLAPGSAQT NSMVLGCLV
 151 ~~KGYFPEPVTV~~ TWNSGSLSSG VHTFPAVLQS ~~DLYTLSSSVT~~ VPSSTWPSET
 201 VTCNVAPAS ~~STKVDDKIVP~~ RDCGCKPCIC TVPEYSSVFI FPPKPKDVLV
 251 ~~ITLTPKVTCTV~~ VVDISKDDPE ~~VQFSWFVDDV~~ EVHTAQTPR ~~EEQFNSTFRS~~
 301 ~~VSELPIHQD~~ WLNGKEFKCR VNSAAPPAPI EKTISKTKGR PKAPQVYTIP
 351 ~~PPKEQMAKDK~~ VSLTCMITDF ~~FPEDITVEWQ~~ WNGQPAENYK ~~NTQPIMDTDG~~
 401 ~~SYFIYSKLVN~~ QKSNWEAGNT ~~FTCSVLHEGL~~ HNHTEKSLS HSPGK (SEQ ID
 NO:121)

[0155] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-2 HC:

1 GAGGTTCAAG TGCAGCAGTC TGGGCCAGAA CTTGTGAAGC CAGGGGCCCTC
 51 AGTCAAGTTG TCCTGCACAG CTCTGGCTT CAACATTAAG GACTACTTTA
 101 TACACTGGGT GAAGCAGAGG CCTGAACAGG GCCTGGAGTG GATTGGAAGG
 151 CTTGATCCTG AGGATGGTGA AAGTGATTAT GCCCGAAGT TCCAGGACAA
 201 GGCCATTATG ACAGCAGACA CATCATCCAA CACAGCCTAT CTTAGCTCA
 251 GAAGCCTGAC ATCTGAGGAC ACTGCCATCT ATTATTGTGA GAGAGAGGAC
 301 TACGATGGTA CCTACACCTT TTTTCCTTAC TGGGGCCAAG GGA CTCTGGT
 351 CACTGTCTCT GCAGCCAAAA CGACACCCCC ATCTGTCTAT CCACTGGCCC
 401 CTGGATCTGC TGCCCAAACT AACTCCATGG TGACCCTGGG ATGCCTGGTC
 451 AAGGGCTATT TCCTGAGCC AGTGACAGTG ACCTGGAAC CTGGATCCCT
 501 GTCCAGCGGT GTGCACACCT TCCAGCTGT CCTGCAGTCT GACCTCTACA
 551 CTCTGAGCAG CTCAGTGACT GTCCCTCCA GCACTGGCC CAGCGAGACC
 601 GTCACCTGCA ACGTTGCCCA CCCGGCCAGC AGCACCAAGG TGGACAAGAA
 651 AATTGTGCCC AGGGATTGTG GTTGTAAGCC TTGCATATGT ACAGTCCAG
 701 AAGTATCATC TGTCTTCATC TTCCCCCAA AGCCCAAGGA TGTGCTCACC
 751 ATTACTCTGA CTCCTAAGGT CACGTGTGTT GTGGTAGACA TCAGCAAGGA
 801 TGATCCCGAG GTCCAGITCA GCTGGTTTGT AGATGATGTG GAGGTGCACA
 851 CAGCTCAGAC GCAACCCCGG GAGGAGCAGT TCAACAGCAC TTTCCGCTCA
 901 GTCAGTGAAC TTCCATCAT GCACCAGGAC TGGCTCAATG GCAAGGAGTT
 951 CAAATGCAGG GTCAACAGTG CAGCTTTCCC TGCCCCCATC GAGAAAACCA
 1001 TCTCCAAAAC CAAAGGCAGA CCGAAGGCTC CACAGGTGTA CACCATTCCA
 1051 CCTCCAAAGG 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 CACTCTCTG GTAAATGA (SEQ ID NO:122)

[0156] 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 GQGLTVTVSA AKTTPPSVYP
 151 LAPGSAQIN SMVTLGCLVK GYFPEPVTVT WNSGSLSSGV HTFPAVLQSD
 201 LYTLSSSVTV PSSTWPSETV TCNVAHPASS TKVDKKIVPR DCGCKPCICT
 251 VPEVSSVFIF PPKPKDVLTI TLTPKVTCVV VDISKDDPEV QFSWFVDDVE
 301 VHTAQTPRE EQFNSTFRSV SELPMHQDW LNGKEFKCRV NSAAFPAPIE
 351 KITSKTKGRP KAPQVYTTPP PKEQMAKDKV SLTCMTDFF PEDITVEWQW
 401 NGQPAENYKN TQPMDDTGS YFIYSKLNQV KSNWEAGNTF TCSVLHEGLH
 451 NHHTEKSLSH SPGK (SEQ ID NO:123)

[0157] Nucleic acid sequence of the Ab-2 HC including signal peptide encoding sequence:

1 ATGAAATGCA GCTGGGTCAT CTTCTCCTG ATGGCAGTGG TTACAGGGGT
 51 CAATTCAGAG GTTCAGGTGC AGCAGTCTGG GCCAGAACTT GTGAAGCCAG
 101 GGGCCTCAGT CAAGTTGTCC TGCACAGCTT CTGGCTTCAA CATTAAAGAC
 151 TACTTTATAC ACTGGGTGAA GCAGAGGCCT GAACAGGGCC TGGAGTGGAT
 201 TGGAAAGCCT GATCTGAGG ATGGTGAAAG TGATTATGCC CCGAAGTTCC
 251 AGGACAAGGC CATTATGACA GCAGACACAT CATCCAACAC AGCCTATCTT
 301 CAGCTCAGAA GCCTGACATC TGAGGACACT GCCATCTATT ATTGTGAGAG
 351 AGAGGACTAC GATGGTACCT ACACCTTTTT TCCTTACTGG GGCCAAGGGA
 401 CTCCTGGTAC TGTCTCTGCA GCCAAAACGA CACCCCATC TGTCTATCCA
 451 CTGCCCCCTG GATCTGCTGC CCAAACCTAAC TCCATGGTGA CCCTGGGATG

501 CCTGGTCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAAGTCTG
 551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCTT GCAGTCTGAC
 601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCTCCAGCA CCTGGCCCAG
 651 CGAGACCGTC ACCTGCAACG TTGCCACCC GGCCAGCAGC ACCAAGGTGG
 701 ACAAGAAAAT TGTGCCCAGG GATTGTGTT GTAAGCCTTG CATATGTACA
 751 GTCCAGAAAG TATCATCTGT CTTTCATCTC CCCCCAAAGC CCAAGGATGT
 801 GCTACCATC ACTCTGACTC CTAAGGTCAC GTGTGTTGTG GTAGACATCA
 851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTGTGTAGA TGATGTGGAG
 901 GTGCACACAG CTCAGACGCA ACCCCGGGAG GAGCAGTTCA ACAGCACTTT
 951 CCGCTCAGT AGTGAACCTC CCATCATGCA CCAGGACTGG CTCAATGGCA
 1001 AGGAGTTCAA ATGCAGGGTC AACAGTGCA CTTTCCCTGC CCCCATCGAG
 1051 AAAACCATCT CCAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
 1101 CATTCCACCT CCAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
 1151 GCATGATAAC AGACTTCTC CCTGAAGACA TTAAGTGTGA GTGGCAGTGG
 1201 AATGGGAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
 1251 AGATGGCTCT TACTTCATCT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
 1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTTACATGA GGGCCTGCAC
 1351 AACCACCATA CTGAGAAGAG CCTCTCCAC TCTCTGGTA AATGA (SEQ ID
 NO:124)

Ab-3

[0158] The sequences of the Antibody 3 (also referred to herein as Ab-3) LC and HC are as follows:

Ab-3 Light Chain

[0159] Amino acid sequence of the mature form (signal peptide removed) of the Ab-3 LC:

1 EIVLTQSPAL MAASPGKVT ITCSYSSIS ~~SNLH~~WFQOK SDTSPKPWIY
 51 ~~GTSL~~ASGVP VRFSGSGSGT SYSLTISSME AEDAATYVCQ QWSSYPLTFG
 101 AGTKLELRRA ~~DAAPTYSIFP~~ PSSEQLTSGG ASVVCFLNNF YPKDINVKWK
 151 ~~IDGSE~~RQNGV LNSWTDQDSK DSTYSMSSTL TLTKDEYERH NSYTCEATHK
 201 TSTSPIVKSF NRNEC (SEQ ID NO:125)

[0160] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-3 LC:

1 GAAATTGTGC TCACCCAGTC TCCAGCACTC ATGGCTGCAT CTCGGGGGA
 51 GAAGGTCACC ATCACTGCA GTGTCAGTTC AACTATAAGT TCCAACCACT
 101 TGCACCTGGT CCAGCAGAAG TCAGACACCT CCCCCAAACC CTGGATTAT
 151 GGCACATCCA ACCTGGCTTC TGGAGTCCCT GTTCGCTTCA GTGGCAGTGG
 201 ATCTGGGACC TCTTATTCTC TCACAATCAG CAGCATGGAG GCTGAGGATG
 251 CTGCCACTTA TTACTGTCAA CAGTGGAGTA GTTACCCACT CACGTTCCGC
 301 GCTGGGACCA AGCTGGAGCT GAGACGGGCT GATGCTGCAC CAACTGTATC
 351 CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT GCCTCAGTCG
 401 TGTGCTTCTT GAACAACCTC TACCCCAAAG ACATCAATGT CAAGTGAAG
 451 ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT GGAAGTATCA
 501 GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCTC ACGTTGACCA
 551 AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC CACTACAAG
 601 ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG AGTGTTAG (SEQ
 ID NO:126)

[0161] Amino acid sequence of the Ab-3 LC including signal peptide:

1 MDFHVQFSF MLISVTVILS SGEIVLTQSP ALMAASPGEK VTITCSVSST
 51 ISSNHLHWFC QKSDTSPPKW IYGTSLNLSG VPRFSGSGS GTSYSLTISS
 101 MEAEADAATY CQWSSYPLT FGAGTKLELR RADAAPTYSI FPPSSEQLTS
 151 GGASVVCFLN NFYPKDINVK WKIDGSEKQN GVLNSWTDQD SKDSTYSMS
 201 TLTLTKDEYE RHNSYTCEAT HKTSTSPIVK SFNRNEC (SEQ ID NO:127)

[0162] Nucleic acid sequence of the Ab-3 LC including signal peptide encoding sequence:

1 ATGGAITTTT ATGTGCAGAT TTTAGCTTC ATGCTAATCA GTGTCACAGT
 51 CATTTTGTCC AGTGGAGAAA TTGTGCTCAC CCAGTCTCCA GCACTCATGG
 101 CTGCATCTCC GGGGGAGAAG GTCACCATCA CCTGCAGTGT CAGTTCAACT
 151 ATAAAGTTCCA ACCACTTGCA CTGGTTCCAG CAGAAAGTCA ACACCTCCCC
 201 CAAACCTGG ATTTATGGCA CATCCAACCT GGCTTCTGGA GTCCTGTTC
 251 GCTTCAGTGG CAGTGGATCT GGGACCTCTT ATTCTCTCAC AATCAGCAGC
 301 ATGGAGGCTG AGGATGCTGC CACTTATTAC TGTAACAGT GGAGTAGTTA
 351 CCCACTCAGT TCGGGCGCTG GGACCAAGCT GGAGCTGAGA CGGGCTGATG
 401 CTGCACCAAC TGTATCCATC TTCCACCAT CCAGTGAGCA GTTAACATCT
 451 GGAGGTGCCT CAGTCGTGTG CTTCTTGAAC AACTTCTACC CCAAAGACAT
 501 CAATGTCAAG TGAAGATTTG ATGGCAGTGA ACGACAAAAT GGCCTCCTGA
 551 ACAGTTGGAC TGATCAGGAC AGCAAAGACA GCACCTACAG CATGAGCAGC
 601 ACCCTCAGT TGACCAAGGA CGAGTATGAA CGACATAACA GCTATACCTG
 651 TGAGGCCACT CACAAGACAT CAACTTCACC CATTGTCAAG AGCTTCAACA
 701 GGAATGAGTG TTAG (SEQ ID NO:128)

Ab-3 Heavy Chain

[0163] Amino acid sequence of the mature form (signal peptide removed) of the Ab-3 HC:

1 EVQLQDSGAE LVRFGALVKL SCTASDFNIK DFLHWMRQR PEQGLDWIGR
 51 DPENGDTLY DPKFQDKATL TTDTSNTAY LQLSGLTSET TAVYYCSREA
 101 DYFHDGTSYW YEDVWGAGTT ITVSSAKTTP PSVYPLAPGS AAQTNMVTIL
 151 GCLVKGYPPE PVTVTWNSGS LSSGVHTFPA VLOSDLYTLS SSVTVPSSTW
 201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
 251 DVLITLITPK VTCVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
 301 TFRSVSELPK MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
 351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPLM
 401 DTDGSYFTYS KLVNQESNWE AGNTFTCSVL HEGLHNHTE KSLSHSPGK (SEQ
 ID NO:129)

[0164] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-3 HC:

1 GAGGTTTCAGC TGCAGCAGTC TGGGGCTGAA CTTGTGAGGC CAGGGGCCTT
 51 AGTCAAGTTG TCCTGCACAG CTCTGACTT CAACATTAAA GACTTCTATC
 101 TACACTGGAT GAGGCAGCGG CCTGAACAGG GCCTGGACTG GATTGGAAGG
 151 ATTGATCCTG AGAATGGTGA TACTTTATAT GACCCGAAGT TCCAGGACAA
 201 GGCCACTCTT ACAACAGACA CATCTCCAA CACAGCCTAC CTGCAGCTCA
 251 GCGGCTGAC ATCTGAGACC ACTGCCGTCT ATTACTGTTT TAGAGAGGCG
 301 GATTATTTC ACGATGGTAC CTCCTACTGG TACTTCGATG TCTGGGGCGC
 351 AGGGACCACA ATCACCCTCT CCTCAGCCAA AACGACACCC CCATCTGTCT
 401 ATCCACTGGC CCTGGATCT GCTGCCAAA CTAATCCAT GGTGACCCTG
 451 GGATGCCTGG TCAAGGGCTA TTTCCCTGAG CCAGTGACAG TGACCTGGAA
 501 CTCTGGATCC CTGTCCAGCG GTGTGCACAC CTTCCAGCT GTCTGCAGT
 551 CTGACCTCTA CACTCTGAGC AGCTCAGTGA CTGTCCCTC CAGCACCTGG

 601 CCCAGCGAGA CCGTCACCTG CAACGTTGCC CACCCGGCCA GCAGCACCAA
 651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTGTAAAG CCTTGCATAT
 701 GTACAGTCCC AGAAGTATCA TCTGTCTTCA TCTTCCCCC AAAGCCCAAG
 751 GATGTGCTCA CCATTACTCT GACTCCTAAG GTCACGTGTG TTGTGGTAGA
 801 CATCAGCAAG GATGATCCCG AGGTCCAGTT CAGCTGGTTT GTAGATGATG
 851 TGGAGGTGCA CACAGCTCAG ACGCAACCCC GGGAGGAGCA GTTCAACAGC
 901 ACTTTCGCT CAGTCAGTGA ACTTCCATC ATGCACCAGG ACTGGCTCAA
 951 TGGCAAGGAG TCCAAATGCA GGGTCAACAG TGCAGCTTTC CCTGCCCCCA
 1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGCA GACCGAAGGC TCCACAGGTG
 1051 TACACCATTG 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 CTTTACCTG CTCTGTGTTA CATGAGGGCC
 1301 TGCACAACCA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA
 (SEQ ID NO:130)

[0165] Amino acid sequence of the Ab-3 HC including signal peptide:

1 MKCSWVFFL MAVVTGVNSE VQLQSGAEL VRPGALVKLS CTASDFNIKD
 51 FYLHWMRQRP EQGLDWIGRI DPENGDTLYD PKFQDKATLT TDSSNTAYL
 101 QLSGLTSETT AVYYCSREAD YFHDGTSYWY FDVWGAGTTI TVSSAKITPP
 151 SVYPLAPGSA AQINSMVILG CLVKGYFPEP VVTWNHSGSL SSGVHTFPAV
 201 LQSDLYTLSS SVTVPSSTWP SETVTCNVAH PASSTKVDDK IVPRDCGCKP
 251 CICTVPEVSS VFIFPPKPKD VLTITLTPKV TCVVVDISKD DPEVQFSWFV
 301 DDVEVHTAQT QPREEQFNST FRVSSELPIM HQDWLNGKEF KCRVNSAAFP
 351 APIEKTISKI KGRPKAPQVY TIPPKEQMA KDKVSLTCMI TDFFPEDITV
 401 EWQWNGQPAE NYKNTQPMID TDGSYFYSK LNVQKSNWEA GNTFTCSVLH
 451 EGLHNHHTEK SLSHSPGK (SEQ ID NO:131)

[0166] Nucleic acid sequence of the Ab-3 HC including signal peptide encoding sequence:

1 ATGAAATGCA GCTGGGTCAT CTCTTCCTG ATGGCAGTGG TTACAGGGGT
 51 CAATTCAGAG GTTCAGCTGC AGCAGTCTGG GGCTGAACTT GTGAGGCCAG
 101 GGGCCTTAGT CAAGTTGTCC TGCACAGCTT CTGACTTCAA CATTAAAGAC
 151 TTCTATCTAC ACTGGATGAG GCAGCGGCTT GAACAGGGCC TGGACTGGAT
 201 TGGAAAGGATT GATCCTGAGA ATGGTGATAC TTTATATGAC CCGAAGTTCC
 251 AGGACAAGGC CACTCTTACA ACAGACACAT CCTCCAACAC AGCCTACCTG
 301 CAGCTCAGCG GCCTGACATC TGAGACCACT GCCGTCTATT ACTGTTCTAG
 351 AGAGGCGGAT TATTTCCACG ATGGTACCTC CTACTGGTAC TTCGATGTCT
 401 GGGGCGCAGG GACCACAATC ACCGTCTCCT CAGCCAAAAC GACACCCCA
 451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAATA ACTCCATGGT
 501 GACCCTGGGA TGCTGTGCA AGGGCTATTT CCCTGAGCCA GTGACAGTGA
 551 CCTGGAATC TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
 601 CTGCAGTCTG ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCCTCCAG
 651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCAC CCGGCCAGCA
 701 GCACCAAGGT GGACAAGAAA ATTGTGCCCA GGGATTGTGG TTGTAAGCCT
 751 TGCATATGTA CAGTCCGAGA AGTATCATCT GTCTTCATCT TCCCCCAAA
 801 GCCCAAGGAT GTGCTCACCA TTAATCTGAC TCCTAAGGTC ACGTGTGTG
 851 TGGTAGACAT CAGCAAGGAT GATCCGAGG TCCAGTTCAG CTGGTTGTGA
 901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
 951 CAACAGCACT TTCCGCTCAG TCAGTGAACT TCCATCATG CACCAGGACT

1001 GGCTCAATGGCAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCCT
 1051 GCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGCAGAC CGAAGGCTCC
 1101 ACAGGTGTAC ACCATTCCAC CTCCAAAGGA GCAGATGGCC AAGGATAAAG
 1151 TCAGTCTGAC CTGCATGATA ACAGACTTCT TCCCTGAAGA CATTACTGTG
 1201 GAGTGGCAGT GGAATGGGCA GCCAGCGGAG AACTACAAGA ACACTCAGCC
 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

[0167] The sequences of the Antibody 4 (also referred to herein as Ab-4) LC and HC are as follows:

Ab-4 Light Chain:

[0168] Amino acid sequence of the mature form (signal peptide removed) of the Ab-4 LC:

1 DIQMTQITSS LSASLGDRVS ISCRASQDIS NYLNWYQKP DGTFLKLLIF
 51 TSRLSGVPS RFGSGSGTD YSLITYNLEQ EDFATYFCQQ GDITLPYTFGG
 101 GTKLEIKRAD APTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
 151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:133)

[0169] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-4 LC:

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

[0170] Amino acid sequence of the Ab-4 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGTRC DIQMTQITSS LSASLGDRVS ISCRASQDIS
 51 NYLNWYQKP DGTFLKLLIF TSRLSGVPS RFGSGSGTD YSLITYNLEQ
 101 EDFATYFCQQ GDITLPYTFGG GTKLEIKRAD APTVSIFPP SSEQLTSGGA
 151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:135)

[0171] Nucleic acid sequence of the Ab-4 LC including signal peptide encoding sequence:

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTGCTCT GTTTTCAAGG
 51 TACCAGATGT GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT

101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
 151 AATTATTATA ACTGGTATCA GCAGAAACCA GATGGAACCT TAAACTCCT
 201 TATCTTCTAC ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAGTG
 251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTACAA CCTGGAGCAA
 301 GAAGATTTTG CCACCTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
 351 TTTCGGAGGG GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGCGTCCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTACG
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GTTAG (SEQ ID NO:136)

Ab-4 Heavy Chain:

[0172] Amino acid sequence of the mature form (signal peptide removed) of the Ab-4 HC:

1 EVQLQDSGPE LMKPGASVKM SCKASGYTFT DYNMHWVKON QGKILEWIGF
 51 INPNSGGAGY NQKFKGKATL TVDKSSTAY MELRSLTSED SAVVYCARLG
 101 YDDYDWFY DVWGAGTTVT VSSAKTPPS VYPLAPGSA QTNISMVTLGC
 151 LVKGYFPEPV TVTWNSSGLS SGVHTFPAVL QSDLYTLSS VTPSSTWPS
 201 ETVTCNVVHP ASSTKVDEKI VPRDCGCKPC ICTVPEVSSV FIFPPEKDV
 251 LTITLTPEVT CVVVDISKDD PEVQFSWFVD DVEVHTAQIQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAAPP AIEKTISETK GRPKAPQVYT
 351 IPPPEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTOPIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHTEKS LSHSPGK (SEQ ID
 NO:137)

[0173] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-4 HC:

1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGCAAGG CTCTGGATA TACATTCACT GACTACAACA
 101 TGCACTGGGT GAAGCAGAAC CAAGGAAAGA CCTAGAGTG GATAGGAGAA
 151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAAGT TCAAGGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCTCCAC CACAGCCTAC ATGGAGCTCC
 251 GCAGGCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCCTCAG CAAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCT TGAGCCAGTG ACAGTGACCT GGAACCTCTG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCTTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
 601 GAGACCGTCA CCGCAACGT TGCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCAGGG ATGTGGTTG TAAGCCTTGC ATATGTACAG
 701 TCCAGAAAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTACAG TGTGTGTGG TAGACATCAG
 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACCTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
 1001 AAACCATCTC CAAAACCAA GGCAGACCGA AGGCTCCACA GGTGTACACC

1051 ATTCCAACCT 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 CTCTCGTAA ATGA (SEQ ID
 NO:138)

[0174] Amino acid sequence of the Ab-4 HC including signal peptide:

1 MGWSWTFLL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
 51 YNMHWVKONQ GKILEWIGEL NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
 101 ELRSLTSEDS AVYYCARLGY DDIYDDWYFD VWGAGTTVTV SSAKTTTPSV
 151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFAVLQ
 201 SDLYTLSSSV TVPSTWVPE TVTCNVAFPA SSTKVDKKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTPQ REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 351 IEKTIKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMTD FFPEDITVEW
 401 QWNGQPAENY KNTQPMIDTD GSYFYISKLN VQKSNWEAGN TFTCSVLHEG
 451 LHNHHTKSL SHSPGK (SEQ ID NO:139)

[0175] Nucleic acid sequence of the Ab-4 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAACTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCAGTGAC
 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 TACTTTCGAT GTCTGGGGCG
 401 CAGGACCCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCTGCAG
 601 TCTGACCTCT ACACCTTGAG CAGCTCAGTG ACTGTCCCTT CCAGCACCTG
 651 GCCCAGCGAG ACCGTACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCC CAAAGCCCCA
 801 GGATGTGCTC ACCATTACTC TGA CTCTAA GGTCACGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 1001 ATGGCAAGGA GTTCAAATGC AGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCA AACCAGAGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGGAAATG GGCAGCCAGC GGAGAACTAC AAGAACA CT AGCCATCAT
 1251 GGACACAGAT GGCTCTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCACTCTC CTGGTAAATG

1401 A (SEQ ID NO:140)

[0176] Ab-4 was humanized to generate Ab-5.

Ab-5

[0177] The sequences of the Antibody 5 (also referred to herein as Ab-5) LC and HC are as follows:

Ab-5 Light Chain:

[0178] Amino acid sequence of the mature form (signal peptide removed) of the Ab-5 LC:

1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKPK GKAPKLLIVY
 51 TSRLLSGVPS RFSGSGSGTD FILTISLQP EDFATYYCQQ GDITLPYTFGG
 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNFFY PREAKVQWVKV
 151 DNALQSGNSQ ESYTEQDSKD STYLSSTLT LSKADYEKHK VYACEVTHQG
 201 LSSPVTKSFN RGEK (SEQ ID NO:141)

[0179] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-5 LC:

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCCGCAT CCGTAGGCGA
 51 CCGCGTAACC ATAACATGTA GAGCATCTCA AGATATTTC AACTATTTGA
 101 ATTGGTACCA AAAAAACCC GGCAAAGCAC CTAAACTCCT CATTTACTAT
 151 ACATCAAGAC TCCTCTCCGG CGTTCCATCA CGATTCTCAG GCTCCGGCTC
 201 CGGCACAGAT TTCACACTCA CTATTTCTCT CCTCCAACCA GAAGATTTTG
 251 CAACCTATTA CTGTCAACAA GGCATACAC TCCCATACAC ATTCGGCGGC
 301 GGCACAAAAG TTGAAATTA ACGTACGGTG GCTGCACCAT CTGTCTTCAT
 351 CTTCGCCCA TCTGATGAGC AGTTGAAATC TGGAAGTCC TCTGTTGTGT
 401 GCCTGCTGAA TAACTTCTAT CCCAGAGAGG CCAAAGTACA GTGGAAGGTG
 451 GATAACGCC TCCAATCGGG TAACTCCAG GAGAGTGTC CAGAGCAGGA
 501 CAGCAAGGAC AGCACCTACA GCCTCAGCAG CACCCTGACG CTGAGCAAAG
 551 CAGACTACGA GAAACACAAA GTCTACGCCT GCGAAGTCAC CCATCAGGGC
 601 CTGAGCTCGC CCGTCACAAA GAGCTTCAAC AGGGGAGAGT GT (SEQ ID
 NO:142)

[0180] Amino acid sequence of the Ab-5 LC including signal peptide:

1 MDMRVPALL GLLLWLRGA RCDIQMTQSP SLSASVGDV VITCRASQD
 51 ISNYLNWYQ KPGKAPKLLI YYTSRLSGV PSRFSGSGS TDFLTISL
 101 QPEDFATYYC QQGDTLPYTF GGGTKVEIKR TVAAPSVFIF PPSDEQLKSG
 151 TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSYSLSSST
 201 LTLKADYDK HKVYACEVTH QGLSPVTKS FNRGEC (SEQ ID NO:143)

[0181] 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
 151 ATTTCCAAT ATTTGAATTG GTACCAACAA AAACCCGGCA AAGCACCTAA
 201 ACTCTCTATT TACTATACAT CAAGACTCCT CTCCGGCGTT CCATCACGAT
 251 TCTCAGGCTC CGGCTCCGGC ACAGATTCA CACTCACTAT TTCTCCCTC
 301 CAACCAAGA ATTTTGCAAC CTATTACTGT CAACAAGGCG ATACACTCCC
 351 ATACACATTC GCGCGCGGCA CAAAAGTTGA AATTAACGT ACGGTGGCTG
 401 CACCATCTGT CTTCATCTTC CCGCCATCTG ATGAGCAGTT GAAATCTGGA
 451 ACTGCCTCTG TTGTGTGCTT GCTGAATAAC TTCTATCCA GAGAGGCCAA

501 AGTACAGTGG AAGGTGGATA ACGCCCTCCA ATCGGGTAAC TCCCAGGAGA
 551 GTGTACAGA GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC
 601 CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCTGCGA
 651 AGTACCCAT CAGGGCCTGA GCTCGCCGT CACAAAGAGC TTCAACAGGG
 701 GAGAGTGT (SEQ ID NO:144)

Ab-5 Heavy Chain:

[0182] Amino acid sequence of the mature form (signal peptide removed) of the Ab-5 HC:

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVVRQA PGQGLEWMGE
 51 INPNSGGAGY NQKFKGRVTM TDTSTSTAY MELRSLRSD TAVYYCARLG
 101 YDDIYDDWYF DYWGQGTIVT VSSASTKGPS VFPLAPCSRS TSESTAALGC
 151 LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLS VVTPSSNFG
 201 TQTYTCNVDH KPSNTKVDEK VERKCCVECP PCPAPPVAGP SVFLFPPKPK
 251 DTLISRTPV VTCVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS
 301 TFRVSVLTV VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGPPEPQV
 351 YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPML
 401 DSDGSFFLYS KLTVDKSRWQ QGNVFCSSVM HEALHNHYTQ KSLSLSPGK (SEQ
 ID NO:145)

[0183] Amino acid sequence of the mature form (signal peptide removed) of the Ab-5 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVVRQA PGQGLEWMGE
 51 INPNSGGAGY NQKFKGRVTM TDTSTSTAY MELRSLRSD TAVYYCARLG
 101 YDDIYDDWYF DYWGQGTIVT VSSASTKGPS VFPLAPCSRS TSESTAALGC
 151 LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLS VVTPSSNFG
 201 TQTYTCNVDH KPSNTKVDEK VERKCCVECP PCPAPPVAGP SVFLFPPKPK
 251 DTLISRTPV VTCVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS
 301 TFRVSVLTV VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGPPEPQV
 351 YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPML
 401 DSDGSFFLYS KLTVDKSRWQ QGNVFCSSVM HEALHNHYTQ KSLSLSPG (SEQ
 ID NO:392)

[0184] 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 TACATTACA 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 CTGGTATTTC GATGTTGGG GCCAGGGAAC
351 AACAGTTACC GTCTCTAGTG CCTCCACCAA GGGCCCATCG GTCTTCCCCC
401 TGGCGCCCTG CTCCAGGAGC ACCTCCGAGA GCACAGCGGC CCTGGGCTGC
451 CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT GGAAGTCAGG
501 CGCTCTGACC AGCGGCGTGC ACACCTTCCC AGCTGTCCTA CAGTCTCAG
551 GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG CAACTTCGGC
601 ACCCAGACCT ACACCTGCAA CGTAGATCAC AAGCCCAGCA ACACCAAGGT
651 GGACAAGACA GTTGAGCGCA AATGTTGTGT CGAGTGCCCA CCGTGCCCA
701 CACCACCTGT GGCAGGACCG TCAGTCTTCC TCTTCCCCC AAAACCCAAAG

751 GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACGTGCG TGGTGGTGA
801 CGTGAGCCAC GAAGACCCCG AGGTCCAGTT CAACTGGTAC GTGGACGGCG
851 TGGAGGTGCA TAATGCCAAG ACAAGCCAC GGGAGGAGCA GTTCAACAGC
901 ACGTTCCGTG TGGTCAGCGT CCTCACCCTT GTGCACCAGG ACTGGCTGAA
951 CGGCAAGGAG TACAAGTGA AGGTCTCAA CAAAGGCCTC CCAGCCCCCA
1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGCG 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 CTCGTGATG CATGAGGCTC
1301 TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC GGGTAAA (SEQ
ID NO:146)

[0185] Amino acid sequence of the Ab-5 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASGYTFD
51 YNMHWVRQAP GQGLEWMGEI NPNSGGAGYN QKFKGRVTMT TDTSTSTAYM
101 ELRSLRSDDT AVYYCARLGY DDIYDDWYFD VWGQGTITV SSASTKGPSV
151 FFLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ
201 SSGLYSLSSV VTPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVECP
251 CPAPPVAGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVQFNWYV
301 DGVVEVHNAKT KPREEQFNST FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP
351 APIETISKTK KQPREPQVY TLPPSREEMT KNQVSLTCLV KGFYPSDIAV
401 EWESNGQPEN NYKTTTPMLD SDGSFFLYSK LTVDKSRWQK GNVFSCSVMH
451 EALHNHYTQK SLSLSPGK (SEQ ID NO:147)

[0186] Nucleic acid sequence of the Ab-5 HC including signal peptide encoding sequence:

1 ATGGACTGGA CCTGGAGGAT CCTTCTCTTG GTGGCAGCAG CCACAGGAGC
51 CCACTCCGAG GTGCAGCTGG TGCAGAGCGG CGCCGAGGTA AAAAAACCAG
101 GAGCAAGCGT TAAAGTTTCT TGTAAGCAA GCGGATATAC ATTTACAGAT
151 TACAACATGC ATTGGGTAAG ACAAGCGCCA GGACAAGGAT TGAATGGAT
201 GGGCGAAATT AACCTAATA GTGGAGGAGC AGGCTACAAT CAAAAATTCA
251 AAGGGAGAGT TACAATGACA ACAGACACAA GCACCTTCAAC AGCATATATG
301 GAACTGCGAT CACTTAGAAG CGACGATACA GCTGTATACT ATTGCGCACG
351 ACTTGGGTAT GATGATATAT ATGATGACTG GTATTTTCAT GTTTGGGGCC
401 AGGGAACAAC AGTTACCGTC TCTAGTGCCT CCACCAAGGG CCCATCGGTC
451 TTCCCCCTGG CGCCCTGCTC CAGGAGCACC TCCGAGAGCA CAGCGGCCCT
501 GGGCTGCCTG GTCAAGGACT ACTTCCCGA ACCGGTGACG GTGTCGTGGA
551 ACTCAGGCGC TCTGACCAGC GCGGTGCACA CCTTCCAGC TGTCCTACAG
601 TCCTCAGGAC TCTACTCCCT CAGCAGCGTG GTGACCGTGC CCTCCAGCAA
651 CTTCGGCACC CAGACCTACA CCTGCAACGT AGATCACAAG CCCAGCAACA
701 CCAAGGTGGA CAAGACAGTT GAGCGCAAAT GTTGTGTCGA GTGCCACCG
751 TGCCAGCAC CACCTGTGGC AGGACCGTCA GTCTTCTCT TCCCCCAAA
801 ACCCAAGGAC ACCCTCATGA TCTCCCGGAC CCCTGAGGTC ACGTGCCTGG
851 TGGTGGACGT GAGCCACGAA GACCCCGAGG TCCAGTTCAA CTGGTACGTG
901 GACGGCGTGG AGGTGCATAA TGCCAAGACA AAGCCACGGG AGGAGCAGTT
951 CAACAGCACG TTCCGTGTGG TCAGCGTCTT CACCGTTGTG CACCAAGACT
1001 GGCTGAACGG CAAGGAGTAC AAGTGAAGG TCTCCAACA AGGCCTCCCA
1051 GCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGGCAGC CCGGAGAACC

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

Ab-5 Variable domains:

[0187] Ab-5 light chain variable domain amino acid sequence (without signal sequence):

1 DIQMTQSPSS LSASVGDRTV ITCRASQDIS NYLNWYQOKP GKAPKLLIY
 51 YSRLLSGVPS RFGSGSGTD FTLTISSLQP EDFATYYCQQ GDTLPYTFGG
 101 GTKVEIK (SEQ ID NO:376)

[0188] Ab-5 light chain variable domain DNA sequence (without signal sequence):

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCCGCAT CCGTAGGCCGA
 51 CCGCGTAAACC ATAACATGTA GAGCATCTCA AGATATTTC AACTATTGA
 101 ATTGGTACCA ACAAAAACCC GGCAAAGCAC CTAAACTCCT CATTACTAT
 151 ACATCAAGAC TCCTCTCCGG CGTTCCATCA CGATTCTCAG GCTCCGGCTC
 201 CGGCACAGAT TTCACACTCA CTATTCCTC CCTCCAACCA GAAGATTTTG
 251 CAACCTATTA CTGTCAACAA GGCGATACAC TCCATACAC ATTCGGCGGC
 301 GGCACAAAAG TTGAAATTAA A (SEQ ID NO:377)

[0189] Ab-5 heavy chain variable domain amino acid sequence (without signal sequence):

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
 51 INPNSGGAGY NQKPKGRVTM TTDSTSTAY MELRSLRSDD TAVYYCARLFG
 101 YDDIYDDWYFDV DWVGQTTVT VSS (SEQ ID NO:378)

[0190] Ab-5 heavy chain variable domain DNA sequence (without signal sequence):

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTAAAAAAC CAGGAGCAAG
 51 CGTTAAAGTT TCTGTAAAG CAAGCGGATA TACATTACA GATTACAACA
 101 TGCAATTGGGT AAGACAAGCG CCAGGACAAG GATTGGAATG GATGGGCGAA
 151 ATTAACCTTA ATAGTGGAGG AGCAGGCTAC AATCAAAAAT TCAAAGGGAG
 201 AGTTACAATG ACAACAGACA CAAGCACTTC AACAGCATAT ATGGAACCTGC
 251 GATCACTTAG AAGCGACGAT ACAGCTGTAT ACTATTGCGC ACGACTTGGG
 301 TATGATGATA TATATGATGA CTGGTATTTC GATGTTGGG GCCAGGGAAC
 351 AACAGTTACC GTCTCTAGT (SEQ ID NO:379)

[0191] 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:	LGYYDDIYDDWYFDV (SEQ ID NO:247)

[0192] 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

[0193] The sequences of the Antibody 6 (also referred to herein as Ab-6) LC and HC are as follows:

Ab-6 Light Chain:

[0194] Amino acid sequence of the mature form (signal peptide removed) of the Ab-6 LC:

1 DIQMTQTSS LSASLGDRVT ISCRASQDIS NYLNWFQOKP DGTILKLLIFY
 51 TSRLHSGVPS RFGSGSGTD YSLTISNLEQ EDIATYFCQQ GDITLPYTFGG
 101 GTKLEIRRAD AAPTYSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
 151 DGSEKQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:149)

[0195] 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 AATTATTAA
 101 ACTGGTTTCA GCAGAAACCA GATGGAAGTC TAAACTCCT GATCTTCTAC
 151 ACATCAAGAT TACACTCAGG AGTTCCATCA AGGTTCACTG CAGTGGGTC
 201 TGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAGCAA GAAGATATTG
 251 CCATTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC GTTCGGGGG
 301 GGGACCAAGC TGAAATAAG ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 351 CTTCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCCTACA GCATGAGCAG CACCCTCAG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
 NO:150)

[0196] Amino acid sequence of the Ab-6 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTSS LSASLGDRVT ISCRASQDIS
 51 NYLNWFQOKP DGTILKLLIFY TSRLHSGVPS RFGSGSGTD YSLTISNLEQ
 101 EDIATYFCQQ GDITLPYTFGG GTKLEIRRAD AAPTYSIFPP SSEQLTSGGA
 151 SVVCFLNNFY PKDINVKWKI DGSEKQNGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:151)

[0197] Nucleic acid sequence of the Ab-6 LC including signal peptide encoding sequence:

1 ATGATGTCCT CTGCTCAGT CTTGGTCTC CTGTTGCTCT GTTTCAAGG
 51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
 101 CTCTGGGAGA CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC
 151 AATTATTAA ACTGGTTTCA GCAGAAACCA GATGGAAGTC TAAACTCCT
 201 GATCTTCTAC ACATCAAGAT TACACTCAGG AGTTCCATCA AGGTTCACTG
 251 CAGTGGGTC TGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAGCAA
 301 GAAGATATTG CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC
 351 GTTCGGGGGG GGGACCAAGC TGAAATAAG ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCCTACA GCATGAGCAG CACCCTCAG
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GTTAG (SEQ ID NO:152)

Ab-6 Heavy Chain:

[0198] Amino acid sequence of the mature form (signal peptide removed) of the Ab-6 HC:

1 EVQLQDSGPE LMKPGASVKM SCKASGYTFT DYNMHWVKON QGKSLEWIG
 51 INDSGGSGY NQKFKQKATL TVDKSSSTAY MELRSLTSED SAVYYCARLY
 101 YDGSYEDWAF DYWGAGITVT VSSAKTTPS VYPLAPGSA QTNMVTLG
 151 LVKGYFPFV TVTWNAGSL SGVHTFPAVL QSDLYTLSS VTPSSSTWPS
 201 ETVTCNV AHP ASSTKYDEKI VPRDCGCKPC ICTYPEVSSV FIFPPKPKDV
 251 LITITLTPKVT CVYVDISKDD PEVQFSWFFD DVEVHTAQTQ PREEQNSTF
 301 RSVSELPIMH QDWLNGKEFK CRYNSAAFP A PIEKTISKTK GRPKAPQVYT
 351 IPPPKQMAK DKVSLTCLMT DFFPEDITVE WQWNGQPAEN YKNTQPMIDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTKS LSHSPGK (SEQ ID
 NO:153)

[0199] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-6 HC:

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1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGCAAGG CTCTGGATA CACATTCAC TACTACAACA
101 TGCACCTGGG TAAACAGAAG 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 CCAAAACGAC ACCCCCATCT GTCTATCCAC
401 TGGCCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC CCTGGGATGC
451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACCTCTGG
501 ATCCTGTGCC AGCGGTGTGC ACACCTCCC AGCTGTCTG CAGTCTGACC
551 TCTACACTCT GAGCAGTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
601 GAGACCGTCA CCTGCAACGT TGCCCAACCG GCCAGCAGCA CCAAGGTGGA
651 CAAGAAAATT GTGCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
701 TCCAGAAAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
751 CTCACCATTA CTCTGACTCC TAAGGTACAG TGTGTGTGG TAGACATCAG
801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC

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901 TCGTCACTCA GTGAACCTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCTGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
1051 ATTCACCTC CAAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
1251 GGAGGCAGGA AATCATTTCA CTGCTCTGT GTTACATGAG GGCCTGCACA
1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID
NO:154)

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[0200] Amino acid sequence of the Ab-6 HC including signal peptide:

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1 MGWSWTFLL LSGTAGVLSE VQLQSGPEL MKPGASVKMS CKASGYTFD
51 YNMHWVKQNG KSLSEWIGEI NPNSGGSGYN QKFKGKATLT VDKSSSTAYM
101 ELRLTSEDS AVYYCARLVY DGSYEDWYFD VWGAGTTVTV SSAKTTTPSV
151 YPLAPGSAAG TNSMVTGLCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
201 SDLYTLSSSV TVPSTWPSB TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
251 CTVPEVSSVF IPPPKPDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
301 VEVHTAQTPQ REQFNSTFR SVSELPIMHQ DWLNGKEKFC RVNSAAFPAP
351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMIDT FFPEDITVEW
401 QWNGQPAENY KNTQPMIDT GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
451 LHNHHTESL SHSPGK (SEQ ID NO:155)

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[0201] Nucleic acid sequence of the Ab-6 HC including signal peptide encoding sequence:

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1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCACTGAC
151 TACAACATGC ACTGGGTGAA ACAGAAACCA GGAAGAGGCC TAGAGTGGAT
201 AGGAGAAATT AATCCTAACA GTGGTGGTAG TGGCTACAAC CAAAAGTTCA
251 AAGGCAAGGC CACATTGACT GTAGACAAGT CTTCCAGCAC AGCCTACATG
301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 ATTGGTCTAC GATGGCAGCT ACCAGGACTG GTACTTCGAT GTCTGGGGCG
401 CAGGGACCAAC GGTCAACGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
451 TATCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
501 GGGATGCTG GTCAAGGCTT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCTGCAAG
601 TCTGACCTCT AACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
651 GCCCAGCGAG ACCGTACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGACATA
751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCCA
801 GGATGTGCTC ACCATTACTC TGAATCCTAA GGTCAACGTT GTTGTGGTAG
851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
951 CACTTCCGCG TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCTGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAGGC AGACCGAAGG CTCCACAGGT
1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
1151 TGACCTGCAT GATAACAGAC TTCTCCCTG AAGACATTAC TGTGGAGTGG
1201 CAGTGGAAATG GGCAGCCAGC GGAGAACTAC AAGAACAATC AGCCCATCAT

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

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Ab-7

[0202] The sequences of the Antibody 7 (also referred to herein as Ab-7) LC and HC are as follows: Ab-7 Light Chain:

[0203] Amino acid sequence of the mature form (signal peptide removed) of the Ab-7 LC:

1 DIQMTQTSS LSASLGDRVT ICCRASQVIT NYLYWYQQKP DGI~~FKLLIYY~~
 51 ~~TSRLHSGVPS~~ RFSGSGSGTD YSLTISNLEQ EDIATYFCQ~~Q~~ GDILPYTFGG
 101 GTKLEIKRAD AAPTYSIFPP SSEQLTSGGA SVVCFLNNFY PKDINV~~KWKI~~
 151 DGSE~~RQNGVL~~ NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:157)

[0204] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-7 LC:

1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
 51 CAGAGTCACC ATCTGTTGCA GGGCAAGTCA GGTCAATTACC AATTATTTAT
 101 ACTGGTATCA GCAGAAACCA GATGGAACCT TAAACTCCT GATCTACTAC
 151 ACATCAAGAT TACACTCAGG AGTCCCATCA AGGTTCAAGT GCAGTGGGTC
 201 TGGAAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAACAG GAAGATATTG
 251 CCACTTACTT TTGCCAACAG GGTGATACGC TTCCTGACAC GTTCGGAGGG
 301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 351 CTTC~~CCACCA~~ TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GT (SEQ ID
 NO:158)

[0205] Amino acid sequence of the Ab-7 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGRIC DIQMTQTSS LSASLGDRVT ICCRASQVIT
 51 NYLYWYQQKP DGI~~FKLLIYY~~ TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ
 101 EDIATYFCQ~~Q~~ GDILPYTFGG GTKLEIKRAD AAPTYSIFPP SSEQLTSGGA
 151 SVVCFLNNFY PKDINV~~KWKI~~ DGSE~~RQNGVL~~ NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:159)

[0206] Nucleic acid sequence of the Ab-7 LC including signal peptide encoding sequence:

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTCAAGG
 51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
 101 CTCTGGGAGA CAGAGTCACC ATCTGTTGCA GGGCAAGTCA GGTCAATTACC
 151 AATTATTTAT ACTGGTATCA GCAGAAACCA GATGGAACCT TAAACTCCT
 201 GATCTACTAC ACATCAAGAT TACACTCAGG AGTCCCATCA AGGTTCAAGT
 251 GCAGTGGGTC TGGAAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAACAG
 301 GAAGATATTG CCACTTACTT TTGCCAACAG GGTGATACGC TTCCTGACAC
 351 ~~CTTC~~CTGAGG~~CC~~ GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GT (SEQ ID NO:160)

Ab-7 Heavy Chain:

[0207] Amino acid sequence of the mature form (signal peptide removed) of the Ab-7 HC:

1 EVQLQDSGPE LMKPGASVKM SCKASGYTFT DYNMHWMKQN QGKSLEWIG
 51 INPNSGGAGY NQQFKGKATL TVDKSSRTAY MELRSLTSED SAVVYCARLG
 101 YVGNVEDWYF DYWGAGTTVT VSSAKTTPPS VYPLAPGSAA QTNMVTLG
 151 LVKGYFPEPV TVTWNSSLS SGVHTFPAVL QSDLYTLSSS VTPSSTWPS
 201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAAFP A PIKTIKTK GRPKAPQVYT
 351 IPPPKQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPMIDT
 401 DGSYFIYSKL NVQKSNWEAG NTFCTSVLHE GLENNHTEKS LSHSPGK (SEQ ID
 NO:161)

[0208] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-7 HC:

1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
 51 AGTGAAGATG TCCTGCAAGG CTCTGGATA CACATTCAC TACTACAACA
 101 TGCACCTGAT GAAGCAGAAC CAAGGAAAGA GCCTAGAATG GATAGGAGAA
 151 ATTAATCTTA ACAGTGGTGG TGCTGGCTAC AACCAGCAGT TCAAAGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAG GACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACGTTGGTA ATTACGAGGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCTCAG CAAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC CTTGGGATGC
 451 CTGGTCAAGG GCTATTTCCT TGAGCCAGTG ACAGTGACCT GGAACCTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CTTCCAGCAC CTGCCCCAGC
 601 GAGACCGTCA CTTGCAACGT TGCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
 701 TCCCAGAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTG TAGACATCAG
 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACCTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTCCCTGCC CCCATCGAGA
 1001 AAACCATCTC CAAAACCAA GGCAGACCGA AGGCTCCACA GGTGTACACC
 1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
 1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGA
 1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
 1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
 1251 GGAGGCAGGA AATACTTCA CCGTCTCTGT GTTACATGAG GGCCTGCACA

- 130T ACCACCATATCTGAGAAGAGC CTCTCCCACT CTCTGGTAA A (SEQ ID
 NO:162)

[0209] Amino acid sequence of the Ab-7 HC including signal peptide:

1 MGWSWTFLE LSGTAGVLSE VQLQDSGP EL MKPGASVKMS CKASGYTFTD
 51 YNMHWKQNG QKSLEWIG EI NPNSGGAGYN QQFKGKATLT VDKSSRTAYM
 101 ELRSLTSEDS AVYYCARLGY VGNVEDWYFD VWGAGTTVT VSSAKTTPPSV
 151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPV TVTWNSSLS GVHTFPAVLQ
 201 SDLYTLSSSV TVPSSTWPS TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTQ PREEQFNSTF RSVSELPIMH QDWLNGKEFK CRVNSAAFPAP
 351 IEKTIKTKG RPKAPQVYTI PPPKQMAKD KVS LTCMITD FFPEDITVEW
 401 QWNGQPAEN YKNTQPMIDT DGSYFIYSKL NVQKSNWEAG NTFCTSVLHEG
 451 LHNHTEKSL SHSPGK (SEQ ID NO:163)

[0210] Nucleic acid sequence of the Ab-7 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTCCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGAACCTA ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCACTGAC
 151 TACAACATGC ACTGGATGAA GCAGAACCAA GGAAAGAGCC TAGAATGGAT
 201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGCAGTTCA
 251 AAGGCAAGGC CACATTGACT GTAGACAAGT CCTCCAGGAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 351 ATTGGGCTAC GTTGGTAATT ACGAGGACTG GACTTTCGAT GTCTGGGGCG
 401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCTGCAG
 601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTACCTT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGTTGTAA GCCTTGCATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
 801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTACCGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGATAGATGAT
 901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCGCG TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 1001 ATGGCAAGGA GTTCAAATGC AGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAAGAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGAATG GGCAGCCAGC GGAGAACTAC AAGAACACTC AGCCCATCAT
 1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAA
 (SEQ ID NO:164)

Ab-8

[0211] The sequences of the Antibody 8 (also referred to herein as Ab-8) LC and HC are as follows:

Ab-8 Light Chain:

[0212] Amino acid sequence of the mature form (signal peptide removed) of the Ab-8 LC:

1 DIQMTQTSS LSASLGDRVS ISCRASQDIS NYLNWYQKP DGTFLKLIYF
 51 TSRLLSGVPS RFSGSGSGTD YSLITYNLEQ EDFATYFCQQ GDTLPYTFGG
 101 GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFLLNFF PKDINVKWKI
 151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:165)

[0213] 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 AATTATTAA
 101 ACTGGTATCA GCAGAAACCA GATGGAACCT TAAACTCCT TATCTTCTAC
 151 ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCACTG GCAGTGGGTC
 201 TGGAAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA GAAGATTITG
 251 CCAGTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
 301 GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 351 CTTCACCA CAAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
 NO:166)

[0214] Amino acid sequence of the Ab-8 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTSS LSASLGDRVS ISCRASQDIS
 51 NYLNWYQKP DGTFLKLIYF TSRLLSGVPS RFSGSGSGTD YSLITYNLEQ
 101 EDFATYFCQQ GDTLPYTFGG GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA
 151 SVVCFLLNFF PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:167)

[0215] Nucleic acid sequence of the Ab-8 LC including signal peptide encoding sequence:

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1 ATGATGTCCT CTGCTCAGTT CTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGCTGCGCT
101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAACIT TAAACTCCT
201 TATCTTCTAC ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAAGT
251 GCAGTGGGTC TGGACAGAT TATTCTCTCA CCATTACAA CCTGGAGCAA
301 GAAGATTTTG CCAGTTACTT TGGCAACAG GGAGATACGC TTCCGTACAC
351 TTTCCGAGGG GGGACAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACCTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCTCG AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCAG
601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GTTAG (SEQ ID NO:168)

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Ab-8 Heavy Chain:

[0216] Amino acid sequence of the mature form (signal peptide removed) of the Ab-8 HC:

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1 EVQLQDSGPE LMKPGASVKM SCKASGYTFT DYNMHVVKQN QGKTLDWIGE
51 NPNSGGAGY NQKFKGKATL TVDKSSTAY MELRSLTSED SAVYYCARLG
101 YDDIYDDWYF DVWGAGTTVT VSSAKTPPS VIPLAPGSAA QTNMVTLGCL
151 LVKGYFPEPV TVTWSGSL SSVHTFPAVL QSDLYTLSSS VTPSSTWPS
201 ETVTCNVAP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
251 LITILTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
301 RSVSELPIMH QDWLNGKEFK CRVNSAAFP A PIEKTISKTK GRPKAPQVYT
351 IPPPKQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
401 DGSYFIYSKL NVQKSNWEAG NTFCTSVLHE GLBNHHTKES LSHSPGK (SEQ ID
NO:169)

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[0217] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-8 HC:

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1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA TACATTCATC GACTACAACA
101 TGCACCTGGT GAAGCAGAAC CAAGGAAAGA CCTAGACTCG GATAGGAGAA
151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAAGT TCAAGGGCAA
201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
351 CACGGTCACC GTCTCCTCAG CCAAAACGAC ACCCCCATCT GTCTATCCAC
401 TGGCCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC COTGGGATGC
451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACCTCTGG
501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCTCT CAGTCTGACC
551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCAGC
601 GAGACCGTCA CCTGCAACGT TGCCACCCCG GCCAGCAGCA CCAAGGTGGA
651 CAAGAAAATT GTGCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
701 TCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAGGCC CAAGGATGTG
751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTGTAGAT GATGTGGAGG
851 TGCACACAGC TCAGACGCAA CCCCGGGAGG AGCAGITCAA CAGCACTTTC
901 CGCTCAGTCA GTGAACCTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTCCCTGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA 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 TGAGAAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID
NO:170)

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[0218] Amino acid sequence of the Ab-8 HC including signal peptide:

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1 MGWSWTFLEF LSGTAGVLSE VQLQDSGP EL MKPGASVKMS CKASGYTFD
51 YNMHWVKQNQ GKTLDWIGE NPNSGGAGY NQKFKGKATL TVDKSSTAYM
101 ELRSLTSEDS AVYYCARLGY DDIYDDWYFD VWGAGTTVT VSSAKTPPSV
151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPV TVTWSGSLSS GVHTFPAVLQ

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201 SDLYTLSSSV TVPSTWPSE TVTCNVAHPA SSTKVDKKTIV PRDCGCKPCI
 251 CTVPVSVSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP BVQFSWFVDD
 301 VEVHTAQTOP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 351 IEKTIKTKG RPKAPQVYTI PPPKEQMAKD KVS LTCMTD FFPEDITVEW
 401 QWNGQPAENY KNTQPMIDTD GSYFTYSKLN VQKSNWEAGN TFTCSVLHEG
 451 LHNHHTKSL SHSPGK (SEQ ID NO:171)

[0219] Nucleic acid sequence of the Ab-8 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTCCTC CTGTCAGGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAACCTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCACTGAC
 151 TACAACATGC ACTGGGTGAA GCAGAACCAA GGAAAGACCC TAGACTGGAT
 201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA
 251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
 301 GAGTCCGCA 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 ATTCCCTGA GCCAGTGACA GTGACCTGGA
 551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCTGTCAG
 601 TCTGACCTCT AACTCTGAG CAGCTCAGTG ACTGTCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAATTTGTG CCCAGGGATT GTGGITGTAA GCCTGCATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCC CAAAGCCCAA
 801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTCACGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGAATG GGCAGCCAGC GGAGAACTAC AAGAACAATC AGCCCATCAT
 1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGTCAAT GTGCAGAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTACCT GCTCTGTGT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCACTCTC CTGGTAAATG
 1401 A (SEQ ID NO:172)

Ab-9

[0220] The sequences of the Antibody 9 (also referred to herein as Ab-9) LC and HC are as follows:

Ab-9 Light Chain:

[0221] Amino acid sequence of the mature form (signal peptide removed) of the Ab-9 LC:

1 DIQMTQITSS LSASLGDRVS ISCRASQDIS NYLNWYQKP DGTFKLLIF?
 51 TSRLFSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDITLPTFGG
 101 GTKVEIKRAD AAPTVISFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
 151 DGSEERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:173)

[0222] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-9 LC:

1 GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT CTCTGGGAGA
 51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
 101 ATTGGTATCA GCAGAAACCA GATGGAACCT TAAACTCCT TATCTTCTAC
 151 ACATCAAGAT TATTTTCAGG AGTCCCATCA AGGTTCACTG GCAGTGGGTC
 201 TGGAACAGAT TATTCTCTCA CCATTACAA CCTGGAGCAA GAAGATTTTG
 251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTCCGGAGGG
 301 GGGACCAAGG TGGAATAAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 351 CTTCCCAACA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCAGCTACA GCATGAGCAG CACCTTCAG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GT (SEQ ID
 NO:174)

[0223] Amino acid sequence of the Ab-9 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGTIC DIQMTQITSS LSASLGDRVS ISCRASQDIS
51 NYLNLWYQQKP DGTFLKLLIFY TSRLFSGVPS RFSGSGSGTD YSLTIYNLEQ
101 EDFATYFCQQ GDTLPYTFGG GTKVEIKRAD AAPTVSIFPP SSEQLTSGGA
151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:175)

[0224] Nucleic acid sequence of the Ab-9 LC including signal peptide encoding sequence:

1 ATGATGTCTC CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT
101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
151 AATTATTTAA ATTGGTATCA GCAGAAACCA GATGGAACCT TAAACTCCT
201 TATCTTCTAC ACATCAAGAT TATTTTCAGG AGTCCCATCA AGGTTCAAGT
251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
351 TTTCCGAGGG GGGACCAAGG TGAAATAAAA ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCTCT AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCAGC
601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GT (SEQ ID NO:176)

Ab-9 Heavy Chain:

[0225] Amino acid sequence of the mature form (signal peptide removed) of the Ab-9 HC:

1 EVQLQSGPE LMKPGTSVKM SCKASGYTFT DYNMHVVKQT QGKILEWIGB
51 INPNSGQAGY NQKFKGKATL TVDKSSTTAY MELRSLTSED SAVVYCAKLG
101 YDDTYDDWYF DVWGAAGTIVT VSSAKTTAPS VYPLAPVCGD TTGSSVTLGC
151 LVKGYFPEPV TLTWNSGSL SDVHTFPALL QSGLYTLSSS VYVTTWPSQT
201 ITCNVAHPAS STKVDKKIEP RGSPTHEKPC PCPAPNLLGG PSVFIFPPKI
251 KDVLMISLSP MYTCVYVDVS EDDPDVHVSW FVNNVEVHTA QTQTHREDYN

301 STIRVVSALP IQHQDWMSGK EFCKKYNKA LPAPIERTIS KPKGVPVRAQ
351 VYVLPPEEEE MTKKQVTLTC MITDFMPEDI YVEWTNNGQT ELNYKNTEPV
401 LDSDGSYFMY SKLRVEKKNW VERNYSYCSV VHEGLHNHHT TKSFSRTPGK
(SEQ ID NO:177)

[0226] 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
151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAGT TCAAGGGCAA
201 GGCCACATTG ACTGTAGACA AGTCTCCAC CACAGCCTAC ATGGAGCTCC
251 GCAGCCTGAC ATCTGAGGAC TCTGCACTCT ATTACTGTGC AAAATTGGGC
301 TACGATGATA TCTACGACGA CTGGTATTTC GATGTCTGGG GCGCAGGGAC
351 CACGGTCACC GTCTCCTCAG CCAAAACAAC AGCCCCATCG GTCTATCCAC
401 TGGCCCCTGT GTGTGGAGAT ACAACTGGCT CCTCGGTGAC TCTAGGATGC
451 CTGGTCAAGG GTTATTTCCC TGAGCCAGTG ACCTTGACCT GGAACCTTGG
501 ATCCCTGTCC AGTGATGTGC ACACCTCCC AGCTCTCTG CAGTCTGGCC
551 TCTACACCCT CAGCAGCTCA GTGACTGTAA CCACCTGGCC CAGCCAGACC
601 ATCACCTGCA ATGTGGCCCA CCCGGCAAGC AGCACCAAAG TGGACAAGAA
651 AATTGAGCCC AGAGGGTCCC CAACACATAA ACCCTGTCTT CCATGCCAG
701 CTCCTAACCT CTTGGGTGGA CCATCCGTCT TCATCTTCCC TCCAAAGATC
751 AAGGATGTAC TCATGATCTC CTTGAGCCCC ATGGTCACGT GTGTGGTGGT
801 GGATGTGAGC GAGGATGACC CAGATGTCCA TGTCAGCTGG TTCGTGAACA
851 ACGTGGAAGT ACACACAGCT CAGACACAAA CCCATAGAGA GGATTACAAC
901 AGTACTATCC GGGTGGTCAG TGCCCTCCCC ATCCAGCACC AGGACTGGAT
951 GAGTGGCAAG GAGTCAAAAT GCAAGGTCAA CAACAAAGCC CTCCCAGCGC
1001 CCATCGAGAG AACCATCTCA AAACCCAAAG GGCCAGTAAG AGCTCCACAG
1051 GTATATGTCT TGCTCCACC AGAAGAAGAG ATGACTAAGA AACAGGTAC
1101 TCTGACCTGC ATGATCACAG ACTTCATGCC TGAAGACATT TACGTGGAGT
1151 GGACCAACAA CGGGCAAACA GAGCTAAACT ACAAGAACAC TGAACCACTC
1201 CTGGACTCTG ATGGTTCTTA CTTATGTAC AGCAAGCTGA GAGTGGAAAA
1251 GAAGAACTGG GTGGAAAGAA ATAGCTACTC CTGTTCAAGT GTCCACGAGG
1301 GTCTGCACAA TCACCACACG ACTAAGAGCT TCTCCCGGAC TCCGGGTAAA
(SEQ ID NO:178)

[0227] Amino acid sequence of the Ab-9 HC including signal peptide:

1 MGWSWTFLL LSGTAGVLSE VQLQSGPEL MKPGTSVKMS CKASGYTFTD
51 YNMHWVKQTQ GKTLWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
101 ELRLTSEDS AVYYCAKLG YDDIYDDWYFD VWGAGTTVTV SSAKTTAPSV
151 YPLAPVCGDT TGSSVTLGCL VKGYFPEPVT LTWNSGSLSS DVHTFPALLQ
201 SGLYTLSSSV TVTTPWSQTI TCNVAHPASS TKVDKKIEPR GSPTHKPCPP
251 CPAPNLLGGP SVFIFPPKIK DVLMSLSPM VTCVVVDVSE DDPDVHVSWF
301 VNNVEVHTAQ TQTHREDYNS TIRVVSALPI QHQDWMSGKE FKCKVNNKAL
351 PAPIERTISK PKGPVRAPOV YVLPPEEEM TKKQVLTTCM ITDFMPEDIY
401 VEWTTNNGQTE LNYKNTEPVL DSDGSYFMYS KLRVEKKNWV ERNSYSCSVV
451 HEGLEHNHHTT KSFSRTPGK (SEQ ID NO:179)

[0228] Nucleic acid sequence of the Ab-9 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAACTGC 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 CCTTCCAGC TCTCCTGCAG
601 TCTGGCCTCT ACACCCTCAG CAGCTCAGTG ACTGTAACCA CCTGGCCCAG
651 CCAGACCATC ACCTGCAATG TGGCCCACCC GGCAAGCAGC ACCAAAGTGG
701 ACAAGAAAAT TGAGCCCAAG GGTGCCCAA CACATAAACC CTGTCTCTCA
751 TGCCAGCTC CTAACCTCTT GGGTGGACCA TCCGTCTTCA TCTTCCCTCC
801 AAAGATCAAG GATGTACTCA TGATCTCCCT GAGCCCCATG GTCACGTGTG
851 TGGTGGTGA TGTGAGCGAG GATGACCCAG ATGTCCATGT CAGCTGGTTC
901 GTGAACAACG TGAAGTACA CACAGCTCAG ACACAAACCC ATAGAGAGGA
951 TTACAACAGT ACTATCCGGG TGGTCAAGTG CCTCCCCATC CAGCACCAGG
1001 ACTGGATGAG TGGCAAGGAG TTCAAATGCA AGGTCAACAA CAAAGCCCTC
1051 CCAGCGCCCA TCGAGAGAAC CATCTCAAAA CCAAAGGGC CAGTAAGAGC
1101 TCCACAGGTA TATGTCTTGC CTCACCAGA AGAAGAGATG ACTAAGAAAC
1151 AGGTCACTCT GACCTGCATG ATCACAGACT TCATGCCTGA AGACATTTAC
1201 GTGGAGTGA CCAACAACGG GCAAAACAGAG CTAAACTACA AGAACTGTA
1251 ACCAGTCTG GACTCTGATG GTTCTTACTT CATGTACAGC AAGCTGAGAG
1301 TGGAAAAGAA GAACTGGGTG GAAAGAAATA GCTACTCCTG TTCAGTGGTC
1351 CACGAGGGTC TGCACAAATCA CCACACGACT AAGAGCTTCT CCCGGACTCC
1401 GGGTAAA (SEQ ID NO:180)

Ab-10

[0229] The sequences of the Antibody 10 (also referred to herein as Ab-10) LC and HC are as follows:

Ab-10 Light Chain:

[0230] Amino acid sequence of the mature form (signal peptide removed) of the Ab-10 LC:

1 DIQMTQTTSS LSASLGDRVS ISCRASQDISNLYLNWYQKP DGTFKLLIFV
51 TSRLLSGVPS RFGSGSGTD YSLTYNLEQ EDFATYFCQQ GDTPYTFGG
101 GTKLEIKRAD AAPTYSIFPL SSEQLTSGGA SVVCFLNIFY PKDINVKKI
151 DGSEKQNGVL NSWTDQDSK STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:181)

[0231] 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 TAAACTCCT TATCTTCTAC
 151 ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCACTG GCAGTGGGTC
 201 TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA GAAGATTTTG
 251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
 301 GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 351 CTTCCCACTA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT

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

[0232] Amino acid sequence of the Ab-10 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTSS LSASLGDRVS ISCRASQDIS
 51 NYLNWYQQKP DGTFKLLIFY TSRLLSGVPS RFGSGSGTD YSLTIYNLEQ
 101 EDFATYFCQQ GDTLPYTFGG GTKLEIKRAD AAPTVSIFPL SSEQLTSGGA
 151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNBC (SEQ ID NO:183)

[0233] Nucleic acid sequence of the Ab-10 LC including signal peptide encoding sequence:

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

Ab-10 Heavy Chain:

[0234] Amino acid sequence of the mature form (signal peptide removed) of the Ab-10 HC:

1 EVQLQDSGPE LMKPGASVKM SCKASGYTFT ~~DYNMH~~WVKQN QGKLEWIG
 51 ~~INENSGGAGY~~ ~~NQKEK~~GKATL TVDKSSTAY MELRSLTSED SAVVYCARL
 101 YDDIYDDWYF DWVGAGTIVT VSSAKTTPS ~~VIPLAPGSA~~ ~~QTN~~SMVTLGC
 151 ~~LYKGYFPEPV~~ ~~TVTWN~~SGSLSGVHTFPAVL ~~QSD~~LYTLSSS ~~VTVPS~~STWPS
 201 ETVTCNVAHP ASSTKVDEKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLIPKVT CVVVDISKDD PEVQFSWFYD DVEVHTAQTQ PREEQFNSTF
 301 RSVSELPIMH ~~QDWL~~NGKEFK CRVNSAAFP ~~PIEKTISKTK~~ GRPKAPQVYT
 351 IPPPEQMAK DKVSLTCMIT DFFPEDITVE ~~WQWNGQPAEN~~ YKNTQIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE ~~GLHNHHT~~TEKS ~~LSHSPGK~~ (SEQ ID
 NO:185)

[0235] 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 TGCACTGGGT GAAGCAGAAC CAAGGAAAGA CCCTAGAATG GATAGGAGAA

151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAAGT TCAAGGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCCTCAG CCAAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAAGTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCTG CAGTCTGACC
 551 TCTACACTCT GAGCAGTCA GTGACTGTCC CCTCCAGCAC CTGGCCAGC
 601 GAGACCGTCA CCTGCAACGT TGCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCAGGG ATTGTGGTGG TAAGCCTTGC ATATGTACAG
 701 TCCAGAAAGT ATCATCTGTC TTCATCTTCC CCCCAGGACC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 801 CAAGGATGAT CCGGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGACACAGC TCAGACGCAA CCCCGGGAGG AGCAGTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAAGTCC 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 CTGCTCTGT GTTACATGAG GGCCTGCACA
 1301 ACCACCATA TGAGAAGAGC CTCTCCCACT CTCTGGTAA ATGA (SEQ ID
 NO:186)

[0236] Amino acid sequence of the Ab-10 HC including signal peptide:

1 MGWSWTFLEL LSGTAGVLSE VQLQSGPEL MKPGASVKMS CKASGYTFD
 51 YNMHWVKQNG GKLEWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTIAYM
 101 ELRSLTSEDS AVYYCARLGY DDIYDDWYFD VWGAGTIVTV SSAKTTPPSV
 151 YPLAPGSAAG TNSMVTGLCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
 201 SDLYTLSSSV TVPSSTWPSE TVTCNVHPA SSTKVDKKIV PRDCGCKPCI
 251 CTVEPVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 351 IEKITSKTKG RPKAPQVYTI PPPKEQMAKD KVSITCMITD FFPEDITVEW
 401 QWNGQPAENY KNTQPMIDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
 451 LHNHHTKSL SHSPGK (SEQ ID NO:187)

[0237] Nucleic acid sequence of the Ab-10 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTTCTCTC CTGTCAAGAA CTGCAGGTGT
 51 CCTCTCTGAG GTCCAACTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCACTGAC
 151 TACAACATGC ACTGGGTGAA GCAGAACCA GGAAGAGCCC TAGAATGGAT
 201 AGGAGAAAT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAAGTTCA
 251 AGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
 301 GAGTCCGCA GCCTGACATC TGAGGACTCT CGAGTCTATT ACTGTGCAAG
 351 ATTGGGCTAC GATGATATCT ACGACGACTG GACTTTCGAT GTCTGGGGCG
 401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCTGGATC TGCTGCCAA ACTAACTCCA TGGTGACCCT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA

551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CTTTCCCAGC TGTCTGCAG
 601 TCTGACCTCT AACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTCACTT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 751 TGTACAGTCC CAGAAATATC ATCTGTCTTC ATCTTCCCC CAAAGCCCAA
 801 GGATGTGCTC ACCATTACTC TGAAGCTTAA GGTCAAGTGT GTTGTGGTAG
 851 ACATGACCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCGCG TCAGTCAAGT AACTTCCCAT CATGCACCAG GACTGGCTCA
 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGGAAAT 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:188)

Ab-11

[0238] The sequences of the Antibody 11 (also referred to herein as Ab-11) LC and HC are as follows:

Ab-11 Light Chain:

[0239] Amino acid sequence of the mature form (signal peptide removed) of the Ab-11 LC:

1 QIVLSQSPAF LSVSPGDKVT MTCRASSIS YIHWFQKPG SSPRSWIYAT
51 SNLASGVPR FSGSGSGTSY SLTISRVEAE DAATYYCQW SSDPLTFGAG
101 TKLELKRA DA APTVSIFPPS SEQLTSGGAS VVCFLNFPY KDINVWKID
151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
201 TSPIVKSFN NEC (SEQ ID NO:189)

[0240] 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 GGTTCAGCA GAAGCCAGGA TCCTCCCCCA GATCCTGGAT TTATGCCACA
151 TCCAACCTGG CTTCTGGAGT CCCTGGTCGC TTCAGTGGCA GTGGGTCTGG
201 GACCTCTTAC TCTCTCAAA TCAGCAGAGT GGAGGCTGAG GATGCTGCCA
251 CTATTACTG 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 CGTCTGAAC AGTTGGACTG ATCAGGACAG
501 CAAAGACAGC ACCTACAGCA TGAGCAGCAC CCTCACGTTG ACCAAGGACG
551 AGTATGAACG ACATAACAGC TATACCTGTG AGGCCACTCA CAAGACATCA
601 ACTTCACCCA TTGTCAAGAG CTTCAACAGG AATGAGTGT AG (SEQ ID
NO:190)

[0241] Amino acid sequence of the Ab-11 LC including signal peptide: 1 MDFVQVIFSF LLISASVIMS RGQIVLSQSP
AFLSVSPGDK VTMTCRASSS

51 ISYIHWFPQK PGGSPRSWIY ATSNLASGVPR FSGSGSGST SYSLTISRVE
101 AEDAATYYCQ QWSSDPLTFG AGTKLELKRA DAAPTVSIFP PSSEQLTSGG
151 ASVVCFLNFP YPKDINVWK IDGSERQNGV LNSWTDQDSK DSTYSMSSTL
201 TLTKDEYERH NSYTCEATHK TSTSPIVKSFN NRNEC (SEQ ID NO:191)

[0242] Nucleic acid sequence of the Ab-11 LC including signal peptide encoding sequence:

1 ATGGATTTC AAGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCTTCAGT
51 CATAATGTCC AGAGGACAAA TTGTTCTCTC CCAGTCTCCA GCATTCTGT
101 CTGTATCTCC AGGGGATAAG GTCACAATGA CTGTCAGGGC CAGCTCAAGT
151 ATAAATTACA TACTCTGGT TCAGCAGAA GAGGATCCT CCCCAGATC
201 CTGGATTTAT GCCACATCCA ACCTGGCTTC TGGAGTCCCT GGTGCTTCA
251 GTGGCAGTGG GTCTGGGACC TCTTACTCTC TCACAATCAG CAGAGTGGAG
301 GCTGAGGATG CTGCCACTTA TACTGCCAG CAGTGGAGTA GTGACCCACT
351 CACGTTCTGGT GCTGGGACCA AGCTGGAGCT GAAACGGGCT GATGCTGCAC
401 CAACTGTATC CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
451 GCCTCAGTCG TGTGCTTCTT GAACAACCTC TACCCCAAAG ACATCAATGT
501 CAAGTGGAAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
551 GGACTGATCA GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCTC
601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
651 CACTCACAAG ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG
701 AGTGTTAG (SEQ ID NO:192)

Ab-11 Heavy Chain:

[0243] Amino acid sequence of the mature form (signal peptide removed) of the Ab-11 HC:

1 EVQLQSGAD LVQPASVKV SCTASGFDIK DYIHWKQR PDQGLEWIGR
51 VDDPNGETEF APKFPGKATF TIDTSSNTAY LQLRGLTSED TAIYYCGRED
101 YDGTYYTWEY WGQGLVTVS AAKTPPSVY PLAPGSAQT NSMVTLGCLV
151 KGFYFPEPTV TWNSGSLSSG VHTFPAVLQS DLYTLSSSVT VPSSTWPSST
201 VTCNVAHPAS STKYDKIIV RDCGCKPCIC TPEVSSVFI FPPKPKDVL
251 ITLTPKVTCTV VVDISKDDPE VQSWFVDDV EVHTAQTPR EEQFNSTFRS
301 VSELPIMHQD WLNGKEFKCR VNSAAPPAPI EKTISKTKGR PKAPQVYITP
351 PPKEQMAKDK VSLTCMITDF FPEDITVEWQ WNGQPAENYK NTQPMIDTDG
401 SYFIYSKLVN QKSNWEAGNT FTCSVLHEGL HNHHTKSLS HSPGK (SEQ ID
NO:193)

[0244] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-11 HC:

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1 GAAGTTCAGC TGCAACAGTC TGGGGCAGAC CTTGTGCAGC CAGGGGCCTC
51 AGTCAAGGTG TCTGCACAG CTTCCTGGCT CGACATTAAG GACTACTATA
101 TACACTGGAT GAAACAGAGG CCTGACCAGG GCCTGGAGTG GATTGGAAGG
151 GTTGATCCTG ACAATGGTGA GACTGAATTT GCCCGAAGT TCCCGGGCAA
201 GGCCACTTTT ACAACAGACA CATCCTCAA CACAGCCTAC CTACAACCTCA
251 GAGGCTGAC ATCTGAGGAC ACTGCCATCT ATTACTGTGG GAGAGAAGAC
301 TACGATGGTA CCTACACCTG GTTCCCTTAT TGGGGCCAAG GGAATCTGGT
351 CACTGTCTCT GCAGCCAAAA CGACACCCCT ATCTGTCTAT CCACTGGCCC
401 CTGGATCTGC TGCCCAAACT AACTCCATGG TGACCTGGG ATGCCTGGTC
451 AAGGGCTATT TCCCTGAGCC AGTGACAGTG ACCTGGAAC CTGGATCCCT
501 GTCCAGCGGT GTGCACACCT TCCAGCTGT CCTGCAGTCT GACCTCTACA
551 CTCTGAGCAG CTCAGTGACT GTCCCTCCA GCACCTGGCC CAGCGAGACC

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

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[0245] Amino acid sequence of the Ab-11 HC including signal peptide:

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1 MKCSWVIFFL MAVVTGVNSE VQLQSGADL VQPGASVKVS CTASGFDIKD
51 YYIHWMKQRP DQGLEWIGRV DPDNGETEFK PKFPGKATFT TDTSSNTAYL
101 QLRGLTSEDT AIYYCGREDY DGTYTWFYVW GQGLTVTVA AKTTPSPVYP
151 LAPGSAQTN SMVTLGCLVK GYFPEPVTVT WNSGSLSSGV HTFPAVLQSD
201 LYTLSSSVTV PSTWPSETV TCNVAHPASS TKVDKKIVPR DCGCKPCICT
251 VPEVSSVFI PPKPKDVLTI ILTPKVTCTV VDISKDDPEV QFSWFVDDVE
301 VHTAQTPRE EQFNSTFRSV SELPMHQDW LNGKEFKCRV NSAAFPAPIE
351 KTISKTKGRP KAPQVYTIPP PKEQMAKDKV SLTCMTDFF PEDITVEWQW
401 NGQPAENYKN TQPMDDTGS YFTYSKLNQV KSNWEAGNTF TCSVLHEGLH
451 NHHTEKSLSH SPGK (SEQ ID NO:195)

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[0246] Nucleic acid sequence of the Ab-11 HC including signal peptide encoding sequence:

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1 ATGAAATGCA GCTGGGTCA CTCTTCCTG ATGGCAGTGG TTACAGGGGT
51 CAATTCAGAA GTTCAGCTGC AACAGTCTGG GGCAGACCTT GTGCAGCCAG
101 GGGCCTCAGT CAAGGTGTCC TGCACAGCTT CTGGCTTCCA CATTAAAGGAC
151 TACTATATAC ACTGGATGAA ACAGAGGCCT GACCAGGGCC TGGAGTGGAT
201 TGGAAAGGTT GATCTGACA ATGGTGAGAC TGAATTGGC CCGAAGTTCC
251 CGGGCAAGGC CACTTTTACA ACAGACACAT CCTCCAACAC AGCCTACCTA
301 CAACTCAGAG GCCTGACATC TGAGGACACT GCCATCTATT ACTGTGGGAG
351 AGAAGACTAC GATGGTACCT ACACCTGGT TCCTTATTGG GGCCAAGGGA
401 CTCTGGTCAC TGCTCTGCA GCCAAAACGA CACCCCATC TGTCTATCCA
451 CTGGCCCCTG GATCTGCTGC CCAAATAAC TCCATGGTGA CCCTGGGATG
501 CCTGTGCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAACCTG
551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCTT CAGTCTGAC
601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCCTCCAGCA CCTGGCCAG
651 CGAGACCGTC ACCTGCAACG TTGCCACCC GGCCAGCAGC ACCAAGGTGG
701 ACAAGAAAAT TGTGCCCAGG GATTGTGTT GTAAGCCTTG CATATGTACA
751 GTCCAGAAAG TATCATCTGT CTTCATCTTC CCCCCAAGC CCAAGGATGT
801 GCTCACCATT ACTCTGACTC CTAAGGTAC GTGTGTTGTG GTAGACATCA
851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTGTGTAGA TGATGTGGAG
901 GTGCACACAG CTCAGACGCA ACCCGGGAG GAGCAGTTCA ACAGCACTTT
951 CCGCTCAGTC AGTGAACCTC CCATCATGCA CCAGGACTGG CTCAATGGCA
1001 AGGAGTTCAA ATGCAGGGTC AACAGTGCA CTTCCTCTGC CCCCATCGAG

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1051 AAAACCATCT CCAAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
1101 CATTCCACCT CCCAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
1151 GCATGATAAC AGACTCTTC CCTGAAGACA TTAATGTGGA GTGGCAGTGG
1201 AATGGGCAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
1251 AGATGGCTCT TACTTCATCT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTTACATGA GGGCTGCAC
1351 AACCACCATA CTGAGAAGAG CCTCTCCAC TCTCTGGTA AATGA (SEQ ID
NO:196)

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Ab-12

[0247] The sequences of the Antibody 12 (also referred to herein as Ab-12) LC and HC are as follows:

Ab-12 Light Chain:

[0248] Amino acid sequence of the mature form (signal peptide removed) of the Ab-12 LC:

1 DLQMTQTSS LSASLGDRVT ISCRASQDIS NYL~~NWYQKP~~ DGT~~VKLLIF~~
 51 ~~T~~STLQSGVPS RFS~~GS~~SGGTN YSLTITNLEQ DDAATYFCQ~~Q~~ GDTLPYTFGG
 101 GTKLEIKRAD AAPT~~V~~SIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKW~~KI~~
 151 DG~~SERQ~~NGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
 201 STSPIVKSFN RNEC (SEQ ID NO:197)

[0249] 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 GATGGAAC~~TG~~ TTAAGCTCCT GATCTTCTAC
 151 ACATCAACAT TACAGTCAGG AGTCCCATCG AGGTTCA~~GTG~~ GCAGTGGGTC
 201 TGGAAACAAAT TATTCTCTCA CCATTACCAA CCTGGAGCAA GATGATGCTG
 251 CCAC~~T~~TACTT TTGCCAACAG GGTGATACGC TTCCGTACAC GTTCGGAGGG
 301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
 351 CTTCCCA~~CCA~~ TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
 401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
 451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
 501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCAGG TTGACCAAGG
 551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
 601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID
 NO:198)

[0250] Amino acid sequence of the Ab-12 LC including signal peptide:

1 MMSSAQFLGL LLLCFQGSRC DLQMTQTSS LSASLGDRVT ISCRASQDIS
 51 NYL~~NWYQKP~~ DGT~~VKLLIF~~Y TSTLQSGVPS RFS~~GS~~SGGTN YSLTITNLEQ
 101 DDAATYFCQ~~Q~~ GDTLPYTFGG GTKLEIKRAD AAPT~~V~~SIFPP SSEQLTSGGA
 151 SVVCFLNNFY PKDINVKW~~KI~~ DG~~SERQ~~NGVL NSWTDQDSKD STYSMSSTLT
 201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:199)

[0251] 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 ~~ACT~~GGTATCA GCAGAAACCA GATGGAAC~~TG~~ TTAAGCTCCT
 201 GATCTTCTAC ACATCAACAT TACAGTCAGG AGTCCCATCG AGGTTCA~~GTG~~
 251 GCAGTGGGTC TGGAAACAAAT TATTCTCTCA CCATTACCAA CCTGGAGCAA
 301 GATGATGCTG CCAC~~T~~TACTT TTGCCAACAG GGTGATACGC TTCCGTACAC
 351 GTTCGGAGGG GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
 401 CTGTATCCAT CTTC~~CA~~CCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
 451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
 501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
 551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCAGG
 601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
 651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
 701 GTTAG (SEQ ID NO:200)

Ab-12 Heavy Chain:

[0252] Amino acid sequence of the mature form (signal peptide removed) of the Ab-12 HC:

1 EVQLQDSGPE LKPGASVKM SCKASGYTFT DYNMHWMKQN QGKSLEWIGE
 51 NPNSSGGSGY NQKFKGKATL TVDKSSSTAY MELRLTSBD SAVYYCARLG
 101 YGNYEDWYFD VVWAGITVT VSSAKTTPPS VYPLAPGSAA QTNMVTLG
 151 LVKGYFPEPV TVTWNSSLS SGVHTFPAVL QSDLYTLSSS VTPSSSTWPS
 201 ETVTCNVAHP ASSTKVDDKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
 251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
 301 RSVSELPIMH QDWLNGKEFK CRVNSAAPP PIEKTISKTK GRPKAPQVYT
 351 IPPPKQMAK DGVSLTCMIT DFPEDITVE WQWNGQPAEN YKNTQPIMDT
 401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTSKS LSHSPGK (SEQ ID
 NO:201)

[0253] 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 CACATTCAC TACTACAACA
 101 TGCACCTGAT GAAGCAGAAC CAAGGAAAGA GCCTAGAGTG GATAGGAGAG
 151 ATTAATCCTA ACAGTGGTGG TTCTGGTTAC AACCAGAAGT TCAAAGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAG CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACTATGTA ACTACGAGGA CTGGTATTTC GATGTCGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCTCTG CCAAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCT TGAGCCAGTG ACAGTGACCT GGAACCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCAGC
 601 GAGACCGTCA CCTGCAACGT TGCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCAGGG ATTGTGTTG TAAGCCTGC ATATGTACAG
 701 TCCAGAGAT ATCATCTGTC TTCATCTCC CCCCAGGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCAGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACCTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC 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 GGCTGCACA
 1301 ACCACATAC TGAGAAAGAG CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID
 NO:202)

[0254] Amino acid sequence of the Ab-12 HC including signal peptide:

1 MGWSWTFLL LSGTSGVLSE VQLQDSGPEL MKPGASVKMS CKASGYTFTD
 51 YNMHWKQNK QKSLEWIGEI NPNSSGGSGYN QKFKGKATLT VDKSSSTAYM
 101 ELRLTSBDS AVYYCARLGY YGNYEDWYFD VVWAGITVTV SSKTTPPSV
 151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPV TVTWNSSLS SGVHTFPAVLQ
 201 SDLYTLSSSV TTPSSSTWSE TVTCNVAHPA SSTKVDDKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVT VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTQ PREEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAPPAP
 351 IEKTISKTKG RPKAPQVYTI PPPKEQMAK DGVSLTCMITD FFPEDITVEW
 401 QWNGQPAEN YKNTQPIMDT DGSYFIYSKL NVQKSNWBAGN TFTCSVLHEG
 451 LHNHHTSKS LSHSPGK (SEQ ID NO:203)

[0255] Nucleic acid sequence of the Ab-12 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTGGACCTT TCTCTCCTC CTGTCAGGAA CTTGGGGTGT
 51 CCTCTCTGAG GTCCAGTTGC AACAGTCTGG ACCTGAAC TAATGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCAGTGAC
 151 TACAACATGC ACTGGATGAA GCAGAACCAA GGAAAGAGCC TAGAGTGGAT
 201 AGGAGAGATT AATCCTAACA GTGGTGGTTC TGGTTACAAC CAGAAGTTCA
 251 AAGGCAAGGC CACATTGACT GTAGACAAGT CCTCCAGCAC AGCCTACATG
 301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 351 ATTGGGCTAC TATGGTAACT ACGAGGACTG GTATTTTCAT GTCTGGGGCG
 401 CAGGGACAC GGTACCGTTC TCCTCTGCCA AAACGACACC CCCATCTGTC
 451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCTT
 501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCAGC TGTCCTGCAG
 601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
 651 GCCCAGCGAG ACCGTACCTT GCAACGTTGC CCACCCGGCC AGCAGCACCA
 701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTCCCCC CAAAGCCCAA
 801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTACAGTGT GTTGTGGTAG
 851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
 901 GTGGAGGTGC ACACAGTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
 1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
 1051 ATCGAGAAAA CCATCTCCAA AACCAAGGC AGACCGAAGG CTCCACAGGT
 1101 GTACACCAT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
 1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
 1201 CAGTGGAAATG GGCAGCCAGC GGAGAACTAC AAGAACAATC AGCCCATCAT
 1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
 1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
 1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCCTCTC CTGGTAAATG
 1401 A (SEQ ID NO:204)

Ab-13

[0256] The sequences of the Antibody 13 (also referred to herein as Ab-13) LC and HC are as follows:

Ab-13 Light Chain:

[0257] Amino acid sequence of the mature form (signal peptide removed) of the Ab-13 LC:

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

[0258] 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 CCCCCAACT CTGGATTAT
 151 AGCACATCCA ACCTGGCTTC AGGAGTCCA GCTCGCTTCA GTGGCAGTGG
 201 GTCTGGGACC TCTTACTCTC TCACAATCAG 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 GGAAGTATCA
 501 GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCCTC ACGTTGACCA
 551 AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC CACTACAAG
 601 ACATCAACTT CACCCATCGT CAAGAGCTTC AACAGGAATG AGTGT (SEQ ID
 NO:206)

[0259] Amino acid sequence of the Ab-13 LC including signal peptide:

1 MDSQVQIFSF LLISALVKMS RGQIVLTQSP AIMSASPGEK VTMTCRASSS
 51 VTSSYLNWYQ QKPGSSPKLW IYSTSNLASG VPARFSGSGS GTSYSLTISV
 101 VEAEDAATYY CQYDFFPST FGGTKLEIK RADAAPT^{VS}I FPPSSEQLTS
 151 GGASVVCFLN NFYPKDINVK WKIDGSE^{RQ}N GVLNSWT^{DQ}D SKDSTYS^{MS}SS
 201 TLTLTKDEYE RHNSYTCEAT HKTSTSPIVK SFNRNEC (SEQ ID NO:207)

[0260] Nucleic acid sequence of the Ab-13 LC including signal peptide encoding sequence:

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1 ATGGATTCTC AAGTGCAGAT TTTGAGCTTC CTTCTAATCA GTGCCCTTAGT
51 CAAAATGTCC AGAGGACAGA TTGTTCTCAC CCAGTCTCCA GCAATCATGT
101 CTGCATCTCC AGGGGAGAAAG GTCACCATGA CCTGCAGGGC CAGCTCAAGT
151 GTAACTTCCA GTTACTTGAA CTGGTACCAG CAGAAGCCAG GATCTTCCCC
201 CAAACTCTGG ATTATAGCA CATCCAACCT GGCTTCAGGA GTCCCAGCTC
251 GCTTCAGTGG CAGTGGGTCT GGGACCTCTT ACTCTCTCAC AATCAGCAGT
301 GTGGAGGCTG AGGATGCTGC CACTTATTAC TGCCAGCAGT ATGATTTTTT
351 CCCATCGACG TTCGGTGGAG GCACCAAGCT GGAAATCAAG CGGGCTGATG
401 CTGCACCAAC TGTATCCATC TTCCCACCAT CCAGTGAGCA GTTAACATCT
451 GGAGGTGCCT CAGTCGTGTG CTTCTTGAAC AACTTCTACC CCAAAGACAT
501 CAATGTCAAG TGGAAGATTG ATGGCAGTGA ACGACAAAAT GCGCTCCTGA

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

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Ab-13 Heavy Chain:

[0261] Amino acid sequence of the mature form (signal peptide removed) of the Ab-13 HC:

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1 EVQLQDSGPE LVKPGASVKM SCKASGYTFT DYYMNWVKQS HGESLEWIGD
51 INPYNDTTY NHKFKGKATL TVDKSSNTAY MQLNSLTSED SAVVYCARETI
101 AVITTNAMDY WGQGSVTVS SAKTTPPSVY PLAPGSAQT NSMVTLGCLV
151 KGYFFPEPVTV TWNSGSLSSG VHTFPAVLQS DLYTLSSSVT VPSSTWPSSET
201 VTCNVAHPAS STKYDEKIVP RDCGCKPCIC TVPEVSSVFI FPPKPKDVLV
251 IITLTPKVTCTV VDISKDDPE VQFSWFVDDV EVHTAQTPR EEQFNSTFRS
301 VSELPIMHQD WLNKKEFKCR VNSAAFPAPI EKTISKTKGR PKAPQVYTIP
351 PPKEQMAKDK VSLTCMITDF FPEDITVEWQ WNGQPAENYK NTQPIMDTDG
401 SYFIYSKLVN QKSNWEAGNT FTCSVLHEGL HNHTEKSLS HSPGK (SEQ ID
NO:209)

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[0262] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-13 HC:

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1 GAGGTCCAGC TGCAACAATC TGGACCTGAG CTGGTGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGTAAGG CTTCTGGATA CACATTCAC TACTACTACA
101 TGAAGTGGGT GAAGCAGAGC CATGGAGAGA GCCTTGAGTG GATTGGAGAT
151 ATTAATCCTT ACAACGATGA TACTACCTAC AACCACAAGT TCAAGGGCAA
201 GGCCACATTG ACTGTAGACA AATCCTCCAA CACAGCCTAC ATGCAGCTCA
251 ACAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGAGAGACG
301 GCCGTTATTA CTACGAATGC TATGGACTAC TGGGGTCAAG GAACCTCAGT
351 CACCGTCTCC TCAGCCAAAA CGACACCCCC ATCTGTCTAT CCACTGGCCC
401 CTGGATCTGC TGCCCAAACT AACTCCATGG TGACCCTGGG ATGCCTGGTC
451 AAGGGCTATT TCCTTGAGCC AGTGACAGTG ACCTGGAAC TGGATCCCT
501 GTCCAGCGGT GTGCACACCT TCCCAGCTGT CTTGCAGTCT GACCTCTACA
551 CTCTGAGCAG CTCAGTGACT GTCCCCTCCA GCACCTGGCC CAGCGAGACC
601 GTCACCTGCA ACGTTGCCA CCCGCCAGC AGCACCAAGG TGGACAAGAA
651 AATTGTGCC AGGGATTGTG GTTGTAAAGC TTGCATATGT ACAGTCCAG
701 AAGTATCATC TGTCTTCATC TTCCCCCAA AGCCCAAGGA TGTGCTCACC
751 ATTACTCTGA CTCCTAAGGT CACGTGTGTT GTGGTAGACA TCAGCAAGGA
801 TGATCCCGAG GTCCAGTTCA GCTGTTTGT AGATGATGTG GAGGTGCACA
851 CAGCTCAGAG GCAACCCCGG GAGGAGCAGT TCAACAGCAC TTTCCGCTCA
901 GTCAGTGAAC TTCCCATCAT GCACCAGGAC TGGCTCAATG GCAAGGAGTT
951 CAAATGCAGG GTCAACAGTG CAGCTTTCCC TGCCCCATC GAGAAAACCA
1001 TCTCCAAAAC CAAAGGCAGA CCGAAGGCTC CACAGGTGTA CACCATTTCA
1051 CCTCCCAAGG AGCAGATGGC CAAGGATAAA GTCAGTCTGA CCTGCATGAT
1101 AACAGACTTC TTCCCTGAAG ACATTACTGT GGAGTGGCAG TGGAATGGGC
1151 AGCCAGCGGA GAACTACAAG AACACTCAGC CCATCATGGA CACAGATGGC
1201 TCTTACTTCA TCTACAGCAA GCTCAATGTG CAGAAGAGCA ACTGGGAGGC
1251 AGGAAATACT TTCACCTGCT CTGTGTTACA TGAGGGCCTG CACAACCACC
1301 ATACTGAGAA GAGCCTCTCC CACTCTCTG GTAAA (SEQ ID NO:210)

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[0263] Amino acid sequence of the Ab-13 HC including signal peptide:

1 MGWNWIFLFL LSGTAGVYSE VQLQSGPEL VKPGASVKMS CKASGYTFTD
 51 YYMNVWKQSH GESLEWIGDI NPYND DTTYN HKFKGKATLT VDKSSNTAYM
 101 QLNSLTSEDS AVYYCARETA VITTNAMDYW GQGTSTVTVSS AKTTPPSVYP
 151 LAPGSAAQTN SMVTLGCLVK GYFPEPTVT WNSGSLSSGV HTFPAVLQSD
 201 LYTLSSSVTV PSSTWPSETV TCNVAHPASS TKVDKKTIVPR DCGCKPCICT
 251 VPEVSSVFIF PPKPKDVLTI TLTPKVTCVV VDISKDDPEV QFSWFVDDVE
 301 VHTAQTPRE BQFNSTFRSV SELPMHQDW LNGKEFKCRV NSAAFPAPIE
 351 KTISKTKGRP KAPQVYTIPP PKEQMAKDKV SLTCMITDDF PEDITVEWQW
 401 NGQPAENYKN TQPMDDTGS YFTYSKLVNQ KSNWEAGNTF TCSVLHEGLH
 451 NHHTEKSLSH SPGK (SEQ ID NO:211)

[0264] Nucleic acid sequence of the Ab-13 HC including signal peptide encoding sequence:

1 ATGGGATGGA ACTGGATCTT TCTCTCCTC TTGTCAGGAA CTGCAGGTGT
 51 CTACTCTGAG GTCCAGCTGC AACAATCTGG ACCTGAGCTG GTGAAGCCTG
 101 GGGCTTCAGT GAAGATGTCC TGTAAAGCCT CTGGATACAC ATTCACGTAC
 151 TACTACATGA ACTGGGTGAA GCAGAGCCAT GGAGAGAGCC TTGAGTGGAT
 201 TGGAGATATT AATCCTTACA ACGATGATAC TACCTACAAC CACAAGTTCA
 251 AGGGCAAGGC CACATTGACT GTAGACAAAT CCTCCAACAC AGCCTACATG
 301 CAGCTCAACA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
 351 AGAGACGGCC GTTATTACTA CGAATGCTAT GGACTIONG GGTCAAGGAA
 401 CCTCAGTCAC CGTCTCCTCA GCCAAAACGA CACCCCATC TGTCTATCCA
 451 TTGGCCCCCTG GATCTGCTGC CCAAATAAC TCCATGGTGA CCTGGGATG
 501 CCTGGTCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAACTCTG
 551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCTT GCAGTCTGAC
 601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCCTCCAGCA CCTGGCCAG
 651 CGAGACCGTC ACCTGCAACG TTGCCACCCC GGCCAGCAGC ACCAAGGTGG
 701 ACAAGAAAAAT TGTGCCCAGG GATTGTGGTT GTAAGCCTTG CATATGTACA
 751 GTCCACAGAAG TATCATCTGT CTTCATCTTC CCCCCAAAGC CCAAGGATGT
 801 GCTCACCATT ACTCTGACTC CTAAGGTCAC GTGTGTTGTG GTAGACATCA
 851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTGTGTAGA TGATGTGGAG
 901 GTGCACACAG CTCAGACGCA ACCCGGGGAG GAGCAGTTCA ACAGCACTTT
 951 CCGCTCAGTC AGTGAACCTC CCATCATGCA CCAGGACTGG CTCAATGGCA
 1001 AGGAGTTCAA ATGCAGGGTC AACAGTGCAG CTTTCCCTGC CCCCATCGAG
 1051 AAAACCATCT CCAAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
 1101 CATTCCACCT CCAAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
 1151 GCATGATAAC AGACTTCTTC CCTGAAGACA TTACTIONG GGTGCACTGG
 1201 AATGGGCAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
 1251 AGATGGCTCT TACTCTACTT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
 1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTACATGA GGCCTGCAC
 1351 AACCACCATA CTGAGAAGAG CCTCTCCAC TCTCTGGTA AA (SEQ ID
 NO:212)

[0265] Ab-13 was humanized to generate Ab-14.

[0266] The sequences of the Antibody 14 (also referred to herein as Ab-14) LC and HC are as follows:

Ab-14 Light Chain:

[0267] Amino acid sequence of the mature form (signal peptide removed) of the Ab-14 LC:

1 DIQLTQSPSF LSASVGDRVT ITCRASSSVT SSYLNWYQOK PGKAPKLLIY
 51 STSNLASGVP SRFGSGSGT EFILTISSLQ PEDFATYYCQ QYDFPSTFG
 101 GGTKVEIKRT VAAPSVFIFF PSDEQLKSGT ASVVCLNNF YPREAKVQWK
 151 VDNALQSGNS QESVTEQDSK DSTYLSSTL TLSEADYERK KFYACEVTHQ
 201 GLSSPVTKSF NRGEC (SEQ ID NO:213)

[0268] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-14 LC:

1 GACATCCAGC TGACCCAGAG CCCAGCTTC CTTCCGCAT CCGTTGGTGA
 51 CCGAGTAACA ATCACATGCC GCGCCTCATC TTCAGTTACA TCTTCTATC
 101 TTAATTGGTA TCAACAAAAA CCAGGAAAAAG CACCTAACT TCTTATATAC
 151 TCTACATCTA ATCTCGCATC AGGAGTTCCC TCTCGATTTT CAGGATCTGG
 201 ATCAGGCACA GAATTTACAC TTACTIONG ATCACTCCA CCAGAAGACT
 251 TCGCCACTTA TTACTIONG CAATACGATT TTTTCCAAG CACATTCCGA
 301 GGAGGTACAA AAGTAGAAAT CAAGCGTACG GTGGCTGCAC CATCTGTCTT
 351 CATCTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAAGT GCCTCTGTTG
 401 TGTGCCTGCT GAATACTTC TATCCAGAG AGGCCAAAGT ACAGTGGAAAG
 451 GTGGATAACG CCTTCCAATC GGGTAACTCC CAGGAGAGTG TCACAGAGCA
 501 GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCCTG ACGCTGAGCA
 551 AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT CACCCATCAG
 601 GGCCTGAGCT CGCCGTCAC AAAGAGCTTC AACAGGGGAG AGTGT (SEQ ID
 NO:214)

[0269] Amino acid sequence of the Ab-14 LC including signal peptide:

1 MDMRVPAQLL GLLLLWLPGA RCDIQLTQSP SFLSASVGDR VITTCRASSS
51 VTSSYLNWYQ QKPGKAPKLL IYSTSNLASG VPSRFSGSGS GTEFTLTSS
101 LQPEDFATYY CQYDFPST FGGGTVKVEIK RTVAAPSVFI FPPSDEQLKS
151 GTASVVCLLN NFYPREKVVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS
201 TLTLSKADYE KHKVYACEVT HQGLSPVTK SFNRGEC (SEQ ID NO:215)

[0270] Nucleic acid sequence of the Ab-14 LC including signal peptide encoding sequence:

1 ATGGACATGA GGGTCCCCGC TCAGTCCTG GGGTCCTGC 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 GATTTCAGG ATCTGGATCA GGCACAGAAT TTAACCTAC 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 TGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCAGG
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:

[0271] Amino acid sequence of the mature form (signal peptide removed) of the Ab-14 HC:

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT ~~DYYM~~NWVRQA PGQRLEWMG~~D~~
51 INPYND~~DTTY~~ ~~NHKFKGRVTI~~ TRDTSASTAY MELSSLRSED TAVYYCARE~~T~~
101 ~~AVITTNAMDY~~ WGQGTIVTVS ~~SASTKGPSVF~~ ~~PLAPCSRSTS~~ ~~ESTAALGCLV~~
151 ~~KDYFPEPVTV~~ ~~SWNSGALTSG~~ ~~VHTFPAVLQS~~ ~~SGLYSLSSVV~~ ~~TVPSSNFGTQ~~
201 ~~TYTCNV~~DH~~KP~~ ~~SN~~TK~~V~~DK~~TV~~ ~~RKCCVECP~~PC~~~~ ~~PAPPVAGPSV~~ ~~FLFPPKPKDT~~
251 ~~LMISRTPEVT~~ ~~CVVVDVSHED~~ ~~PEVQFNWYVD~~ ~~GVEVHNATK~~ ~~PREEQFNSTF~~
301 ~~RVVSVLT~~TV~~VH~~ ~~QDWLNGKEYK~~ ~~CKVSNKGLPA~~ ~~PIEKTISKTK~~ ~~GQPREPQVYT~~
351 ~~LPPSREEMTK~~ ~~NQVSLTCLVK~~ ~~GFYP~~SD~~IAVE~~ ~~WESNGQ~~PE~~NN~~ ~~YK~~TP~~PM~~LD~~S~~
401 ~~DGSFFLYSKL~~ ~~TVDKSRWQ~~QG~~~~ ~~NVFSCSV~~M~~HE~~ ~~ALHNHYTQ~~KS~~~~ ~~LSLSPGK~~ (SEQ ID
NO:217)

[0272] Amino acid sequence of the mature form (signal peptide removed) of the Ab-14 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT ~~DYYM~~NWVRQA PGQRLEWMG~~D~~
51 INPYND~~DTTY~~ ~~NHKFKGRVTI~~ TRDTSASTAY MELSSLRSED TAVYYCARE~~T~~
101 ~~AVITTNAMDY~~ WGQGTIVTVS ~~SASTKGPSVF~~ ~~PLAPCSRSTS~~ ~~ESTAALGCLV~~
151 ~~KDYFPEPVTV~~ ~~SWNSGALTSG~~ ~~VHTFPAVLQS~~ ~~SGLYSLSSVV~~ ~~TVPSSNFGTQ~~
201 ~~TYTCNV~~DH~~KP~~ ~~SN~~TK~~V~~DK~~TV~~ ~~RKCCVECP~~PC~~~~ ~~PAPPVAGPSV~~ ~~FLFPPKPKDT~~
251 ~~LMISRTPEVT~~ ~~CVVVDVSHED~~ ~~PEVQFNWYVD~~ ~~GVEVHNATK~~ ~~PREEQFNSTF~~
301 ~~RVVSVLT~~TV~~VH~~ ~~QDWLNGKEYK~~ ~~CKVSNKGLPA~~ ~~PIEKTISKTK~~ ~~GQPREPQVYT~~
351 ~~LPPSREEMTK~~ ~~NQVSLTCLVK~~ ~~GFYP~~SD~~IAVE~~ ~~WESNGQ~~PE~~NN~~ ~~YK~~TP~~PM~~LD~~S~~
401 ~~DGSFFLYSKL~~ ~~TVDKSRWQ~~QG~~~~ ~~NVFSCSV~~M~~HE~~ ~~ALHNHYTQ~~KS~~~~ ~~LSLSPG~~ (SEQ ID
NO:393)

[0273] 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 ATTAACCCCTT ATAACGACGA CACTACATAC AATCATAAAT TTAAGGAAG
 201 AGTTACAATT ACAAGAGATA CATCCGCATC AACCGCCTAT ATGGAACCTT
 251 CCTCATTTAG ATCTGAAGAC ACTGCTGTTT ATTACTGTGC AAGAGAAACT
 301 GCCGTIATTA CTAATAACGC TATGGATTAC TGGGGTCAAG GAACCACTGT
 351 TACCGTCTCT AGTGCCTCCA CCAAGGGCCC ATCGGTCTTC CCCCTGGCGC
 401 CCTGCTCCAG GAGCACCTCC GAGAGCACAG CGGCCCTGGG CTGCCTGGTC
 451 AAGGACTACT TCCCGAACC GGTGACGGTG TCGTGGAAC TACGGCCTCT
 501 GACCAGCGGC GTGCACACCT TCCAGCTGT CCTACAGTCC TCAGGACTCT
 551 ACTCCCTCAG CAGCGTGGTG ACCGTGCCCT CCAGCAACTT CGGCACCCAG
 601 ACCTACACCT GCAACGTAGA TCAAGGCC AGCAACCCA AGGTGGACAA
 651 GACAGTTGAG CGCAAATGTT GTGTCGAGTG CCCACCGTGC CCAGCACCAC
 701 CTGTGGCAGG ACCGTCAATC TTCTCTTCC CCCCAAAACC CAAGGACACC
 751 CTCATGATCT CCCGGACCCC TGAGGTCACG TCGTGGTGG TGGACGTGAG
 801 CCACGAAGAC CCCGAGGTCC AGTTCAACTG GTACGTGGAC GCGTGGAGG
 851 TGCATAATGC CAAGACAAAG CCACGGGAGG AGCAGTTCAA CAGCAGTTT
 901 CGTGTGGTCA GCGTCTCAC CGTTGTGCAC CAGGACTGGC TGAACGGCAA
 951 GGAGTACAAG TGCAAGTCT CCAACAAAGG CCTCCAGCC OCCATCGAGA
 1001 AAACCATCTC CAAACCAAA GGGCAGCCCC GAGAACCA GGTGTACACC

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

[0274] Amino acid sequence of the Ab-14 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASGYTFTD
 51 YYMNNWVRQAP GQRLEWMGDI NPYNDTTYN HKFKGRVTIT RDTASTAYM
 101 ELSSLRSEDV AVYYCARETA VITTNAMDYW GQGIVTVSS ASTKGPSVFP
 151 LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
 201 GLYSLSSVVT VPSSNFGTQT YTCNVDPKPS NTKVDKTVR KCCVECPPCP
 251 APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG
 301 VEVHNAKTKP REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNGKLPAP
 351 IEKTSKTKG QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDLA VEW
 401 ESNQGPENNY KTTTPMLDSG GSFLYSKLT VDKSRWQQGN VFSCSVMEHA
 451 LHNHYTQKSL SLSPGK (SEQ ID NO:219)

[0275] Nucleic acid sequence of the Ab-14 HC including signal peptide encoding sequence:

1 ATGGAAGTGA CTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACTCCGAG GTGCAGCTGG TGCAGAGCGG CGCCGAGGTC AAGAAACCTG
 101 GAGCAAGCGT AAAGGTAGT TGCAAAGCAT CTGGATACAC ATTTACCGAC
 151 TACTACATGA ATTGGGTACG ACAAGCCCCC GGACAAAGAC TTGAATGGAT
 201 GGGAGACATT AACCTTATA ACGACGACAC TACATACAAT CATAAATTA
 251 AAGGAAGAGT TACAATTACA AGAGATACAT CCGCATCAAC CGCCTATATG
 301 GAACTTTCTT 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 CCGAACCAGT GACGGTGTG TGAAGTCAAG
 551 GCGCTCTGAC CAGCGGCGTG CACACCTTCC CAGCTGTCTT ACAGTCTCTA
 601 GGAATCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG
 651 CACCCAGACC TACACCTGCA ACGTAGATCA CAAGCCAGC AACACCAAGG
 701 TGGACAAGAC AGTTGAGCGC AAATGTTGTG TCGAGTGCCC ACCGTGCCCA
 751 GCACCACTTG TGGCAGGACC GTCAAGTCTT CTCTTCCCCC CAAACCCCAA
 801 GGACACCTTC ATGATCTCCC GGACCCCTGA GGTACAGTGC 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 AACACAGGT
 1101 GTACACCTTG CCCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTGAGCC
 1151 TGACCTGCCT GTTCAAGAGC TTCTACCCA GCGACATCGC CGTGGAGTGG
 1201 GAGAGCAATG GGCAGCCGGA GAACAACCTAC AAGACCACAC CTCCATGCT
 1251 GGAATCCGAC GGCTCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA
 1301 GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT
 1351 CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAA

(SEQ ID NO:220)

[0276] The CDR sequences in the variable region of the heavy chain of Ab-14 are:

CDR-H1:	DYYMN (SEQ ID NO:296)
CDR-H2:	DINPYNDDTTYNHKFKG (SEQ ID NO:297)
CDR-H3:	ETAVITTNAMD (SEQ ID NO:298)

[0277] The light chain variable region CDR sequences of Ab-14 are:

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

Ab-14 Variable domains:

[0278] Ab-14 light chain variable domain amino acid sequence (without signal sequence):

1 DIQLTQSPSF LSASVGDRVT ITCRASSSVT SSYLNWYQOK PGKAPKLLIY
51 STSNLASGVP SRFSGSGSGT EFTLTSSLQ PEDFATYYCQ QYDFFPSTFG
101 GGTKVEIK (SEQ ID NO:380)

[0279] Ab-14 light chain variable domain DNA sequence (without signal sequence):

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

[0280] Ab-14 heavy chain variable domain amino acid sequence (without signal sequence):

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFI DYVMNWVROA PGORLEWMGL
51 INPYNDDTTY NHKFKGRVTI TRDTSASTAY MELSSLRSED TAVYYCARFI
101 AVITTNAMDY WGQGTITVTS S (SEQ ID NO:382)

[0281] 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 ATTAACCTTT ATAACGACGA CACTACATAC AATCATAAAT TTAAAGGAAG
201 AGTTACAATT ACAAGAGATA CATCCGCATC AACC GCCTAT ATGGAAC TTT
251 CCTCATTGAG ATCTGAAGAC ACTGCTGTTT ATTACTGTGC AAGAGAAACT

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

[0282] Ab-3 was humanized to generate Ab-15.

Ab-15

[0283] The sequences of the Antibody 15 (also referred to herein as Ab-15) LC and HC are as follows:

Ab-15 Light Chain:

[0284] Amino acid sequence of the mature form (signal peptide removed) of the Ab-15 LC:

1 DIQMTQSPSS LSASVGDRTV ITCVSSTIS ~~SNHLHW~~FQOK PGKAPKSLIY
 51 ~~GTSNLA~~SGVP SRFSGSGSGT DFILTISSLQ PEDFATYYCQ QWSSYPLTIFG
 101 GGTKEVEIKRT VAAPSVFIFF PSDEQLKSGT ASVVCLLNNF YPREAKVQWK
 151 VDNALQSGNS QESVTEQDSK DSTYSLSSL TLSEADYEKH KYVACEVTHQ
 201 GLSSPVTKSF NRREC (SEQ ID NO:221)

[0285] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-15 LC:

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 CTCCTCCAA CCCGAAGACT
 251 TCGCAACCTA TTACTGTCAA CAATGGTCCT CATATCCACT CACATTGGC
 301 GCGGCGACAA AAGTAGAAAT TAAACGTACG GTGGCTGCAC CATCTGTCTT
 351 CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAAGT GCCTCTGTTG
 401 TGTGCCCTGT GAATAACTTC TATCCCAGAG AGGCCAAAGT ACAGTGGAAG
 451 GTGGATAACG CCTTCAATC GGGTAACTCC CAGGAGAGTG TCACAGAGCA
 501 GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCCTG ACGCTGAGCA
 551 AAGCAGACTA CGAGAAACAC AAAGTCTACG CCGCGAAGT CACCCATCAG
 601 GGCCTGAGCT CGCCCGTAC AAAGAGCTTC AACAGGGGAG AGTGT (SEQ ID
 NO:222)

[0286] Amino acid sequence of the Ab-15 LC including signal peptide:

1 MDMRVPAQLL GLLLLWLRGA RCDIQMTQSP SLSASVGDRTVITCSVSST
 51 ISSNHLHWFK QKPGKAPKSL IYGTSLASG VPSRFSGSGS GTDFTLTISS
 101 LQPEDFATYY CQWSSYPLT FGGGTKEVEIK RTVAAPSVFI FPPSDEQLKS
 151 GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS
 201 TLTLSEADYE KHKVYACEVT HQGLSSPVTK SFNRREC (SEQ ID NO:223)

[0287] Nucleic acid sequence of the Ab-15 LC including signal peptide encoding sequence:

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TACTCTGGCT
 51 CCGAGGTGCC AGATGTGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTCT
 101 CAGCATCCGT AGGCGATAGA GTTACAATAA CATGCAGCGT ATCATCAACT
 151 ATATCATCAA ATCATCTTCA TTGGTTCCAA CAGAAACCCG GCAAAGCACC
 201 TAAATCACTT ATATACGGCA CATCAAATCT CGCATCAGGC GTTCCTTCAA
 251 GATTTTCAGG CTCTGGCTCA GGCACCGACT TACTCTTAC AATATCCTCC
 301 CTCCAACCCG AAGACTTCGC AACCTATTAC TGTCACAAAT GGTCTCATA
 351 TCCACTCACA TTGGCGGCG GCACAAAAGT AGAAATTAAG CGTACGGTGG
 401 CTGCACCATC TGCTTTCATC TTCCCGCCAT CTGATGAGCA GTTGAAATCT
 451 GGAAGTGCCT CTGTTGTGTG CCGTCTGAAT AACTTCTATC CCAGAGAGGC
 501 CAAAGTACAG TGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCAGG
 551 AGAGTGTAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC
 601 ACCCTGAGC TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG
 651 CGAAGTACAC CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA
 701 GGGGAGAGTG T (SEQ ID NO:224)

Ab-15 Heavy Chain

[0288] Amino acid sequence of the mature form (signal peptide removed) of Ab-15 HC.

1 EVQLVQSGAE VKKPGASVKV SCKASDENIK ~~DEY~~LHWVRQA PGQGLEWIGR
 51 ~~DEP~~ENGDIY DPKFQEKVIM TTDSTSTAY MELRSLRSDD TAVYYCARBA
 101 ~~DYF~~HDGTSYWEYEDVWGRGTL VTVSSASTKG PSVFPLAPCS RSTSESTAAL
 151 GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTPSSN
 201 FGTQTYTCNV DHKPSNTKVD KTVRKCCVE CPPCPAPPVA GPSVFLFPPK
 251 PKDTLMISRT PEVTCVVVDV SHEDPEVQFN WYVDGVEVHN AKTKPREEQF
 301 NSTFRVVSZL TVVHQDWLNG KEYKCKVSNK GLPAPIEKTI SKTKGQPREP
 351 QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD LAWEWESNGQ PENNYKTTTP
 401 MLDSGDSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG
 451 K (SEQ ID NO:225)

[0289] Amino acid sequence of the mature form (signal peptide removed) of Ab-15 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGASVKV SCKASDFNIK DYFLHWVRQA PGQGLEWIGR
 51 IDPENGDTLY DPKFQDKVTM TDTSTSTAY MELRSLRSD TAVYYCAREA
 101 DYFHDGTSY WYFDVWGRGTL VTVSSASTKG PSVFLAPCS RSTSESTAAL
 151 GCLVKDYFPE PVTVSWNSGA LITSGVHTFPA VLQSSGLYSL SSVTVPSN
 201 FGTQTYTCNV DHKPSNTKVD KTVKRCCKVE CPPCPAPPVA GPSVFLFPPK
 251 PKDTLMISRT PEVTCVVVDV SHEDPEVQFN WYVDGVEVHN AKTKPREEQF
 301 NSTFRVSVL TVVHQDWLNG KEYKCKVSNK GLPAPIEKTI SKTKGQPREP
 351 QVYTLPPSRE EMTKNQVSLT CLVKGFPYSD LAVEWESNGQ PENNYKTTTP
 401 MLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG
 451 (SEQ ID NO:394)

[0290] 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 CAACATTAAG 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 TGGCACCCCTG GTCACCGTCT CTAGTGCCTC CACCAAGGGC CCATCGGTCT
 401 TCCCCCTGGC GGCCTGTCTC AGGAGCACCT CCGAGAGCAC AGCGGCCCTG
 451 GGCTGCCTGG TCAAGGACTA CTTCCCCGAA CCGGTGACGG TGTCGTGGAA
 501 CTCAGGCGCT CTGACCAAGC GCGTGCACAC CTTCCCAAGT 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 CCTGAGGTCA CGTGCCTGGT
 801 GGTGGACGTG AGCCACGAAG ACCCGAGGT CCAAGTCAAC TGGTACGTGG
 851 ACGGCGTGA GGTGCATAAT GCCAAGACAA AGCCACGGGA GGAGCAGTTC
 901 AACAGCACGT TCCGTGTGGT CAGCGTCTC ACCGTTGTGC ACCAGGACTG
 951 GCTGAACGGC AAGGAGTACA AGTGCAAGGT CTCCAACAAA GGCCTCCAG
 1001 CCCCCATCGA GAAAACCATC TCCAAAACCA AAGGGCAGCC CCGAGAACCA
 1051 CAGGTGTACA CCCTGCCCCC ATCCGGGAG GAGATGACCA AGAACCAGGT
 1101 CAGCCTGACC TGCCTGGTCA AAGGCTTCTA CCCCAGCGAC ATCGCCGTGG
 1151 AGTGGGAGAG CAATGGGCGC CCGGAGAACA ACTACAAGAC CACACCTCCC
 1201 ATGCTGGACT CCGACGGCTC CTTCTTCTC TACAGCAAGC TCACCGTGA
 1251 CAAGAGCAGG TGGCAGCAGG GGAACGTCTT CTCATGCTCC GTGATGCATG
 1301 AGGCTCTGCA CAACCACTAC ACGCAGAAGA GCCTCTCCCT GTCTCCGGT
 1351 AAA (SEQ ID NO:226)

[0291] Amino acid sequence of the Ab-15 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPASVVKVS CKASDFNIKD
 51 FYLHWVRQAP GQGLEWIGRI DPENGDTLYD PKFQDKVTMT TDTSTSTAYM
 101 ELRSLRSDDT AVYYCAREAD YFHDGTSYWY FDVWGRGTLV TVSSASTKGP
 151 SVFLAPCSR STSESTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV
 201 LQSSGLYSLS SVVTVPSNFI GTQTYTCNVD HKPSNTKVDK TVKRCCKVEC
 251 PPCPAPPVAG PSVFLFPPKP KDTLMISRT PEVTCVVVDV SHEDPEVQFNW
 301 YVDGVEVHNA KTKPREEQFN STFRVSVLT VVHQDWLNGK EYKCKVSNKQ
 351 LPAPIEKTI KTKGQPREPQ VYTLPPSREE MIKNQVSLTCLVKGFPYSDI
 401 AVEWESNGQP ENNYKTTTPM LDDSDGSFFLY SKLTVDKSRW QQGNVFSCSV
 451 MHEALHNHYT QKSLSLSPGK (SEQ ID NO:227)

[0292] Nucleic acid sequence of the Ab-15 HC including signal peptide encoding sequence:

1 ATGGACTGGA CCTGGAGGAT CCTCTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACTCCGAG GTGCAGCTGG TGCACTCTGG GGCTGAGGTG AAGAAGCCTG
 101 GGGCCTCAGT GAAGGTCTCC TGCAAGGCTT CTGACTTCAA CATTAAAGAC
 151 TTCTATCTAC ACTGGGTGCG ACAGGCCCTT GGACAAGGGC TTGAGTGGAT
 201 TGGAAAGGAT GATCTGAGA ATGGTGATAC TTTATATGAC CCGAAGTTCC
 251 AGGACAAGGT CACCATGACC ACAGACACGT CCACCAGCAC AGCCTACATG
 301 GAGCTGAGGA GCCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG

351 AGAGGCGGAT TATTTCCACG ATGGTACCTC CTA CTGGTAC TTCGATGTCT
 401 GGGGCCGTGG CACCCTGGTC ACCGTCTCTA GTGCCTCCAC CAAGGGCCCA
 451 TCGGTCTTCC CCCTGGCGCC CTGCTCCAGG AGCACCTCCG AGAGCACAGC
 501 GGCCCTGGGC TGCCTGGTCA AGGACTACTT CCCC GAACCG GTGACGGTGT
 551 CGTGGAATC 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 GAGGTCACGT
 851 GCGTGGTGGT GGACGTGAGC CACGAAGACC CCGAGGTCCA GTTCAACTGG
 901 TACGTGGACG GCGTGGAGGT GCATAATGCC AAGACAAAGC CACGGGAGGA
 951 GCAGTTCAAC AGCACGTTC GTGTGGTCAG CGTCCTCACC GTTGTGCACC
 1001 AGGACTGGCT GAACGGCAAAG GAGTACAAGT GCAAGGTCTC CAACAAAGGC
 1051 CTCCCAGCCC CCATCGAGAA AACCATCTCC AAAACCAAAG GGCAGCCCCG
 1101 AGAACCACAG GTGTACACC TGCCCCATC CCGGGAGGAG ATGACCAAGA
 1151 ACCAGGTGAG CCGTACCTGC CTGGTCAAAG GCTTCTACCC CAGCGACATC
 1201 GCGTGGAGT GGGAGAGCAA TGGGCAGCCG GAGAACAAC ACAAGACCAC
 1251 ACCTCCCATG CTGGACTCCG ACGGCTCCTT CTTCCTTAC AGCAAGCTCA
 1301 CCGTGGACAA GAGCAGGTGG CAGCAGGGA ACCTCTTCTC ATGCTCCGTG
 1351 ATGCATGAGG CTCTGCACAA CCACTACAG CAGAAGAGCC TCTCCCTGTC
 1401 TCCGGGTAAA (SEQ ID NO:228)

[0293] 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)

[0294] The light chain variable region CDR sequences of Ab-15 are:

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

Ab-15 Variable domains:

[0295] Ab-15 light chain variable domain amino acid sequence (without signal sequence):

1 DIQMTQSPSS LSASVGDRTV ITCSVSSTIS SNHLHWFQOK PGKAPKSLIY
 51 GTSNLASGVP SRFSGSGSGT DFTLTISLQ PEDFATYYCQ QWSSYPLTFG
 101 GGTKVEIK (SEQ ID NO:384)

[0296] Ab-15 light chain variable domain DNA sequence (without signal sequence):

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCAGCAT CCGTAGGCCGA
 51 TAGAGTTACA ATAACATGCA GCGTATCATC AACTATATCA TCAATCATC
 101 TTCATTGGTT CCAACAGAAA CCCGGCAAAG CACCTAAATC ACTTATATAC
 151 GGCACATCAA ATCTCGCATC AGGCGTTCCT TCAAGATTTT CAGGCTCTGG
 201 CTCAGGCACC GACTTTACTC TTACAATATC CTCCCTCCAA CCCGAAGACT
 251 TCGCAACCTA TTA CTGTCAA CAATGGTCCT CATATCCACT CACATTGGC
 301 GCGGCACAAA AAGTAGAAAT TAAA (SEQ ID NO:385)

[0297] Ab-15 heavy chain variable domain amino acid sequence (without signal sequence):

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

[0298] Ab-15 heavy chain variable domain DNA sequence (without signal sequence):

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC
 51 AGTGAAGGTC TCCTGCAAGG CTCTGACTT 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 CTCTACTGG TACTTCGATG TCTGGGGCCG
 351 TGGCACCCCTG GTCACCGTCT CTAGT (SEQ ID NO:387)

[0299] Ab-11 was humanized to generate Ab-16.

Ab-16

[0300] The sequences of the Antibody 16 (also referred to herein as Ab-16) LC and HC are as follows:

Ab-16 Light Chain:

[0301] Amino acid sequence of the mature form (signal peptide removed) of the Ab-16 LC:

1 DIQLTQSPSF LSASVGDRTV ITCRASSSS~~SYIH~~WYQQKPG KAPKLLIYAT
 51 SNLASGVPSR FSGSGSGTEF TLTISSLQPE DFATYYCQW SSDPLTFGGG
 101 TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD
 151 NALQSGNSQE SVTEQDSKDS TYSLSSLTL SKADYEKHKV YACEVTHQGL
 201 SSPVTKSFNR GEC (SEQ ID NO:229)

[0302] 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 TACATACACT
 101 GGTATCAGCA AAAACCAAGG AAAGCCCCTA AGCTCCTGAT CTATGCCACA
 151 TCCAACCTGG CTCTGGGGT CCCATCAAGG TTCAGCGGCA GTGGATCTGG
 201 GACAGAATTC ACTCTCACAA TCAGCAGCCT GCAGCCTGAA GATTTTGCAA
 251 CTTATTACTG TCAGCAGTGG AGTAGTGACC CACTCACGTT CGGCGGAGGG
 301 ACCAAGGTGG AGATCAAACG TACGGTGGCT GCACCATCTG TCTTCATCTT
 351 CCCGCCATCT GATGAGCAGT TGAATCTGG AACTGCCTCT GTTGTGTGCC

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

[0303] Amino acid sequence of the Ab-16 LC including signal peptide:

1 MDMRVPQALL GLLLLWLPGA RCDIQLTQSP SFLSASVGDV VTITCRASSS
 51 ISYIHWWYQK PGKAPKLLIY ATSNLASGVP SRFSGSGSGT EFTLTSSLQ
 101 PEDFATYYCQ QWSSDPLTFG GGTKVEIKRT VAAPSVFIFF PSDEQLKSGT
 151 ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSL
 201 TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC (SEQ ID NO:231)

[0304] Nucleic acid sequence of the Ab-16 LC including signal peptide encoding sequence:

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TGCTCTGGCT
 51 CCCAGGTGCC AGATGTGACA TCCAGTTGAC CCACTCTCCA TCCTTCTGT
 101 CTGCATCTGT AGGAGACAGA GTCACCATCA CTGCAAGGC CAGCTCAAGT
 151 ATAAAGTTACA TACACTGGTA TCAGCAAAAA CCAGGGAAAAG CCCCTAAGCT
 201 CCTGATCTAT GCCACATCCA ACCTGGCTTC TGGGGTCCCA TCAAGGTTCA
 251 GCGGCAGTGG ATCTGGGACA GAATTCACTC TCACAATCAG CAGCCTGCAG
 301 CCTGAAGATT TTGCAACTTA TTAAGTTCAG CAGTGGAGTA GTGACCACT
 351 CACGTTCCGC GGAAGGACCA AGGTGGAGAT CAAACGTACG GTGGCTGCAC
 401 CATCTGTCTT CATCTCCCG CCACTGTATG AGCAGTTGAA ATCTGGAAC
 451 GCCTCTGTGT TGTGCCTGCT GAATAACTTC TATCCAGAG AGGCCAAAGT
 501 ACAGTGGAAAG GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG
 551 TCACAGAGCA GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCTG
 601 ACGCTGAGCA AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT
 651 CACCCATCAG GGCTGTGAGT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG
 701 AGTGT (SEQ ID NO:232)

Ab-16 Heavy Chain:

[0305] Amino acid sequence of the mature form (signal peptide removed) of the Ab-16 HC:

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDYIHVVRQA PGQGLEWIGR
51 VDPDNGETEF APKFPQKVTM TTDTSISTAY MELSRLRSDD TAVYYCARE
101 YDGTYYTWPY WGQGLVTVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV
151 KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ
201 TTYCNVDHKP SNTKVDKTYE RKCCVECPCP PAPPVAGPSV FLFPKPKDT
251 LMSRTEPVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF
301 RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT
351 LPPSREEMTK NQVSLTCLVK GFYPSDLAVE WESNGQPENN YKTTTPMLDS

401 DGSFFLYSKL TVDKSRWQQG NVFSCSVME ALHNHYTQKS LSLSPGK (SEQ ID NO:233)

[0306] Amino acid sequence of the mature form (signal peptide removed) of the Ab-16 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDYIHVVRQA PGQGLEWIGR
51 VDPDNGETEF APKFPQKVTM TTDTSISTAY MELSRLRSDD TAVYYCARE
101 YDGTYYTWPY WGQGLVTVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV
151 KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ
201 TTYCNVDHKP SNTKVDKTYE RKCCVECPCP PAPPVAGPSV FLFPKPKDT
251 LMSRTEPVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF
301 RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT
351 LPPSREEMTK NQVSLTCLVK GFYPSDLAVE WESNGQPENN YKTTTPMLDS
401 DGSFFLYSKL TVDKSRWQQG NVFSCSVME ALHNHYTQKS LSLSPG (SEQ ID NO:395)

[0307] 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 TCCCGGCCAA
201 GGTCACCATG ACCACAGACA CGTCCATCAG CACAGCCTAC ATGGAGCTGA
251 GCAGGCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAAGAC
301 TACGATGGTA CCTACACCTG GTTTCCTTAT TGGGGCCAAG GGA CTCTGGT
351 CACCGTCTCT AGTGCCCTCA CCAAGGGCCC ATCGGTCTTC CCCCTGGCGC
401 CCTGCTCAG GAGCACCTCC GAGAGCACAG CGGCCCTGGG CTGCCTGGTC
451 AAGGACTACT TCCCGAACC GGTGACGGTG TCGTGGA ACT CAGGCGCTCT
501 GACCAGCGGC GTGCACACCT TCCAGCTGT CCTACAGTCC TCAGGACTCT
551 ACTCCCTCAG CAGCGTGGTG ACCGTGCCCT CCAGCAACTT CGGCACCCAG
601 ACCTACACCT GCAACGTA GA TCACAAGCCC AGCAACACCA AGGTGGACAA
651 GACAGTTGAG CGCAATGTT GTGTGAGTG CCCACCGTGC CCAGCACCAC
701 CTGTGGCAGG ACCGTGAGT TTTCTCTTCC CCCAAAACCA CAAGGACACC
751 CTCATGATCT CCCGGACCCC TGAGGTCACG TGCCTGGTGG TGGACGTGAG
801 CCACGAAGAC CCCGAGGTCC AGTTCAACTG GTACGTGGAC GGCCTGGAGG
851 TGCATAATGC CAAGACAAAG CCACGGGAGG AGCAGTTCAA CAGCAGTTT
901 CGTGTGGTCA GCGTCTCAC CGTTGTGCAC CAGGACTGGC TGAACGGCAA
951 GGAGTACAAG TGCAAGGTCT CCAACAAAGG CCTCCAGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGGCAGCCCC GAGAACCACA GGTGTACACC
1051 CTGCCCCCAT CCCGGGAGGA GATGACCAAG AACCAGGTCA GCCTGACCTG
1101 CCTGGTCAAA GGCTTCTACC CCAGCGACAT CGCCGTGGAG TGGGAGAGCA
1151 ATGGGACGCC GGGAACAAC TACAAGACCA CACCTCCAT GCTGGACTCC
1201 GACGGCTCCT TCTTCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGTG
1251 GCAGCAGGGG AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA
1301 ACCACTACAC GCAGAAAGAG CTCTCCCTGT CTCCGGGTAA A (SEQ ID NO:234)

[0308] Amino acid sequence of the Ab-16 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPASVKVS CKASGFDIKD
 51 YYIHWVRQAP GQGLEWIGRV DPDNGETEFK PKFPGKVTMT TDSISTAYM
 101 ELSRLRSDDT AVYYCAREDY DGTYTWFYVW GQGITLVTVSS ASTKGPSVFP
 151 LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
 201 GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVR KCCVECPPCP
 251 APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDF EVQFNWYVDG
 301 VEVHNAKTKP REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNGKLPAP
 351 IEKTISKTKG QPREPVYTL PPSREEMTKN QVSLTCLVKG FYPSTIAVEW
 401 ESNQGPENNY KTTTPMLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA
 451 LHNHYTQKSL SLSPGK (SEQ ID NO:235)

[0309] Nucleic acid sequence of the Ab-16 HC including signal peptide encoding sequence:

1 ATGGACTGGA CCTGGAGGAT CCTCTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACCTCCGAG GTGCAGCTGG TGCAGTCTGG GGCTGAGGTG AAGAAGCCTG
 101 GGGCCTCAGT GAAGGTCTCC TGCAAGGCTT CTGGATTCTGA CATTAAAGGAC
 151 TACTATATAC ACTGGGTGCG ACAGGCCCTT GGACAAGGGC TTGAGTGGAT
 201 CGGAAGGGTT GATCCTGACA ATGGTGAGAC TGAATTTGCC CCGAAGTTCC
 251 CGGGCAAGGT CACCATGACC ACAGACACGT CCATCAGCAC AGCCTACATG
 301 GAGCTGAGCA GGCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG
 351 AGAAGACTAC GATGGTACCT ACACCTGGTT TCCTTATTGG GGCCAAGGGA
 401 CTCTGGTCAC CGTCTCTAGT GCCTCCACCA AGGGCCCATC GGTCTTCCCC
 451 CTGGCGCCCT GCTCCAGGAG CACCTCCGAG AGCACAGCGG CCCTGGGCTG
 501 CCTGGTCAAG GACTACTTCC CCGAACCCTG GACGGTGTCTG TGGAACTCAG
 551 GCGCTCTGAC CAGCGGCGTG CACACCTTCC CAGCTGTCTT ACAGTCTCTA
 601 GGACTCTACT CCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG
 651 CACCCAGACC TACACCTGCA ACGTAGATCA CAAGCCCAGC AACACCAAGG
 701 TGGACAAGAC AGTTGAGCGC AATGTTGTG TCGAGTGCCC ACCGTGCCCC
 751 GCACCACCTG TGGCAGGACC GTCAGTCTTC CTCTTCCCCC AAAAACCCAA
 801 GGACACCCTC ATGATCTCCC GGACCCCTGA GGTACGTGC 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 ATCAGAGAAA CCATCTCAA AACCAAAGGG CAGCCCGAG AACACAGGT
 1101 GTACACCCTG CCCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTCAGCC
 1151 TGACCTGCCT GGTCAAAGGC TTCTACCCA GCGACATCCG CGTGGAGTGG
 1201 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACAC CTCCCATGCT
 1251 GGACTCCGAC GGCTCCTTCT TCCTCTACAG CAAGTCTACC GTGGACAAAG
 1301 GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT
 1351 CTGCACAACC ACTACACGCA GAAGAGCCTC TCCTGTCTC CGGGTAAA (SEQ
 ID NO:236)

[0310] The CDR sequences in the variable region of the heavy chain of Ab-16 are:

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

[0311] The light chain variable region CDR sequences of Ab-16 are:

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

Ab-16 Variable domains:

[0312] Ab-16 light chain variable domain amino acid sequence (without signal sequence):

1 DIQLTQSPSF LSASVGDRVT ITCRASSIS YHWYQKPG KAPKLLIYAT
 51 ENLASGVPSR FSGSGSTEF TLTISSLQPE DFATYYCQQW SSDPLTFGGG
 101 TKVEIK (SEQ ID NO:388)

[0313] Ab-16 light chain variable domain DNA sequence (without signal sequence):

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

[0314] Ab-16 heavy chain variable domain amino acid sequence (without signal sequence):

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDY~~Y~~HWVRQA PGQGLEWIGR
 51 YDPDNGSTEF APK~~P~~FGKVTM TTDTSISTAY MELSLRSD TAVYYCARE~~D~~
 101 ~~Y~~VDGT~~Y~~WFPY WGQGLVTVS S (SEQ ID NO:390)

[0315] Ab-16 heavy chain variable domain DNA sequence (without signal sequence):

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

[0316] 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~~V~~SI~~F~~PPS~~E~~QLTSGGASVVCFLN~~F~~PKDINVKWKIDG~~S~~ERQNGVLNSWTDQD
 SKDSTYSMSSTLILTKDEYERHNSYTCEATHKTSTSPIVKSFN~~R~~NBC (SEQ ID NO:323)

[0317] The Heavy Constant Region for all VH regions of antibodies 17, 19 and 21 is as follows:

AKTTPPSVYPLAPGSA~~A~~QNSMVTLGCLVKGYFPEPVTVWNSGSLSSGVHTFPAVLQS
 DLYTLSSSVTVPSSTWPS~~E~~TVTCNV~~A~~HPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIF
 PFKPKDVLITLTPKVT~~C~~VVVDISKDDPEVQFSWFVDDVEVHTAQTQPREQFNSTFRS
 VSELPMHQDWLNGKEFKCRVNSA~~A~~FPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKD
 KVSLTCMTDFFPEDITV~~E~~WQWNGQPAENYKNTQPM~~D~~TGSGSYFVYSKLN~~V~~QKSNWEA
 GNTFTCSVLHEGLHNHHT~~E~~KSLSHSPGK (SEQ ID NO:324)

[0318] 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

[0319] Amino acid sequence of the Ab-17 LC including signal peptide:

MDFOVQIFSFMLISVTVILSSGEIVLTQSPALMAASPGEKVITTCSVSSSSSSNHWSQOK
 SGTSPKLWIYGT~~S~~NTASGV~~P~~VRFSGSGSGTSYSLTISSMEADAATYYCQQTIT~~Y~~TFG
 SGTKLELKR (SEQ ID NO:299)

[0320] Nucleic acid sequence of the Ab-17 LC including signal peptide:

ATGGATTTTCAGGTGCAGATTTTCAGCTTCATGCTAATCAGTGTACAGTCATATTG
 TCCAGTGGAGAAATTGTGCTCACCCAGTCTCCAGCACTCATGGCTGCATCTCCAGGG
 GAGAAGGTCAACATCACCTGCAGTGTCAAGCTCGAGTATAAGTTCAGCAACTTACA
 CTGGTCCCAGCAGAAGTCAGGAACCTCCCCAACTCTGGATTTATGGCACATCCA
 ACCTTGCTTCTGGAGTCCCTGTTCGCTTCAGTGGCAGTGGATCTGGGACCTCTTATTC
 TCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATTACTGTCAACAGT
 GGACTACTACGTATACGTTCCGATCGGGGACCAAGCTGGAGCTGAAACGT (SEQ ID
 NO:300)

[0321] Amino acid sequence of the Ab-17 HC including signal peptide:

MGWNNWIFFLMAVVTGVNSEVQLRQSGADLVKPGASVKLSCTASGFNIKDYYHWVK
 QRPEQGLEWIGRIDPDNGESTY~~V~~PKFGKAITTADTSSNTAYLQLRLTSED~~T~~ATVY~~C~~GR
EGLDYGDYVAVDYWGQGTSTVTVSS (SEQ ID NO:301)

[0322] Nucleic acid sequence of the Ab-17 HC including signal peptide:

ATGGGATGGAAGTGGATCATCTTCTTCTGATGGCAGTGGTTACAGGGGTCAATTCA
GAGGTGCAGTTGCGGCAGTCTGGGGCAGACCTTTGTGAAGCCAGGGGCCTCAGTCAA
GTTGTCTGCACAGCTTCTGGCTTCAACATTAAAGACTACTATATACACTGGGTGAA
GCAGAGGCCTGAACAGGGCCTGGAGTGGATTGGAAGGATTGATCCTGATAATGGTG
AAAGTACATATGTCCCGAAGTTCCAGGGCAAGGCCACTATAACAGCAGACACATCA
TCCAACACAGCCTACCTACAACCTCAGAAGCCTGACATCTGAGGACACTGCCATCTA

TTATTGTGGAGAGAGGGGGCTCGACTATGGTGACTACTATGCTGTGGACTACTGGG
GTCAAGGAACCTCGGTACAGTCTCGAGC (SEQ ID NO:302)

[0323] Ab-17 was humanized to generate Ab-18.

Ab-18

[0324] Amino acid sequence of the Ab-18 LC including signal peptide:

MDMRVPAQLLGLLLLWLPGARCDIQLTQSPSFLSASVGDRTTTCSSSSISSNLHWYQ
QKPGKAPKLLIYGTSNLASGVPSRFSGSGSGETFTLTSSLPEDFATYYCQQWTTTTF
GQGTKLEIKR (SEQ ID NO:303)

[0325] Nucleic acid sequence of the Ab-18 LC including signal peptide:

ATGGATATGCGCGTGCCGGCGCAGCTGCTGGGCCTGCTGCTGTGGCTGCCGGG
CGCGCGCTGCGATATTACGTGACCCAGAGCCGAGCTTCTGAGCGCGAGCGTGG
GCGATCGCGTGACCATTAACCTGCAGCGTGAGCAGCAGCATTAGCAGCAGCAACCTG
CATTGGTATCAGCAGAAACCGGGCAAAGCGCCGAACTGCTGATTTATGGCACCAG
CAACCTGGCGAGCGCGTGCCGAGCCGCTTTAGCGGCAGCGGCAGCGGCACCGAAT
TTACCCTGACCATTAAGCAGCCTGCAGCCGGAAGATTTTGCACCTATTATTGCCAGC
AGTGGACACCACTATACCTTTGGCCAGGGCACCAAACTGGAAATTAAACGT (SEQ
ID NO:304)

[0326] Amino acid sequence of the Ab-18 HC including signal peptide:

MDWTWSILFLVAAPTGAHSEVQLVQSGAEVKKPGASVKYSCKASGFNIKDYTFHWVR
QAPGQGLEWMGRIDPDNGESTYVPKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYY
CARGLDYGDYYAVDYWGQGLTVTVSS (SEQ ID NO:305)

[0327] Nucleic acid sequence of the Ab-18 HC including signal peptide:

ATGGATTGGACCTGGAGCATTCTGTTTCTGGTGGCGCGCGCCGACCGGCGCGCATAG
CGAAGTGCAGCTGGTGACAGCGCGCGGAAGTGAAAAACCGGGCGCGAGCGTG
AAAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATTCATTGGGT
GCGCCAGGCGCGGGCCAGGGCCTGGAATGGATGGGCGCATTGATCCGGATAACG
GCGAAAGCACCTATGTGCCGAAATTTAGGGCCGCGTGACCATGACCACCGATACC
AGCACCAGCACCGCTATATGGAAGTGCAGCAGCTGCGCAGCGATGATACCGCGGT
GTATTATTGCGCGCGCAAGGCCCTGGATTATGGCGATTATTATGCGGTGGATTATTG
GGGCCAGGGCACCTGGTGACCGTCTCGAGC (SEQ ID NO:306)

[0328] Ab-18 light chain variable domain amino acid sequence (without signal sequence):

DIQLTQSPSFLSASVGDRTTTCSSSSISSNLHWYQKPGKAPKLLIYGTSNLASGVPS
RFSGSGSGTEFTLTSSLPEDFATYYCQQWTTTTFGQGTKLEIKR (SEQ ID NO:368)

[0329] Ab-18 light chain variable domain DNA sequence (without signal sequence):

GATATTCAGCTGACCCAGAGCCCGAGCTTCTGAGCGCGAGCGTGGGCGATCGCGT
GACCATTAACCTGCAGCGTGAGCAGCAGCATTAGCAGCAGCAACCTGCATTGGTATC
AGCAGAAACCGGGCAAAGCGCCGAACTGCTGATTTATGGCACCAGCAACCTGGCG
AGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGCAGCGGCACCGAATTTACCCTGAC
CATTAGCAGCTGCAGCCGGAAGATTTTGCACCTATTATTGCCAGCAGTGGACCA
CCACCTATACCTTTGGCCAGGGCACCAAACTGGAAATTAAACGT (SEQ ID NO:369)

[0330] Ab-18 heavy chain variable domain amino acid sequence (without signal sequence):

EVQLVQSGAEVVKPGASVKVSKASGFNKDYYIHWVRQAPGQGLEWMGRIDPDNGE
STYVPKFQGRVTMTTDTSTAYMELRSLRSDDTAVYYCAREGLDYGDYYAVDYWG
QGTLVTVSS (SEQ ID NO:370)

[0331] Ab-18 heavy chain variable domain DNA sequence (without signal sequence):

GAAGTGCAGCTGGTGCAGAGCGGCGGGAAGTGAAAAACCGGGCGCGAGCGTGA
AAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATTCAATTGGGTG
CGCCAGGCGCGCGGCCAGGGCCTGGAATGGATGGGCCGCATTGATCCGGGATAACGG
CGAAAGCACCTATGTGCCGAAATTCAGGGCCGCGTGACCATGACCACCGATACCA
GCACCAGCACCGCGTATATGGAAGTCCGCAGCCTGCGCAGCGATGATACCGCGGTG
TATTATTGCGCGCGCGAAGGCCTGGATTATGCGGATTATTATGCGGTGGATTATTGG
GGCCAGGGCACCTGGTGACCGTCTCGAGC (SEQ ID NO:371)

Ab-19

[0332] Amino acid sequence of the Ab-19 LC including signal peptide:

MMSSAOFGLGLLLCFQGRCDIQMTQTSSLSASLGDRVNISCRASQDISSYLNWYQOK
PDGTVKLLIYSTSRLNSGVPSRFSSGSGTDYSLTISNLAQEDIATYFCQODIKHPTFGGG
TKLELKR (SEQ ID NO:307)

[0333] Nucleic acid sequence of the Ab-19 LC including signal peptide:

ATGATGTCTCTGCTCAGTTCCTTGGTCTCCTGTTGCTCTGTTTTCAAGGTACCAGAT
GTGATATCCAGATGACACAGACTACATCCTCCTGTCTGCCTCTCTGGGAGACAGAG
TCAACATCAGCTGCAGGGCAAAGTCAGGACATTAGCAGTTATTTAAACTGGTATCAG
CAGAAAACAGATGGAAGTCTTAAACTCCTGATCTACTCCACATCAAGATTAAACTC
AGGAGTCCCATCAAGGTTCAAGTGGCAGTGGGTCTGGGACAGATTATTCTCTCACTAT
TAGCAACCTGGCACAGAAGATATTGCCACTTACTTTTGCCAACAGGATATTAAGC
ATCCGACGTTCCGTGGAGGCACCAAGTTGGAGCTGAAACGT (SEQ ID NO:308)

[0334] Amino acid sequence of the Ab-19 HC including signal peptide:

MEWWIFLELLSGTAGVHSEVQLQSGPELVKPGASVKMSCKASGFTFTDYIMHWVKQ
KPGQGLEWIGYINPYNDDEYNEKFKGKATLTSDKSSSTAYMDLSSLTSEGSAVYYCA
RSIYYDAPFAYWGQGLTVTVSS (SEQ ID NO:309)

[0335] Nucleic acid sequence of the Ab-19 HC including signal peptide:

ATGGAATGGATCTGGATATTTCTCTCCTCTGTCAGGAACTGCAGGTGTCCACTCT
GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCAGTGAA
GATGTCTGCAAGGCTTCTGGGTTACATTCAGTACTACATTATGCACTGGGTGAA
GCAGAAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATTAATCCTTACAATGATG
ATACTGAATACAATGAGAAGTTCAAAGGCAAGGCCACACTGACTTCAGACAAATCC
TCCAGCACAGCCTACATGGATCTCAGCAGTCTGACCTCTGAGGGCTCTGCGGTCTAT
TACTGTGCAAGATCGATTATTAATTACTACGATGCCCGTTTGCTTACTGGGGCCAAGGG
ACTCTGGTCACAGTCTCGAGC (SEQ ID NO:310)

[0336] 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

[0337] Amino acid sequence of the Ab-20 LC including signal peptide:

MMSSAOFGLGLLLCFQGRCDIQMTQSPSSLSASVGDRVITTCRASQDISSYLNWYQOK
PGKAPKLLIYSTSRLNSGVPSRFSSGSGTDFILTISSLPEDFATYYCQODIKHPTFGQG
TKVEIKR (SEQ ID NO:311)

[0338] Nucleic acid sequence of the Ab-20 LC including signal peptide:

ATGATGTCCTCTGCTCAGTTCCTTGGTCTCCTGTTGCTCTGTTTTCAAGGTACCAGAT
GTGATATCCAGATGACCCAGTCTCCATCCTCCCTGCTGCATCTGTAGGTGACCGTG
TCACCATCACTTGCCGCGCAAGTCAGGATATTAGCAGCTATTAAATTGGTATCAGC
AGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATTCTACTTCCCGTTTGAATAGTG
GGTCCCATCACGCTTCAGTGGCAGTGGCTCTGGGACAGATTCTACTCTCACCATCA
GCAGTCTGCAACCTGAAGATTTTGCACCTTACTACTGTCAACAGGATATTAACACC
CTACGTTCCGTC AAGGCACCAAGGTGGAGATCAAACGT (SEQ ID NO:312)

[0339] Amino acid sequence of the Ab-20 HC including signal peptide:

MEWIFLELLSGTAGVHSEVQLVQSGAEVKKPSSVKVSCKASGFTFTDYMHWVRQ
APGQGLEWMGYINPYNDDEYNEKFKGRVTITADKSTSTAYMELSLRSEDVAVYYCA
RSYVYDAFPA YWGQGLTVTVSS (SEQ ID NO:313)

[0340] Nucleic acid sequence of the Ab-20 HC including signal peptide:

ATGGAATGGATCTGGATATTTCTCTCTCCTGTCAGGAAGTGCAGGTGTCCACTCT

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAA
GGTCTCCTGCAAGGCTTCTGGTTTTACCTTCACCGACTATATTATGCACTGGGTGCG
TCAGGCCCTGGTCAAGGGCTTGAGTGGATGGGCTATATCAACCCTTATAATGATG
ACACCGAATACAACGAGAAGTTCAAGGGCCGTGTACGATTACCGCGGACAAATCC
ACGAGCACAGCCTACATGGAGCTGAGCAGCCTGCGCTCTGAGGACACGGCCGTGTA
TTACTGTGCGCGTTTCGATTATTACTACGATGCCCGTTTGCTTACTGGGGCCAAGG
GACTCTGGTCACAGTCTCGAGC (SEQ ID NO:349)

Ab-23

IgG2 version

Light Chain:

[0341] Amino acid sequence of the mature form (signal peptide removed) of the Ab-23 LC:

1 DIQMTQSPSS LSASVGDRTVITCRASQDLSYENWYQOKP GKAPKLLIYS
51 TSRLNSGVPS RPSGSGSGTD FTLTISLQP EDFATYYCQQ DIKHTFTGQG
101 TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD
151 NALQSGNSQE SYTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
201 SSPVTEKFNRR GEC (SEQ ID NO:341)

[0342] 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 TTTACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG
251 CAACTTACTA CTGTCAACAG GATATTAAAC ACCCTACGTT CGGTCAAGGC
301 ACCAAGGTGG AGATCAAACG TACGGTGGCT GCACCATCTG TCTTCATCTT
351 CCCGCCATCT GATGAGCAGT TGAATCTGG AACTGCCTCT GTTGTGTGCC
401 TGCTGAATAA CTCTATCCC AGAGAGGCCA AAGTACAGTG GAAGGTGGAT
451 AACGCCCTCC AATCGGGTAA CTCCAGGAG AGTGTCAAG AGCAGGACAG
501 CAAGGACAGC ACCTACAGCC TCAGCAGCAC CCTGACGCTG AGCAAAGCAG
551 ACTACGAGAA ACACAAAGTC TACGCCTGCG AAGTCACCA TCAGGGCCTG
601 AGCTCGCCCG TCACAAAGAG CTCAACAGG GGAGAGTGT (SEQ ID NO:342)

[0343] Amino acid sequence of the Ab-23 LC including signal peptide:

1 MDMRVPAQLL GLLLLWLRGA RCDIQMTQSP SLSASVGDR VTITCRASQD
 51 ISSYLNWYQQ KPGKAPKLLI YTSRLNSGV PSRFSGSGSG TDFTLTISL
 101 QPEDFATYYC QQDIKHPTFG QGTVKEIKRT VAAPSVFIFF PSDEQLKSGT
 151 ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYLSSTL
 201 TLSKADYKXH KVYACEVTHQ GLSSPVTKSF NRGEC (SEQ ID NO:343)

[0344] 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 AAACACAGGA AAGCCCCTAA
 201 GCTCCTGATC TATTCTACTT CCCGTTTGAA TAGTGGGGTC CCATCACGCT
 251 TCAGTGGCAG TGGCTCTGGG ACAGATTTC CTCTACCAT CAGCAGTCTG
 301 CAACCTGAAG ATTTTGCAAC TTAATACTGT CAACAGGATA TTAAACACCC
 351 TACGTTCCGT CAAGGCACCA AGGTGGAGAT CAAACGTACG GTGGCTGCAC
 401 CATCTGTCTT CATCTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAAC
 451 GCCTCTGTG TGTGCCTGCT GAATAACTTC TATCCAGAG AGGCCAAAGT
 501 ACAGTGAAG GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG
 551 TCACAGAGCA GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCTG
 601 ACGCTGAGCA AAGCAGACTA CGAGAAACAC AAAGTCTACG CTGCGAAGT
 651 CACCCATCAG GGCCTGAGCT CGCCGTCAC AAAGAGCTTC AACAGGGGAG
 701 AGTGT (SEQ ID NO:344)

Heavy Chain:

[0345] Amino acid sequence of the mature form (signal peptide removed) of the Ab-23 HC:

1 EVQLVQSGAE VKKPGSSVKV SCKASGFTFT D~~YIMH~~WVRQA PGQGLEWMG~~V~~
 51 ~~INPYND~~TEY ~~NEKFK~~GRVTI TADKSTSTAY MELSSLRSED TAVYYCAR~~SI~~
 101 ~~YY~~YDA~~FFAY~~W GQGITLVTVSS ~~ASTKGPSVFP LAPCSRSTSE STAALGCLVK~~
 151 ~~DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT~~
 201 ~~YTCNV~~DH~~KPS NTKVDKTYER KCCVECP~~PC~~ APPVAGPSVF LFPPKPKDTL~~
 251 ~~MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR~~
 301 ~~VVS~~VLTVVH~~Q~~ DWLNGKEYKC KVSNGLPAP IEKTISKTKG QPREPQVYTL
 351 PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQ~~PENNY~~ K~~TP~~PM~~LDSD~~
 401 GSFFLYSKLT VDKSRW~~Q~~QGN VFSCSV~~M~~HEA LHNHYTQ~~KSL~~ SLSPGK (SEQ ID
 NO:345)

[0346] Amino acid sequence of the mature form (signal peptide removed) of the Ab-23 HC without carboxy-terminal lysine:

1 EVQLVQSGAE VKKPGSSVKV SCKASGFTFT D~~YIMH~~WVRQA PGQGLEWMG~~V~~
 51 ~~INPYND~~TEY ~~NEKFK~~GRVTI TADKSTSTAY MELSSLRSED TAVYYCAR~~SI~~
 101 ~~YY~~YDA~~FFAY~~W GQGITLVTVSS ~~ASTKGPSVFP LAPCSRSTSE STAALGCLVK~~
 151 ~~DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT~~
 201 ~~YTCNV~~DH~~KPS NTKVDKTYER KCCVECP~~PC~~ APPVAGPSVF LFPPKPKDTL~~
 251 ~~MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR~~
 301 ~~VVS~~VLTVVH~~Q~~ DWLNGKEYKC KVSNGLPAP IEKTISKTKG QPREPQVYTL
 351 PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQ~~PENNY~~ K~~TP~~PM~~LDSD~~
 401 GSFFLYSKLT VDKSRW~~Q~~QGN VFSCSV~~M~~HEA LHNHYTQ~~KSL~~ SLSPG (SEQ ID
 NO:396)

[0347] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-23 HC:

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGTCCTC
 51 GGTGAAGGTC TCCTGCAAGG CTTCTGGITT TACCTTACC GACTATATTA
 101 TGCACTGGGT GCGTCAGGCC CCTGGTCAAG GGCTTGAGTG GATGGGCTAT
 151 ATCAACCCIT ATAATGATGA CACCGAATAC AACGAGAAGT TCAAGGGCCG

201 TGTACGATT ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGA
 251 GCAGCCTGCG CTCTGAGGAC ACGGCCGTGT ATTACTGTGC GCGTTCGATT
 301 TATTACTACG ATGCCCGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC
 351 CGTCTCTAGT GCCTCCACCA AGGCCCATC GGTCTTCCCC CTGGCGCCCT
 401 GCTCAGGAG CACCTCCGAG AGCACAGCGG CCCTGGGCTG CCTGGTCAAG
 451 GACTACTTCC CCGAACCGGT GACGGTGTG TGGAACTCAG GCGCTCTGAC
 501 CAGCGGCGTG CACACCTTCC CAGCTGTCTT ACAGTCCTCA GGACTCTACT
 551 CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG CACCCAGACC
 601 TACACTGCA ACGTAGATCA CAAGCCAGC AACACCAAGG TGGACAAGAC
 651 AGTTGAGCGC AAATGTTGTG TCGAGTGCCC ACCGTGCCCA GCACCACTG
 701 TGGCAGGACC GTCAGTCTTC CTCTTCCCCC AAAAACCCAA GGACACCCTC
 751 ATGATCTCCC GGACCCCTGA GGTCACGTGC GTGGTGGTGG ACCTGAGCCA
 801 CGAAGACCCC GAGGTCCAGT TCAACTGGTA CGTGGACGGC GTGGAGGTGC
 851 ATAATGCCAA GACAAAGCCA CGGGAGGAGC AGTTCAACAG CAGTTTCCGT
 901 GTGGTCAGCG TCCTACCCGT TGTGCACCAG GACTGGCTGA ACGCAAGGA
 951 GTACAAAGTGC AAGGTCTCCA ACAAAGGCCT CCCAGCCCCC ATCGAGAAAA
 1001 CCATCTCCAA AACCAAAGGG CAGCCCCGAG AACCAACAGG GTACACCCTG
 1051 CCCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTACGCC TGACCTGCCT
 1101 GGTCAAAGGC TTCTACCCCA GCGACATCGC CGTGGAGTGG GAGAGCAATG
 1151 GGCAGCCGGA GAACAACTAC AAGACCACAC CTCCATGCT GGAATCCGAC
 1201 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA
 1251 GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC
 1301 ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGTAAA (SEQ ID NO:346)

[0348] Amino acid sequence of the Ab-23 HC including signal peptide:

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPSSSVKVS CKASGFTFTD
 51 YIMHWVRQAP GQGLEWMGYI NPYNDDEYNEKFKGRVTIT ADKSTSTAYM
 101 ELSSLRSEDV AVYYCARSIY YYDAPFAYWG QGTLVTVSSA STKGPSVFPL
 151 APCSRSTSES TAALGCLVKD YFPEPVTVSW NSGALTSGVH TTPAVLQSSG
 201 LYSLSVVTV PSSNFGTQTY TCNVDHKPSN TKVDKTVKRC CCVECPCPA
 251 PPVAGPSVFL FPPKPKDILM ISRIPEVTCV VVDVSHEDPE VQFNWYVDGV
 301 EVHNAKTKPR EEQFNSTFRV VSVLTIVVHQD WLNQKEYKCK VSNKGLPAPI
 351 EKTISKTKGQ PREPQVYTLPS REEMTKNQ VSLTCLVKG FYPDI AVEWE
 401 SNGQPENNYK TTPMMLSDG SFFLYSKLT VDKSRWQQGNV FSCSV MHEAL
 451 HNHYTQKSL LSPGK (SEQ ID NO:347)

[0349] Nucleic acid sequence of the Ab-23 HC including signal peptide encoding sequence:

1 ATGGACTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
 51 CCACTCCGAG GTGCAGCTGG TGCACTCTGG GGTGAGGTG AAGAAGCCTG
 101 GGTCCTCGGT GAAGGTCTCC TGCAAGGCTT CTGGTTTAC CTTACCGAC
 151 TATATTATGC ACTGGGTGCG TCAAGCCCTT GGTCAAGGGC TTGAGTGGAT
 201 GGGGTATATC AACCTTATA ATGATGACAC CGAATACAAC GAGAAGTTCA
 251 AGGGCCGTGT CACGATTACC GCGGACAAAT CCACGAGCAC AGCCTACATG
 301 GAGCTGAGCA GCCTGCGCTC TGAGGACACG GCCGTGTATT ACTGTGCGCG
 351 TTCGATTTAT TACTACGATG CCCCCTTTGC TTAAGGGGCA CAAGGGACTC
 401 TGGTCAACCG CTCTAGTGCC TCCACCAAGG GCCCATCGGT CTTCCCCCTG
 451 GCGCCCTGCT CCAGGAGCAC CTCCGAGAGC ACAGCGGCCC TGGGCTGCCT
 501 GGTCAAGGAC TACTTCCCCG AACCGGTGAC GGTGTCTGTG AACTCAGGCG
 551 CTCTGACCAG CGGCGTGCAC ACCTTCCCAG CTGTCTCTACA GTCCTCAGGA

601 CTCTACTCCC TCAGCAGCGT GGTGACCGTG CCCTCCAGCA ACTTCGGCAC
 651 CCAGACCTAC ACCTGCAACG TAGATCACAA GCCCAGCAAC ACCAAGGTGG
 701 ACAAGACAGT TGAGCGCAAA TGTGTGTGCG AGTGCCCAAC GTGCCAGCA
 751 CCACCTGTGG CAGGACCGTC AGTCTTCTTC TCCCCCCTC AACCAAGGA
 801 CACCTCATG ATCTCCCGGA CCCCTGAGGT CAGCTGCGTG GTGGTGGACG
 851 TGAGCCACGA AGACCCCGAG GTCCAGTTCA ACTGGTACGT GGACGGCGTG
 901 GAGGTGCATA ATGCCAAGAC AAAGCCACGG GAGGAGCAGT TCAACAGCAC
 951 GTTCCGTGTG GTCAGCGTCC TCACCGTTGT GCACCAGGAC TGGCTGAACG
 1001 GCAAGGAGTA CAAGTGCAAG GTCTCCAACA AAGGCCTCCC AGCCCCATC
 1051 GAGAAAAACCA TCTCCAAAAC CAAAGGGCAG CCCCAGAAC CACAGGTGTA
 1101 CACCTGCCC CCATCCCGGG AGGAGATGAC CAAGAACCAG GTCAGCCTGA
 1151 CCTGCCCTGGT CAAAGGCTTC TACCCAGCG ACATCGCCGT GGAGTGGGAG
 1201 AGCAATGGGC AGCCGAGGAA 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)

[0350] 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:	YNPYNDDEYNEKFKG (SEQ ID NO:270)

CDR-H3:	STYYDAPFAY (SEQ ID NO:271)
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[0351] 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:

[0352] Ab-23 light chain variable domain amino acid sequence (without signal sequence):

DIQMTQSPSS LSASVGDRTV ITCRASQDIS SYLNWYQQKPKAPKLLIYS
TSRLNSGVPS RFGSGSGTD FTLTISLQP EDFATYYCQQ DIKHPTFGQG
TKVEIK (SEQ ID NO:364)

[0353] 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
TTCACCTCA CCATCAGCAG TCTGCAACCT GAAGATTTGCAACTTACTA
CTGTCAACAG GATATTAAAC ACCCTACGTT CGGTCAAGGCACCAAGGTGG
AGATCAAA (SEQ ID NO:365)

[0354] Ab-23 heavy chain variable domain amino acid sequence (without signal sequence):

EVQLVQSGAE VKKPGSSVKV SCKASGFTFT DYIMHWVRQA
PGQGLEWMGYINPYNDDEY NEKFKGRVTI TADKSTSTAY MELSSLRSED
TAVYYCARSIFYDDAPFAYW GQGITLVTVSS (SEQ ID NO:366)

[0355] Ab-23 heavy chain variable domain DNA sequence (without signal sequence):

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAA
GGTC TCCTGCAAGG CTTCTGGTTT TACCTTCACC GACTATATTATGCACTGGGT
GCGTCAGGCC CCGGTCAAG GGCTTGAGTG GATGGGCTATATCAACCCTT
ATAATGATGA CACCGAATAC AACGAGAAAGT TCAAGGGCCGTGTCACGATT
ACCGCGGACA AATCCACGAG CACAGCCTAC ATGAGCTGAGCAGCCTGCC
CTCTGAGGAC ACGGCCGTGT ATTACTGTGC GCGTTGATTTATTACTACG
ATGCCCGGTT TGCTTACTGG GGCCAAGGGACTCTGGTCACCGTCTCTAGT (SEQ ID
NO:367)

Ab-21

[0356] Amino acid sequence of the Ab-21 LC including signal peptide:

MKSOTOVFVYMLLWLSGVEGDIVMTQSHKFMSTSVGDRVITTCASQDYFTAVAWYQ
QKPGQSPKLLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPIT
FGAGTKLELKR (SEQ ID NO:315)

[0357] Nucleic acid sequence of the Ab-21 LC including signal peptide:

ATGAAGTCACAGACCCAGGTCTTTGTATACATGTTGCTGTGGTGTCTGGTGTGAA
GGAGACATTGTGATGACCCAGTCTCAGAAATTCATGTCCACGTCAGTAGGAGACAG
GGTCACCATCACCTGCAAGGCCAGTCAGGATGTCTTTACTGCTGTAGCCTGGTATCA
ACAGAAACAGGACAATCTCCTAAACTACTGATTTACTGGGCATCCACCCGGCACA
CTGGAGTCCCTGATCGTTTACAGGCAGTGGATCTGGGACAGATTTCACTCTACCA
TTAGCAATGTGCAGTCTGAAGACTTGGCAGATTATTTCTGTCAACAATATAGCAGCT
ATCCTCTCAGTTCCGTGCTGGGACCAAGTTGGAGCTGAAACGT (SEQ ID NO:316)

[0358] Amino acid sequence of the Ab-21 HC including signal peptide:

MGWNIWIFFLMAVVTGVNSEVQLQOSGAELVRPGALVKLSCKASGFNKKDYIMEHWV
KQRPQGLEWIGRIDPENGDIIYDPKFQGGKASITTDSSNTAYLQLSSLTSEDIAVYYCA
YDAGDPAWFFYFWGQGLVTVSS (SEQ ID NO:317)

[0359] Nucleic acid sequence of the Ab-21 HC including signal peptide:

ATGGGATGGAAGCTGGATCATCTTCTCCTGATGGCAGTGGTTACAGGGGTCAATTCA
 GAGGTTGAGCTGCAGCAGTCTGGGGCTGAGCTGTGAGGCCAGGGGCTTAGTCAA
 GTTGTCCTGCAAAGCTTCTGGCTTCAATATTAAGACTACTATATGCACTGGGTGAA
 GCAGAGGCTGAACAGGGCCTGGAGTGGATTGGAAGGATTGATCCTGAGAATGGTG
 ATATTATATGACCCGAAGTTCCAGGGCAAGGCCAGTATAACAACAGACACATCC
 TCCAACACAGCCTACCTGCAGCTCAGCAGCCTGACGCTGAGGACACTGCCGTCTAT
 TACTGTGCTTACGATGCTGGTGACCCCGCTGGTTTACTTACTGGGGCCAAAGGACT
 CTGGTCACCGTCTCGAGC (SEQ ID NO:318)

[0360] Ab-21 was humanized to yield Ab-22.

Ab-22

[0361] Amino acid sequence of the Ab-22 LC including signal peptide:

MDMRVPAOLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRTITCKASQDVFTAVAW
YQQKPGKAPKLLIYWASTRHTGVPSRFGSGSGTDFTLTISLQPEDFATYYCQQYSSYP
LTFGGGTKVEIKR (SEQ ID NO:319)

[0362] Nucleic acid sequence of the Ab-22 LC including signal peptide:

ATGGATATGCGCGTGCCGGCGCAGCTGCTGGGCGCTGCTGCTGCTGGCTGCGCGG
 CGCGCGCTGCGATATCCAGATGACCAGAGCCGAGCAGCCTGAGCGCGAGCGTGG
 GCGATCGCGTGACCATACCTGCAAAGCGAGCCAGGATGTGTTTACCGCGGTGGCG
 TGGTATCAGCAGAAAACCGGGCAAAGCGCCGAAACTGCTGATTATTGGGCGAGCAC
 CCGCCATACCGGCGTGCCGAGTCGCTTTAGCGGCAGCGGCAGCGGCACCGATTTA
 CCTGACCATTAGCAGCCTGCAGCCGGAAGATTTGCGACCTATTATTGCCAGCAGT
 ATAGCAGCTATCCGCTGACCTTTGGCGGGCGCACCAAAGTGGAATTAACGT (SEQ
 ID NO:320)

[0363] Amino acid sequence of the Ab-22 HC including signal peptide:

MDWTWSILFLVAAPTGAHSEVQLVQSGAEVKKPGASVKVSCKASGFNKKDYIMEHWV
RQAPGQGLEWIGRIDPENGDIIYDPKFQGRVTMTITDSTSTAYMELRSLRSDDTAVYYC
AYDAGDPAWFFYFWGQGLVTVSS (SEQ ID NO:321)

[0364] Nucleic acid sequence of the Ab-22 HC including signal peptide:

ATGGATTGGACCTGGAGCATTCTGTTTCTGGTGGCGGCGCCGACCGGCGGCATAG
 CGAAGTGACGCTGGTGACAGCGCGCGGAAGTGAAAAACCGGGCGCGAGCGTG
 AAAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATGCAATTGGGT
 GCGCCAGGCGCGGGCCAGGGCCTGGAATGGATCGGCCGCAATTGATCCGGAAAAC
 GCGGATATTATTTATGATCCGAAATTCAGGGCCGCGTGACCATGACCACCGATACC
 AGCACCAGCACCGGTATATGGAACGCGCAGCCTGCGCAGCGATGATACCGCGGT
 GTATTATTGCGCGTATGATGCGGCGATCCGCGTGGTTACCTATTGGGGCCAGGG
 CACCCTGGTGACCGTCTCGAGC (SEQ ID NO:322)

[0365] Ab-22 light chain variable domain amino acid sequence (without signal sequence):

DIQMTQSPSSLSASVGDRTITCKASQDVFTAVAWYQQKPGKAPKLLIYW
 ASTRHTGVPSRFGSGSGTDFTLTISLQPEDFATYYCQQYSSYPLTFGG
 GTKVEIKR (SEQ ID NO:336)

[0366] Ab-22 light chain variable domain DNA sequence (without signal sequence):

GATATCCAGATGACCCAGAGCCGAGCAGCCTGAGCGCGAGCGTGGGCGATCGCGT
 GACCATTACCTGCAAAGCGAGCCAGGATGTGTTTACCGCGGTGGCGTGGTATCAGC

AGAAACCGGGCAAAGCGCCGAACTGCTGATTTATTGGGCGAGCACCCGCCATACC
GGCGTGCCGAGTCGCTTTAGCGGCAGCGGCAGCGGCACCGATTTTACCCTGACCAT
TAGCAGCCTGCAGCCGGAAGATTTTGCAGCCTATTATTGCCAGCAGTATAGCAGCT
ATCCGCTGACCTTTGGCGGCGGCACCAAAGTGGAATTAACGT (SEQ ID NO:337)

[0367] Ab-22 heavy chain variable domain amino acid sequence (without signal sequence):
EVQLVQSGAE VKKPGASVKV SCKASGFNIK DYIMHWVRQA
PGQGLEWIGRIDFENGDIY DPKFQGRVTM TTDSTSTAY MELRSLRSD
TAVVYCAVDAGDPAWFTYWG QGTLTVSS (SEQ ID NO:338)

[0368] Ab-22 heavy chain variable domain DNA sequence (without signal sequence):
GAAGTGCAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTGA
AAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATATGCAATTGGGTG
CGCCAGGCGCGCGGCCAGGGCTGGAATGGATCGGCGCATGATCCGGAAAAACG
GCATATTATTTATGATCCGAAATTTACAGGCGCGGTGACCATGACCAACGATACCA
GCACACGACCGCGTATATGGAAGTGCAGCAGCTGCGCAGCGATGATACCGCGGTG
TATTATTGCGCGTATGATGCGGCGATCCGCGGTGTTACCTATTGGGGCCAGGGC
ACCGTGGTGACCGTCTCGAGC (SEQ ID NO:339).

[0369] 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:
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSS
GLYSSSVTVTPSSSLGKTYTCNVDPKPSNTKVDKRVSCKYGPCCPAPAEFLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSDPEVQFNWYVDGVEVHNAKTKPREEQFNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSR
WQEGNVFSCSVMHREALHNYTQKSLSLSLGK* (SEQ ID NO:326)

[0370] 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

[0371] The sequences of Antibody 24 (also referred to herein as Ab-24) LC and HC are as follows:

Light Chain:

[0372] Amino acid sequence of the mature form (signal peptide removed) of the Ab-24 LC:

1 DIVLTQSPAS LAVSLGORAT IACKASQSYD YDGTSYMINWY QOKPGOPPKL
51 LIY AASNLES EIPARPSGTG SGTDFILNIH FVEEDITTY YCQSNEDPE
101 IFGGGKLEI KRADAAPTYS IFPPSSEQLT SGGASVVCFL NNFYPKDINV
151 KWKIDGSEERQ NGVLNSWTDQ DSKDSTYSMS STLTLTKDEY ERHNSYTCEA
201 THKTSTSPIV KSFNRNEC (SEQ ID NO:350)

[0373] 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 ACTTACCCT CAACATCCAT CCTGTGGAGG
 251 AGGAGGATAT CACAACCTAT TACTGTCAGC AAAGTAATGA GGATCCGTTT
 301 ACGTTCCGAG GGGGGACCAA GTTGAAATA AAACGGGCTG ATGCTGCACC
 351 AACTGTATCC ATCTTCCAC CATCCAGTGA GCAGTTAACA TCTGGAGGTG
 401 CCTCAGTCGT GTGCTTCTTG AACAACTTCT ACCCAAAGA CATCAATGTC
 451 AAGTGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC TGAACAGTTG
 501 GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC AGCACCTCA
 551 CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC CTGTGAGGCC
 601 ACTCACAAGA CATCAACTTC ACCCATTGTC AAGAGCTTCA ACAGGAATGA
 651 GTGTTAG (SEQ ID NO:354)

[0374] Amino acid sequence of the Ab-24 LC including signal peptide:

1 METDTILLWV LLLWVPGSTG DIVLTQSPAS LAVSLGQRAT IACKASQSV
 51 YDGSYMNWY QQKPGQPKL LIYAASNLES EIPARFSGTG SGTDFTLNH
 101 PVEEDITTY YCQSNEDPF TFGGGTKLEI KRADAAPTVS IFPPSSEQLT
 151 SGGASVVCFL NNFYPKINV KWKIDGSRQ NGVLNSWTDQ DSKDSTYSMS
 201 STLTLTKDEY ERHNSYTCBA THKTSTSPIV KSFNRNEC (SEQ ID NO:355)

[0375] Nucleic acid sequence of the Ab-24 LC including signal peptide encoding sequence:

1 ATGGAGACAG ACACAATCCT GCTATGGGTG CTGCTGCTCT GGGTTCAGG
 51 CTCCACTGGT GACATTGTGT TGACCCAGTC TCCAGCTTCT TTGGCTGTGT
 101 CTCTAGGGCA GAGGGCCACC ATCGCCTGCA AGGCCAGCCA AAGTGTGAT
 151 TATGATGGTA CTAGTTATAT GAATTGGTAC CAACAGAAAC CAGGACAGCC
 201 ACCCAAATC CTCATCTATG CTGCATCCAA TCTAGAATCT GAGATCCCAG
 251 CCAGGTTTAG TGGCACTGGG TCTGGGACAG ACTTACCCT CAACATCCAT
 301 CCTGTGGAGG AGGAGGATAT CACAACCTAT TACTGTCAGC AAAGTAATGA
 351 GGATCCGTTT ACGTTCCGAG GGGGGACCAA GTTGAAATA AAACGGGCTG
 401 ATGCTGCACC AACTGTATCC ATCTTCCAC CATCCAGTGA GCAGTTAACA
 451 TCTGGAGGTG CCTCAGTCGT GTGCTTCTTG AACAACTTCT ACCCAAAGA
 501 CATCAATGTC AAGTGAAGA 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:

[0376] Amino acid sequence of the mature form (signal peptide removed) of the Ab-24 HC:

1 QVQLQPGTE LVRPGTSVKL SCKASGYFT IYWMN~~W~~VVKQR PGQGLEWIGM
 51 ~~I~~HPSASEIRL DQKFKDKATL TLDKSSSTAY MHL~~S~~GPSTVD SAVYYCARSG
 101 EWGSM~~D~~YWGQ GTSVTVSSAK TTPPSVYPLA PGSAAQTNSM VTLGCLVKGY
 151 FPEPVTVTW~~N~~ SGLSSGVHT FPAVLQSDLY TLSSSVTPVS STWPSETVTC
 201 NVAHPASSTK VDKKIVPRDC GCKPCICTVP EVSSVFIFPP KPKDVLITTL
 251 TP~~K~~VT~~C~~VVVD ISKDDPEVQF SWFVDDVEVH TAQTQPREEQ FNSTFRSVSE
 301 LPIMHQDWLN GKEFKCRVNS AAFPAPIEKT ISKTGRPKA PQVYTIPPPK
 351 EQMAKDKVSL TCMITDFFPE DITVEWQWNG QPAENYKNTQ PLMDTDGSYF
 401 IY~~S~~KLNVQKS NWEAGNTFTC SVLHEGLHNH HTEKSLSHSP GK (SEQ ID NO:357)

[0377] Nucleic acid sequence encoding the mature form (signal peptide removed) of the Ab-24 HC:

1 CAGGTCCAAC TACAGCAGCC TGGGACTGAG CTGGTGAGGC CTGGAAC TTC
51 AGTGAAGTTG TCCTGTAAGG CTTCTGGCTA CATCTTCACC ACCTACTGGA
101 TGAAGTGGGT GAAACAGAGG CCTGGACAAG GCCTTGAGTG GATTGGCATG
151 ATTCATCCTT CCGCAAGTGA AATTAGGTTG GATCAGAAAT TCAAGGACAA
201 GGCCACATTG ACTCTTGACA AATCCTCCAG CACAGCCTAT ATGCACCTCA
251 GCGGCCCGAC ATCTGTGGAT TCTGCGGTCT ATTACTGTGC AAGATCAGGG
301 GAATGGGGGT CTATGGACTA CTGGGGTCAA GGAACCTCAG TCACCGTCTC
351 CTCAGCCAAA ACGACACCCC CATCTGTCTA TCCACTGGCC CCTGGATCTG
401 CTGCCCCAAC TAACTCCATG GTGACCTGG GATGCCTGGT CAAGGGCTAT
451 TTCCCTGAGC CAGTGACAGT GACCTGGAAC TCTGGATCCC TGTCCAGCGG
501 TGTGCACACC TTCCAGCTG TCCTGCAGTC TGACCTCTAC ACTCTGAGCA
551 GCTCAGTGAC TGTCCCCTCC AGCACCTGGC CCAGCGAGAC CGTCACCTGC
601 AACGTTGCCC ACCCGGCCAG CAGACCAAG GTGGACAAGA AAATTGTGCC
651 CAGGGAATTGT GGTGTGAAGC CTTGCAATG TACAGTCCCA GAAGTATCAT
701 CTGTCTTCAT CTTCCCCCA AAGCCCAAGG ATGTGCTCAC CATTACTCTG
751 ACTCTAAGG TCACGTGTGT TGTGGTAGAC ATCAGCAAGG ATGATCCCGA
801 GGTCCAGTTC AGCTGGTTTG TAGATGATGT GGAGGTGCAC ACAGCTCAGA
851 CGCAACCCCG GGAGGAGCAG TTCAACAGCA CTTCCGCTC AGTCAGTGAA
901 CTTCCCATCA TGCACCAAGG CTGGCTCAAT GGCAAGGAGT TCAAAATGCAG
951 GGTCAACAGT GCAGCTTTCC CTGCCCCAT CGAGAAAACC ATCTCCAAAA
1001 CCAAAGGCAG ACCGAAGGCT CCACAGGTGT ACACCATTC ACCTCCCAAG
1051 GAGCAGATGG CCAAGGATAA AGTCAGTCTG ACCTGCATGA TAACAGACTT
1101 CTTCCCTGAA GACATTACTG TGGAGTGCCA GTGGAATGGG CAGCCAGCGG
1151 AGAACTACAA GAACACTCAG CCCATCATGG ACACAGATGG CTCTTACTTC
1201 ATCTACAGCA AGCTCAATGT GCAGAAGAGC AACTGGGAGG CAGGAAATAC
1251 TTTACCTGC TCTGTGTAC ATGAGGGCCT GCACAACCAC CATACTGAGA
1301 AGAGCCTTC CCACCTCTCT GTTAAATGA (SEQ ID NO:361)

[0378] Amino acid sequence of the Ab-24 HC including signal peptide:

1 MGWSSILFL VATATGVHSQ VQLQPGTEL VRPGTSVKLS CKASGYIFTT
51 YWMNWVKQRP GQGLEWIGMI HPSASEIRLD QKFKDKATLT LDKSSSTAYM
101 HLSGFTSVDS AVYYCARSGE WGSMDYWGQG TSVTVSSAKT TTPSVYPLAP

151 GSAAQTNSMV TLGCLVKGYF PEPVTVTWS GSLSSGVHTF PAVLQSDLYT
201 LSSSVTVPS TWPSETVCN VAHPASSTKV DKKIVPRDCG CKPCICTVPE
251 VSSVFIPPK PKDVLITLT PKVTCVVVDI SKDDPEVQFS WFVDDDEVHT
301 AQTPREEQF NSTFRSVSEL PIMHQDWLNG KEFKCRVNSA AFPAPIEKT
351 SKTKGRPKAP QVYTPPPKE QMAKDKVSLT CMTDFFPED ITVEWQWNGQ
401 PAENYKNTQP IMDTDGSYFI YSKLNVQKSN WEAGNFTCS VLHEGLHNNH
451 TEKSLSHSPG K (SEQ ID NO:362)

[0379] Nucleic acid sequence of the Ab-24 HC including signal peptide encoding sequence:

1 ATGGGATGGA GCTCTATCAT CCTCTCTTG GTAGCAACAG CTACAGGTGT
51 CCACTCCAG GTCCAACCTAC AGCAGCCTGG GACTGAGCTG GTGAGGCCCTG
101 GAACTTCAGT GAAGTTGTCC TGTAAAGCTT CTGGCTACAT CTTACCACC
151 TACTGGATGA ATGGGTGAA ACAGAGGCCT GGACAAGGCC TTGAGTGGAT
201 TGGCATGATT CATCCTTCCG CAAGTGAAAT TAGGTTGGAT CAGAAATTCA
251 AGGACAAGGC CACATTGACT CTTGACAAAT CCTCCAGCAC AGCCTATATG
301 CACCTCAGCG GCCCGACATC TGTGGATTCT GCGGTCTATT ACTGTGCAAG
351 ATCAGGGGAA TGGGGGTCTA TGGACTACTG GGGTCAAGGA ACCTCAGTCA
401 CCGTCTCTC AGCCAAAACG ACACCCCAT CTGTCTATCC ACTGGCCCCCT
451 GGATCTGCTG CCCAAACTAA CTCCATGGTG ACCCTGGGAT GCCTGGTCAA
501 GGGCTATTTC CCTGAGCCAG TGACAGTGAC CTGGAACCTT GGATCCCTGT
551 CCAGCGGTGT GCACACCTTC CCAGCTGTCC TGCACTCTGA CCTCTACACT
601 CTGAGCAGCT CAGTGACTGT CCCCTCCAGC ACCTGGCCCA GCGAGACCGT
651 CACCTGCAAC GTTGCCACC CGGCCAGCAG CACCAAGGTG GACAAGAAAA
701 TTGTGCCAG GGATTGTGGT TGTAAAGCCTT GCATATGTAC AGTCCAGAA
751 GTATCATCTG TCTTCATCTT CCCCCAAAG CCCAAGGATG TGCTCAACAT
801 TACTCTGACT CCTAAGGTCA CGTGTGTTGT GGTAGACATC AGCAAGGATG
851 ATCCCGAGGT CCAGTTCAGC TGGTTGTAG ATGATGTGGA GGTGCACACA
901 GCTCAGACGC AACCCCGGA GGAGCAGTTC AACAGCACTT TCCGCTCAGT
951 CAGTGAACCT CCCATCATGC ACCAGGACTG GCTCAATGGC AAGGAGTTCA
1001 AATGCAGGGT CAACAGTGCA GCTTCCCTG CCCCCATCGA GAAAACCATC
1051 TCCAAAACCA AAGGCAGACC GAAGGCTCCA CAGGTGTACA CCATTCCACC
1101 TCCCAAGGAG CAGATGGCCA AGGATAAAGT CAGTCTGACC TGCATGATAA
1151 CAGACTTCTT CCCTGAAGAC ATTACTGTGG AGTGGCAGTG GAATGGGCAG
1201 CCAGCGGAGA ACTACAAGAA CACTCAGCCC ATCATGGACA CAGATGGCTC
1251 TTACTTCATC TACAGCAAGC TCAATGTGCA GAAGAGCAAC TGGGAGGCAG
1301 GAAATACTTT CACCTGCTCT GTGTACATG AGGGCCTGCA CAACCACCAT
1351 ACTGAGAAGA GCCTCTCCCA CTCTCTGGT AAATGA (SEQ ID NO:363)

[0380] The CDR sequences in the variable region of the light chain of Ab-24 are as follows:

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

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

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

[0381] 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: SGEWGSMY (SEQ ID NO:360)

[0382] 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
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-B CDR-L3	QQRSTYPPT
57	Ab-B CDR-H1	TSGMGVG
58	Ab-B CDR-H2	HMWDDVKRYNPVLKS
59	Ab-B CDR-H3	EDFDYDEEYAMDY
48	Ab-C CDR-L1	KASQSVYDGD SYMN
49	Ab-C CDR-L2	AASNLES
50	Ab-C CDR-L3	QQSNEPWT
45	Ab-C CDR-H1	DCYMN
46	Ab-C CDR-H2	DINPFNGGTTYNQKFKG
47	Ab-C CDR-H3	SHYYFDGRVPWDAMDY
42	Ab-D CDR-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	DDYDASPFA Y
275	Ab-2 CDR-L1	RASSSVYYMH
276	Ab-2 CDR-L2	ATSNLAS
277	Ab-2 CDR-L3	QQWSSDPLT
287	Ab-2 CDR-H1	DYFIH

Table 1		
SEQ ID NO	DESCRIPTION	AMINO ACID SEQUENCE
288	Ab-2.CDR-H2	RLDPEDGESDYAPKFQD
289	Ab-2 CDR-H3	EDYDGTYTFFPY
278	Ab-3 and Ab-15 CDR-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	RIDPENGDTLYDPKFQD
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
80	Ab-4 and Ab-5 CDR-L3	QQGDTLPYT
245	Ab-4 and Ab-5 CDR-H1	DYNMH
246	Ab-4 and Ab-5 CDR-H2	EINPNSGGAGYNQKFKG
247	Ab-4 and Ab-5 CDR-H3	LGYYDDIYDDWYFDV
81	Ab-6 CDR-L1	RASQDISNYLN
99	Ab-6 CDR-L2	YTSRLHS
100	Ab-6 CDR-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	RASQVITNLY
102	Ab-7 CDR-L2	YTSRLHS
103	Ab-7 CDR-L3	QQGDTLPYT
251	Ab-7 CDR-H1	DYNMH
252	Ab-7 CDR-H2	EINPNSGGAGYNQQFKG
253	Ab-7 CDR-H3	LGYYVGNIEDWYFDV
104	Ab-8 CDR-L1	RASQDISNYLN
105	Ab-8 CDR-L2	YTSRLLS
106	Ab-8 CDR-L3	QQGDTLPYT
254	Ab-8 CDR-H1	DYNMH
255	Ab-8 CDR-H2	EINPNSGGAGYNQKFKG
256	Ab-8 CDR-H3	LGYYDDIYDDWYFDV
107	Ab-9 CDR-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	LGYYDDIYDDWYFDV
110	Ab-10 CDR-L1	RASQDISNYLN
111	Ab-10 CDR-L2	YTSRLLS
112	Ab-10 CDR-L3	QQGDTLPYT
260	Ab-10 CDR-H1	DYNMH

Table 1		
SEQ ID NO	DESCRIPTION	AMINO ACID SEQUENCE
261	Ab-10 CDR-H2	EINPNSGGAGYNQKFKG
262	Ab-10 CDR-H3	LGYYDDIYDDWYFDV
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
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	DYMH
264	Ab-12 CDR-H2	EINPNSGGSGYNQKFKG
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	SVSSSSISSNLH
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	RIDPDNGESTV/PKFQG
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	STSLNS
241	Ab-19, Ab-20 and Ab-23 CDR-L3	QQDIKHPT
269	Ab-19, Ab-20 and Ab-23 CDR-H1	DYMH
270	Ab-19, Ab-20 and Ab-23 CDR-H2	YNPYNDDTEYNEKFKG
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	RIDPENGDIYDPKFQG
274	Ab-21 and Ab-22 CDR-H3	DAGDPAWFTY
351	Ab-24 CDR-L1	KASQSVDYDGTSMN
352	Ab-24 CDR-L2	AASNLES
353	Ab-24 CDR-L3	QQSNEDPFT
358	Ab-24 CDR-H1	TYWMN

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

[0383] 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.

[0384] Sclerostin binding agent polypeptides and 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.

[0385] 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.

[0386] Antibodies according to the invention 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.

[0387] The affinity of a binding agent such as an antibody or binding partner, as well as the extent to which a binding agent (such as an antibody) 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)).

[0388] 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

[0389] 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 or binding agents (*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

[0390] 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.

[0391] 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.

[0392] 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).

[0393] 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 (C4GPARLLPNAIGRGKWWRPSPDFRC5, 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).

[0394] 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.

[0395] 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.

[0396] 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 described. 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.

[0397] 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.

[0398] 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 SAKPVTELVLC3SGQC4GPAR (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.

[0399] 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 SAKPVTELVLC3SGQC4 (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.

[0400] 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 described. 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.

[0401] 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

[0402] 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.

[0403] 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 disclosure, 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

[0404] 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. 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.

[0405] 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).

[0406] 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.

[0407] 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).

[0408] 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.

[0409] 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.

[0410] 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.

[0411] The solution of antibody B* alone is then passed over the sclerostin-coated surface and the amount of binding recorded.

[0412] 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.

[0413] Thus, in general, a cross-blocking antibody or other binding agent 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 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.

[0414] The Biacore assay described above is a primary assay used to determine if antibodies or other binding agents cross-

block each other. 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

[0415] 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. 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.

[0416] 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.

[0417] 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.

[0418] 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. 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. 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.

[0419] 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).

[0420] An example of such an ELISA-based cross blocking assay can be found in Example 7 ("ELISA-based cross-blocking assay").

CELL BASED NEUTRALIZATION ASSAY

[0421] 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.

[0422] 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.

[0423] 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.

[0424] 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

[0425] 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").

[0426] 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.

[0427] Pharmaceutical compositions are provided, comprising an antibody, along with a pharmaceutically or physiologically acceptable carrier, excipient, or diluent wherein the antibody is a monoclonal antibody that (a) binds to human sclerostin with a binding affinity of less than or equal to 1×10^{-10} M and (b) cross-blocks the binding of antibody Ab-13 or Ab-14 to sclerostin and/or is cross-blocked from binding to sclerostin by antibody Ab-13 or Ab-14, wherein antibody Ab-13 has light chains of SEQ ID NO: 205 and heavy chains of SEQ ID NO: 209 and antibody Ab-14 has light chains of SEQ ID NO: 213 and heavy chains of SEQ ID NO: 217 or 393, and wherein the pharmaceutical composition is for use in a method of increasing at least one of bone formation, bone mineral density, bone mineral content, bone mass, bone quality and bone strength in a mammal and thereby treating a condition 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. Pharmaceutical compositions are disclosed in copending Application Serial No. 10/868,497, filed June 16, 2004, which claims priority to Serial No. 60/478,977.

[0428] 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.

[0429] 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.

[0430] 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 hydroxypropylcellulose. 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.

[0431] 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.

[0432] 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.

[0433] 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.

[0434] 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.

[0435] Liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, may be 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 can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

[0436] 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)).

[0437] The disclosure provides for pharmaceutically-acceptable nanocapsule formulations. 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.

[0438] In addition, pharmaceutical compositions 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.

[0439] 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.

[0440] 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 Cornier, 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 Cornier, *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)).

[0441] Particular conditions which may be treated by the compositions of the present invention 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 exotoses, 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.

[0442] 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.

[0443] The disclosure also provides a diagnostic kit comprising at least one anti-sclerostin binding agent. The binding agent may be an antibody. In addition, such a kit may optionally comprise one or more of the following:

1. (1) instructions for using the one or more binding agent(s) for screening, diagnosis, prognosis, therapeutic monitoring or any combination of these applications;
2. (2) a labeled binding partner to the anti-sclerostin binding agent(s);
3. (3) a solid phase (such as a reagent strip) upon which the anti-sclerostin binding agent(s) is immobilized; and
4. (4) a label or insert indicating regulatory approval for screening, diagnostic, prognostic or therapeutic use or any combination thereof.

[0444] 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.

[0445] The following examples are offered by way of illustration, and not by way of limitation.

EXAMPLES

EXAMPLE 1

Recombinant Expression of Sclerostin

[0446] 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).

[0447] 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 (5.0-10.0 X 10⁵ cells/mL X culture volume) is centrifuged at 2,500 RPM for 10 minutes at 4°C to remove the conditioned medium.

[0448] 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.

[0449] 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 4°C.

EXAMPLE 2

PURIFICATION OF recombinant SCLEROSTIN

[0450] 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 Chromatography

[0451] 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.

[0452] 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

[0453] 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

[0454] 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

[0455] 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 1µg/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.

[0456] Antibodies to be tested were diluted to 1µg/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

[0457]

Costar's Sulphydryl Binding Plates (VWR # 29442-278)

Coating Buffer: 1XPBS PH 6.5 + 1mM EDTA

Blocking Buffer: 1XPBS + 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 (RD# RDI-TMSX-1L)

Methods were as follows:

[0458]

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

[0459] The following peptides sequences were screened as described above:

QGWQAFKNDATHPLREYPEPP (SEQ ID NO:82)

TEIIPGLREYPEPPQLENN (SEQ ID NO:83)

PEPPQLENNQTMNRAENG (SEQ ID NO:84)

ENGGRPPHPYDTKDVSEYS (SEQ ID NO:85)

CRELHYTRFVTDGP (SEQ ID NO:86)

CRELHYTRFVTDGPSRSAPVTELV (SEQ ID NO:87)

CRSAKPVELVSSGQSGPRARLL (SEQ ID NO:88)

CGPARLLPNAIGRVKWWRPNGPDFR (SEQ ID NO:89)

RAQRVQLLCPGGAAPRSRKV (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)

KWWRPNGPDFRCIPDRYAQRV (SEQ ID NO:97).

[0460] A high-affinity neutralizing antibody (Ab-19) bound to two overlapping peptide sequences: PNAIGRVKWWRPNGPDFR (SEQ ID NO:96) and KWWRPNGPDFRCIPDRYAQRV (SEQ ID NO:97).

[0461] 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

[0462] 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

[0463] 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.

[0464] 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 Endoprotease Digestions

[0465] 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

[0466] 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

[0467] 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 ESILC-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, AspN18.5, 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 the encompasses all eight cysteines (the four disulfide bonds), the cystine-knot and all of loops 1,2 and 3.

[0468] 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 determine 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 principal of this competition assay.

[0469] 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, couple 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.

BIACORE-BASED HUMAN SCLEROSTIN PEPTIDE EPIOTOPE COMPETITION BINDING ASSAY

Preparation of human sclerostin surface:

[0470] 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:

[0471] 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:

[0472] 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:

[0473] 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:

[0474] 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

[0475] 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.

[0476] 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

[0477] 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

[0478] 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

[0479] 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 ASSAY FOR ANTIBODIES THAT BLOCK BINDING OF AN ANTIBODY TO HUMAN SCLEROSTIN

[0480] 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.

[0481] The antibodies to be tested were diluted to a concentration of 200 μ g/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 100 μ g/ml (1.3 μ M 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 100 μ g/ml (1.3 μ M on a binding site basis).

[0482] 20 μ L of the test mixture was passed over the sclerostin-coated chip at a flow rate of 10 μ L/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 1.3 μ M 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 1.3 μ M in the same buffer as the test mixture on a binding site basis) was passed over the chip and the amount of binding recorded.

[0483] 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 1.3 μ M on a binding site basis) or buffer indicated in the top row of the table were mixed with the antibodies (at 1.3 μ M 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

[0484] 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						

[0485] 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 ASSAY

[0486] 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), Corning 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 it's 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.

[0487] 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. 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. 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.

[0488] 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).

[0489] 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 ASSAY FOR IDENTIFYING AGENTS ABLE TO ANTAGONIZE SCLEROSTIN ACTIVITY

Introduction

[0490] 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.

[0491] 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.

[0492] 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

[0493] 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.

[0494] 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 ~ 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).

[0495] 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.

[0496] 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.

[0497] A detailed MC3T3-E1-BF cell culture protocol is described below.

Reagents and Medias

[0498]

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)
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.		

Expansion Medium (Alpha-MEM/10%FBS/PenStrepGlu) was prepared as follows:

[0499] 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.

[0500] 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 (50µg/ml + 50µg/ml)
β-glycerophosphate	1M	1.0 mls	10 mM

[0501] 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.

[0502] 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:

[0503] 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, 1×10^6 cells were plated in 50 mls Alpha-MEM/10%FBS/PenStrepGlu media in one T175 flask.

[0504] 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 1×10^6 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 $1-2 \times 10^6$ live cells/ml in 90%FBS/10%DMSO.

[0505] 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 1×10^6 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 $1-2 \times 10^6$ live cells/ml in 90%FBS/10%DMSO.

[0506] 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 1×10^6 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 $1-2 \times 10^6$ live cells/ml in 90%FBS/10%DMSO.

[0507] 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, the cells were frozen down at $1-2 \times 10^6$ live cells/ml in 90%FBS/10%DMSO. This "final passage" of frozen cells was the passage that was used for the screening assay.

Cell Culture for mineralizing MC3T3-E1-BF cells.

[0508] Cell culture was performed at 37°C and 5% CO₂. It is desirable to minimize temperature and % CO₂ 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.

[0509] 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/PenStrepGlu. 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).

[0510] 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.

Exemplary cell culture procedure

[0511] 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.

[0512] 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.

[0513] 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.

[0514] 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.

[0515] 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 (RCB 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^{high} TRANSFER MODEL OF COLITIS IN SCID MICE

Summary of model

[0516] 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

[0517] 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

[0518] 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

[0519] 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.

[0520] 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

[0521] 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 $\mu\text{g/ml}$ 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 ~ 4 pM
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.

[0522] 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

[0523] Biacore ® 3000, Biacore AB, Uppsala, Sweden

Sensor chip

[0524] CM5 (research grade) Catalogue Number: BR-1001-14, Biacore AB, Uppsala, Sweden. Chips were stored at 4 °C.

BIAnormalising solution

[0525] 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.

Amine Coupling Kit

[0526] Catalogue Number: BR-1000-50, Biacore AB, Uppsala, Sweden.

[0527] Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC). Made up to 75 mg/mL in distilled water and stored in 200 µL aliquots at -70 °C.

[0528] N-Hydroxysuccinimide (NHS). Made up to 11.5 mg/mL in distilled water and stored in 200 µL aliquots at 70 °C. 1 M Ethanolamine hydrochloride-NaOH pH 8.5. Stored in 200 µL aliquots at -70 °C.

Buffers

[0529] 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.

[0530] 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.

[0531] 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

[0532] 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

[0533] Humanised anti-human sclerostin antibodies Ab5, Ab14 and Ab20.

Analyte

[0534] Recombinant human sclerostin. Aliquots stored at -70°C and thawed once for each assay.

Regeneration Solution

[0535] 40 mM HCl prepared by dilution with distilled water from an 11.6 M stock solution (BDH, Poole, England. Catalogue number: 101254H).

[0536] 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 Method

[0537] 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.

[0538] An example of the procedure is given below:

[0539] BIA (Biomolecular Interaction Analysis) was performed using a BiAcCore 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 ≈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 µl/min. A 10 µl injection of the anti-sclerostin antibody at ~5 µg/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 µL/min. The surface was regenerated by two 10 µL injections of 40 mM HCl, followed by a 5 µL injection of 5 mM NaOH at a flowrate of 10µL/min.

[0540] Background subtraction binding curves were analysed using the BIAevaluation software (version 3.2) following standard procedures. Kinetic parameters were determined from the fitting algorithm.

[0541] 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 CYNOMOLGUS MONKEYS**

[0542] 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)

[0543] AU 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). 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].

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 Diagnostic, Espoo, Finland)

C-telopeptide fragments of collagen type I α 1 chains (sCTXI) (Serum CrossLaps[®] ELISA; Nordic Bioscience Diagnostics A/S, Herlev, Denmark).

[0544] 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)).

[0545] 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.

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Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
180    185    190
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
195    200    205
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
210    215

```

<210> 16

<211> 657

<212> DNA

<213> Mus musculus

<400> 16

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gacattgtgc tgaccaatc tccagcttct ttgactgtgt ctctaggcct gagggccacc 60
atctcctgca aggccagcca aagtgttgat tatgatggg atagttatat gaactggtag 120
cagcagaaac caggacagcc acccaaatc ctcatctatg ctgcatccaa tctagaatct 180
gggatccag ccaggtttag tggcaatggg tctgggacag acttcaccct caacatccat 240
cctgtggagg agggagatgc tgtaacctat tactgtcaac aaagtatga ggatccgtgg 300
acgttcgggt gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc 360
atcttccac catccagtga gcagttaaca tctggaggtg ccicagtcgt gtgcttcttg 420
aacaacttct accccaaga catcaatgic aagtgggaaga ttgatggcag tgaacgacaa 480
aatggcgtcc tgaacagttg gactgatcag gacagcaaa acagcattca cagcatgagc 540
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatcc ctgtgaggcc 600
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```

<210> 17

<211> 238

<212> PRT

<213> Mus musculus

<400> 17

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Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1      5      10      15
Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Thr
20     25     30
Val Ser Leu Gly Leu Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser
35     40     45
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 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
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 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 Ser Thr Leu Thr Leu Thr Lys Asp
195    200    205
Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr
210    215    220
Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225    230    235

```

<210> 18

<211> 717

<212> DNA

<213> Mus musculus

<400> 18

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gacattgtgc tgaccacaatc tccagcttct ttgactgtgt ctctaggcct gagggccacc 120
atctccctgca aggccagcca aagtgttgat tatgatggty atagttatat gaactgggtac 180
cagcagaaac caggacagcc acccaaatc ctcatctatg ctgcatccaa tctagaatct 240
gggatcccgag ccaggttttag tggcaatggg tctgggacag acttcacct caacatccat 300
cctgtggagg agggagatgc tgtaacctat tactgtcaac aaagtaatga ggatcccggtg 360
acgttcgggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc 420
atcttccacac catccagtaga gcagttaaca tctggaggty cctcagtcgt gtgcttcttg 480
aacaacttct acccaagaaga catcaatgtc aagtggaaaga ttgatggcag tgaacgacaa 540
aatggcgctcc tgaacagttg gactgatcag gacagcaaa acagcaccta cagcatgagc 600
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatata ctgtgaggcc 660
actcacaaga catcaacttc acccatgtgc aagagcttca acaggaatga gtgttag 717

```

<210> 19

<211> 449

<212> PRT

<213> Mus musculus

<400> 19

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Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Thr
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Cys
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

```

```

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Asn Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp Asp Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr
115 120 125
Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
130 135 140
Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
180 185 190
Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
195 200 205
Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
210 215 220
Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
225 230 235 240
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
Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
275 280 285
Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
290 295 300
Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
325 330 335
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
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
Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
420 425 430
Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
435 440 445
Lys

```

<210> 20

<211> 1350

<212> DNA

<213> Mus musculus

<400> 20

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tctgttaagg cttctggata cacattcact gactgctaca tgaactgggt gaagcagagc 120
catgggaaga gccttgaatg gattggagat attaatcctt tcaacgggtg tactacctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240
atgcagctca acagcctgac atctgacgac tctgcagtct attactgtgc aagatcccat 300
tattacttgc atggttagagt ccttgggat gctatggact actggggtca aggaacctca 360
gtcaccgtct cctcagcaaa aacgacacc ccactgtct atccactggc cctggatct 420
gctgcccata ctaactccat ggtgacctg gcatgcttg tcaagggtca ttccctgag 480
ccagtacag tgacctggaa ccttgatcc ctgtccagc gtgtgcacac cttccagct 540
gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccttc cagcacctgg 600

```

```

cccagcgaga ccgtcacctg caacgttgcc caccgggcca gcagcaccaa ggtggacaag 660
aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca 720
tctgtcttca tcttccccc aaagcccaag gatgtgtcca ccattactct gactcctaag 780
gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctgggtt 840
gtagatgatg tggaggtgca cacagctcag acgcaacccc gggaggagca gttcaacagc 900
actttccgct cagtcagtga acttcccatc atgcaccagg actggctcaa tggcaaggag 960
ttcaaatgca gggtcaacag tgcagctttc cctgccccca tcgagaaaac catctccaaa 1020
accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg 1080
gccaaggata aagtcagctc gacctgcatg ataacagact tcttccctga agacattact 1140
gtggagtggc agtgggaatg gcagccagcg gagaactaca agaactacta gcccatcatg 1200
gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag 1260
gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag 1320
aagagctctc cccactctcc tggtaaatga          1350

```

<210> 21

<211> 468

<212> PRT

<213> Mus musculus

<400> 21

```

Met Gly Trp Asn Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1      5      10      15
Val Tyr Ser Glu Val Gln Leu Gln Ser Gly Pro Glu Leu Val Lys
20     25     30     35
Pro Gly Thr Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
40     45     50     55
Thr Asp Cys Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu
60     65     70     75
Glu Trp Ile Gly Asp Ile Asn Pro Phe Asn Gly Gly Thr Thr Tyr Asn
80     85     90     95
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
100    105    110    115
Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Asp Asp Ser Ala Val
120    125    130    135
Tyr Tyr Cys Ala Arg Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp
140    145    150    155
Asp Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
160    165    170    175
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
180    185    190    195
Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
200    205    210    215
Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
220    225    230    235
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
240    245    250    255
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
260    265    270    275
Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
280    285    290    295
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
300    305    310    315
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
320    325    330    335
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
340    345    350    355
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
360    365    370    375
Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
380    385    390    395
Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
400    405    410    415
Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
420    425    430    435
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
440    445    450    455
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
460    465

```

```

Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
385    390    395    400
Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
405    410    415    420
Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
425    430    435    440
Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
445    450    455    460
Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
465
Ser Pro Gly Lys
465

```

<210> 22

<211> 1407

<212> DNA

<213> Mus musculus

<400> 22

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gtccagctgc aacaatctgg acctgagctg gtgaagcctg ggacttcagt gaagatgtcc 120
tgtaaggctt ctggatacac attcactgac tgctacatga actgggtgaa gcagagccat 180
gggaagagcc ttgaatggat tggagatatt aatcctttca acggtgggtac tacctacaac 240
cagaagttca agggcaaggc cacattgact gtagacaaat cctccagcac agcctacatg 300
cagctcaaca gcctgacatc tgacgactct gcagtctatt actgtgcaag atccattat 360
tacttcagatg gtagagtccc ttgggatgct atggactact ggggtcaagg aacctcagtc 420
accgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct 480
gcccaacta actccatggt gaccctggga tgccctggta agggctattt ccctgagcca 540
gtgacagtga cctggaactc tggatccctg tccagcgggtg tgacacactt cccagctgtc 600
ctgcagctg acctctacac tctgagcagc tcagtgaact tcccctccag cactggcccc 660
agcgagaccg tcacctgcaa cgttgccac ccggccagca gcaccaaggt ggacaagaaa 720
attgtgcccc gggattgtgg ttgtaagcct tgcatatgta cagtcaccga agtatcatct 780
gtcttcatct tcccccaaa gcccaaggat gtgctacca ttactctgac tcctaaggtc 840
acgtgtgttg tggtagacat cagcaaggat gatcccagg tccagtccag ctggtttgta 900
gatgatgtgg aggtgcacac agctcagacg caaccctggg aggagcagtt caacagcact 960
ttccgctcag tcagtgaact tccctatcat caccaggact ggtcgaatgg caaggagttc 1020
aaaatgcagg tcaacagtg agctttccct gccccatcg agaaaacct ctccaaaacc 1080
aaaggcagac cgaaggctcc acaggtgtac accattccac ctcccaagga gcagatggcc 1140
aaggataaag ctgctctgac ctgcatgata acagacttct tccctgaaga cattactgtg 1200
gagtggtcag ggaatgggca gccagcggag aactacaaga acactcagcc catcatggac 1260
acagatggct ctacttcat ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca 1320
ggaaatactt tcacctgctc tgtgttacat gagggcctgc acaaccacca tactgagaag 1380
agcctctccc actctcctgg taaatga 1407

```

<210> 23

<211> 217

<212> PRT

<213> Rabbit-Mouse chimera

<400> 23

```

Ala Gln Val Leu Thr Gln Thr Pro Ala Ser Val Ser Ala Ala Val Gly
1      5      10      15
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     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
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

```

```

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
160      165      170
Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His
175      180      185
Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile
190      195      200
Val Lys Ser Phe Asn Arg Asn Glu Cys
205      210      215

```

<210> 24

<211> 654

<212> DNA

<213> Rabbit-Mouse chimera

<400> 24

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atcaattgcc agtccagtc gagtgtttat gataacaact ggtagcctg gtttcagcag 120
aaaccagggc agcctcccaa gctcctgatt tatgatgcat ccgatctggc atctggggtc 180
ccatcgcggt tcagtggcag tggatctggg acacagttca ctctcaccat cagcggcggtg 240
cagtggtccg agcctggcac ttactactgt caaggcgctt ataattgatg tatttctgct 300
ttcggcgagg ggacgtggct ggtggtcaaa cgtacggatg ctgcaccaac tgtatccatc 360
ttccaccatc ccagtggaca gtttaacatc ggaggtgcct cagtcgtgtg cttcttgaac 420
aacttctacc ccaagacat caatgtcaag tggagattg atggcagtga acgacaaaat 480
ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctaga catgagcagc 540
accctcagc tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact 600
cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg ttag 654

```

<210> 25

<211> 239

<212> PRT

<213> Rabbit-Mouse chimera

<400> 25

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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1      5      10      15
Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ala Ser
20      25      30
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 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
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
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

```

<210> 26

<211> 720

<212> DNA

<213> Rabbit-Mouse chimera

<400> 26

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gtcaccatca attgccagtc cagtcagagt gtttatgata acaactggtt agcctggttt 180
cagcagaaac cagggcagcc tccaagctc ctgatttatg atgcattcca tctggcatct 240
ggggtcccat cgcggttcag tggcagtggg tctgggacac agttcactct caccatcagc 300
ggcgtgcagt gtgccgatgc tgccacttac tactgtcaag gcgcttataa tgatgttatt 360
tatgttttcg gcggagggac cgaggtgggt gtcaaacgta cggatgctgc accaactgta 420
tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480
ttgaacaact tctaccccaa agacatcaat gtcaagtggg agattgatgg cagtgaacga 540
caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600
agcagcacc ctcatttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660
gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgttag 720

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<210> 27

<211> 433

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody

<400> 27

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

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
 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
 Lys

<210> 28

<211> 1302

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody

<400> 28

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 ggggaggggc tgggaatggaat cggaaccatt gattctgggt gtaggacgga ctacgcgagc 180
 tgggcaaaag gccgattcac catctccaga acctcgacta cgaatggatct gaaaatgacc 240
 agtctgacga ccggggacac ggcccgttat ttctgtgcca gaaattggaa ctgtgtgggg 300
 caaggcacc cgtgcaccgt ctcgagcgt tctacaaagg gccatctgt ctatccactg 360
 gccctggat ctgctgccca aactaactcc atggtgaccc tggatgcct ggtcaagggg 420
 tatttccctg agccagtgac agtgacctgg aactctggat ccctgtccag ggtgtgcac 480
 accttcccag ctgtcctgca gtcgacctc tacactctga cgcagtcagt gactgtcccc 540
 tccagcacct ggcccagcga gaccgtcacc tgcacagtgt cccaccgggc cagcagcacc 600
 aagggtggaca agaaaattgt gccagggat tgtgttga agccttgcac atgtacagtc 660
 ccagaagtat catctgtctt catcttcccc ccaaagccca aggatgtgct caccattact 720
 ctgactccta aggtcacgtg tgtgtggta gacatcagca aggatgatcc cgaggtcag 780
 ttcagctggt ttgtagatga tgtggagggt cacacagctc agacgcaacc ccggaggag 840
 cagttcaaca gcactttccg ctgagtcagt gaacttccca tcatgcacca ggactggctc 900
 aatggcaagg agttcaaatg cagggtcaac agtgcagctt tccctgcccc catcgagaaa 960
 accatctcca aaaccaagg cagaccgaag gctccacagg tgtacacat tccacctccc 1020
 aaggagcaga tggccaaggaa taaagtcagt ctgacctgca tgatacaga cttcttcccc 1080
 gaagacatta ctgtggagt gcaagtgaat gggcagccag cggagaacta caagaacact 1140
 cagcccatca tggacacaga tggctcttac ttctgtcaca gcaagctcaa tgtgcagaag 1200
 agcaactggg aggcaggaaa tactttcacc tgctctgtgt tacatgaggg cctgcacaac 1260
 caccatactg agaagagcct ctcccactct cctggtaaat ga 1302

<210> 29

<211> 452

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody

<400> 29

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
 1 5 10 15
 Val His Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
 20 25 30
 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
 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 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
 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
 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
 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
 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
 Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
 290 295 300
 Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
 305 310 315 320
 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
 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
 Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
 420 425 430
 Leu His Glu Gly Leu His Asn His Thr Glu Lys Ser Leu Ser His
 435 440 445
 Ser Pro Gly Lys
 450

<210> 30

<211> 1359

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody

<400> 30

atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccactgtcag 60
 tcgctggagg agtccggggg tcgcttgggc acgcctggga caccctgac actcacctgc 120
 acagcctctg gattctccct cagtatttat tggatgaact ggggccgcca ggctccaggg 180
 gaggggctgg aatggatcgg aaccattgat tctggtggtg ggacggacta cgcgagctgg 240
 gcaaaaggcc gattcaccat ctccagaacc tcgactacga tggatctgaa aatgaccagt 300
 ctgacgaccg gggacacggc ccgttatttc tgtgccagaa attggaactt gtggggccaa 360

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ggcaccctcg tcaccgtctc gagcgcttct acaaagggcc catctgtcta tccactggcc 420
cctggatctg ctgcccctac taactccatg gtgacctctg gatgcctggc caagggctat 480
ttccctgagc cagtgcacgt gacctggaac tctggatccc tgtccagcgg tgtgcacacc 540
ttccctgagc tcttgcagtc tgacctctac actctgagca gctcagtgac tgtccctccc 600
agcaccctgg ccagcgagac cgtcacctgc aacgttgccc acccgccagc cagcaccagg 660
gtggacaaga aaattgtgcc cagggtatgt ggttgaagc cttgcatatg tacagtccca 720
gaagtatcat ctgtcttcat ctcccccca aagcccaagg atgtgtctac cattactctg 780
actcctaagg tcacgtgtgt tgtggtagac atcagcaagg atgatccca ggctcagttc 840
agctggtttg tagatgatgt ggaggtgcac acagctcaga cgcaaccccg ggaggagcag 900
ttcaacagca ctttccgctc agtcagtcaa cttcccatca tgcaccagga ctggctcaat 960
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gacattactg tggagtggca gtggaatggg cagccagcgg agaactacaa gaacactcag 1200
cccacatcag acacagatgg ctctactctc gtctacagca agctcaatgt gcagaagagc 1260
aactgggagg cagggaatac ttccactctc tctgtgttac atgagggcct gcacaaccac 1320
catactgaga agagcctctc ccactctcct ggtaaatga 1359

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<210> 31

<211> 213

<212> PRT

<213> Mus musculus

<400> 31

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Gln Ile Val Leu Thr Gln Ser Pro Thr Ile Val Ser Ala Ser Pro Gly
1      5      10      15
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
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Thr Tyr Pro Pro Thr
80     85     90
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
95     100    105
Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
110    115    120
Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
125    130    135
Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
140    145    150
Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
155    160    165
Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
170    175    180
Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
185    190    195
Asn Arg Asn Glu Cys
200    205
210

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<210> 32

<211> 642

<212> DNA

<213> Mus musculus

<400> 32

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caaattgttc tcaccagctc tccaacaatc gtgtctgcat ctccagggga gaaggtcacc 60
ctaattctga gtgccagttc aagtgtgaag ttctgtggact ggttcagca gaagccaggc 120
acttctccca aacgtctgat ttacagaaca tccaacctgg gttttggagt ccctgctcgc 180
ttcagtgggc gtggatcttg gatctctcac tctctcaca tcagccgaat ggaggctgaa 240
gatgctgcca cttattactg ccagcaaagg agtacttacc caccacgtt cgggtgctggg 300
accaagctgg aactgaacg ggctgatgct gcaccaactg tatccatctt cccacatcc 360
agtgcagctg taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480

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```

agttggactg atcaggacag caagacagc acctacagca tgagcagcac cctcacgttg 540
accaaggacg agtatgaacg acataacagc tatacctgtg aggcactca caagacatca 600
acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag
642

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<210> 33

<211> 235

<212> PRT

<213> Mus musculus

<400> 33

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Met His Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1      5      10      15
Val Ile Val Ser Arg Gly Gln Ile Val Leu Thr Gln Ser Pro Thr Ile
20
Val Ser Ala Ser Pro Gly Glu Lys Val Thr Leu Ile Cys Ser Ala Ser
35      40      45
Ser Ser Val Ser Phe Val Asp Trp Phe Gln Gln Lys Pro Gly Thr Ser
50      55      60
Pro Lys Arg Trp Ile Tyr Arg Thr Ser Asn Leu Gly Phe Gly Val Pro
65      70      75      80
Ala Arg Phe Ser Gly Gly Ser Gly Thr Ser His Ser Leu Thr Ile
85      90      95
Ser Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg
100      105      110
Ser Thr Tyr Pro Pro 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
195      200      205
Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
210      215      220      225
Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
230      235

```

<210> 34

<211> 708

<212> DNA

<213> Mus musculus

<400> 34

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agagggcaca ttgttctcac ccagtctcca acaatcgtgt ctgcatctcc aggggagaag 120
gtcaccctaa tctgcagtgc cagttcaagt gtaagtctcg tggactgggt ccagcagaag 180
ccaggcactt ctcccaaacg ctggatttac agaaccatcca acctgggttt tggagtccct 240
gctcgcttca gtggcggtgg atctgggacc tctcactctc tcacaatcag ccgaatggag 300
gctgaagatg ctgccactta ttactgccag caaaggagta cttaccacc cactgtcggg 360
gctgggacca agctggaact gaaacgggct gatgctgcac caactgtatc catcttccca 420
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 480
taccctcaag acatcaatgt caagtggag attgatggca gtgaacgaca aaatggcgct 540
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 600
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660
acatcaactt caccctattgt caagagcttc aacaggaatg agtggttag 708

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<210> 35

<211> 449

<212> PRT

<213> Mus musculus

<400> 35

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Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln

```

1 Thr Leu Ser 5 Thr Cys Ser Phe Ser 10 Gly Phe Ser Leu Ser 15 Thr Ser
 20 Gly Met Gly Val Gly Trp Ile Arg His Pro Ser Gly Lys Asn Leu Glu
 35 Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Val
 50 Leu Lys Ser Arg Leu Thr 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
 80 Cys Ala Arg Ile Glu Asp Phe Asp Tyr Asp Glu Glu Tyr Tyr Ala Met
 100 Asp Tyr Trp Gly Gln Gly Thr Ser Val Ile Val Ser Ser Ala Lys Thr
 115 Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
 130 Asn Ser Met Val Thr Leu 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
 160 Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
 175 Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
 190 Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
 205 Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
 220 Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
 235 Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
 250 Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
 265 Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
 280 Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
 295 Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
 310 Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
 325 Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
 340 Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
 355 Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
 370 Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys
 385 Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
 400 Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
 415 Lys

<210> 36

<211> 1350

<212> DNA

<213> Mus musculus

<400> 36

cagggttactc tgaagagtc tggccctggg atattgcagc cctcccagac cctcagtcgt 60
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 caccatcag ggaagaatct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataaccag tcttgaagag cggactgact atctccaagg atacttcaa cagccaggtg 240
 ttcttcaaga tgcgcaatgt ggacactgca gatactgcca catactactg tgcctgaata 300
 gaggactttg attacgacga ggagtattat gctatggact actgggggtc aggaacctca 360
 gtcacgtctt cctcagcaaa aacgacaccc ccactctgtc atccactggc ccttggtact 420
 gctgcccata ctaactccat ggtgaccctg ggatgcctgg tcaagggtca tttccctgag 480
 ccagtgcag tgaactggaa ccttggtacc ctgtccagcg gtgtgcacac cttccagct 540
 gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtccctc cagcacctgg 600
 cccagcgaga ccgtcacctg caacgttgcc caccgggcca cgacaccaa ggtggacaag 660
 aaaattgtgc ccagggttg tggttgtaag ccttgcatat gtacagtccc agaagtatca 720
 tctgtcttca tcttccccc aaagcccaag gatgtgctca ccattactct gactcctaag 780
 gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctgggtt 840
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 actttcgcct cagtcagtga acttcccatc atgcaccagg actggctcaa tggcaaggag 960
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 accaaaggca gaccgaagg tcacaggtg tacaccattc cacttcccaa ggagcagatg 1080
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 gacacagatg gctcttactt cgtctacagc aagctcaatg tgcagaagag caactgggag 1260
 gcaggaaata ctttcaactg ctctgtgtta catgagggcc tgcacaacca ccatactgag 1320
 aagagctctc cccactctcc tggtaaatga

<210> 37

<211> 468

<212> PRT

<213> Mus musculus

<400> 37

Met Gly Arg Leu Thr Ser Ser Phe Leu Leu Leu Ile Val Pro Ala Tyr
 1 Val Leu Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln.
 20 Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
 35 Ser Thr Ser Gly Met Gly Val Gly Trp Ile Arg His Pro Ser Gly Lys
 50 Asn Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr
 65 Asn Pro Val Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Asn
 85 Ser Gln Val Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Thr Ala
 100 Thr Tyr Tyr Cys Ala Arg Ile Glu Asp Phe Asp Tyr Asp Glu Glu Tyr
 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
 165 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
 245 Glu Val Ser Ser Val Phe Ile Phe Pro 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 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

Gly Lys Glu Phe 325 Lys Cys Arg Val Asn Ser Ala Ala Phe 335 Pro Ala Pro
 340 Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
 355 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
 405 Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
 420 Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
 435 Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
 450 Ser Pro Gly Lys 465

<210> 38

<211> 1407

<212> DNA

<213> Mus musculus

<400> 38

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 tgtctcttct ctgggttttc actgagcact tctggtatgg gtgtaggctg gattcgtcac 180
 ccaccaggga agaattctga gtggctggca cacatttggg gggatgatgt caagcgctat 240
 aaccacagtc tgaagagcgg actgactatc tccaaggata cctccaacag ccagggtattc 300
 ctcaagatcg ccaatgtgga cactgcagat actgccacat actactgtgc tcgaatagag 360
 gactttgatt acgacgagga gtattatgct atggactact ggggtcaagg aacctcagtc 420
 atcgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct 480
 gcccaaaacta actccatggt gaccctggga tccctgggtca agggctattt ccttgagcca 540
 gtgacagtga cctggaactc tggatccctg tccagcggtg tgcacacctt cccagctgctc 600
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 agcgagaccg tcacctgcaa cgttgcccac cggccagca gcaccaagg ggacaagaaa 720
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 gagtggcagt ggaatgggca gccagcggag aactacaaga acactcagcc catcatggag 1260
 acagatggct ctacttctg ctacagcaag ctcaatgtgc agaagagcaa ctgggaggga 1320
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<210> 39

<211> 5

<212> PRT

<213> Mus musculus

<400> 39

Asp His Tyr Met Ser
1 5

<210> 40

<211> 17

<212> PRT

<213> Mus musculus

<400> 40

Asp Ile Asn Pro Tyr Ser Gly Glu Thr Thr Tyr Asn Gln Lys Phe Lys
1 5 10 15
Gly

<210> 41

<211> 10

<212> PRT

<213> Mus musculus

<400> 41

Asp Asp Tyr Asp Ala Ser Pro Phe Ala Tyr
1 5 10

<210> 42

<211> 11

<212> PRT

<213> Mus musculus

<400> 42

Gln Ala Ser Gln Gly Thr Ser Ile Asn Leu Asn
1 5 10

<210> 43

<211> 7

<212> PRT

<213> Mus musculus

<400> 43

Gly Ser Ser Asn Leu Glu Asp
1 5

<210> 44

<211> 9

<212> PRT

<213> Mus musculus

<400> 44

Leu Gln His Ser Tyr Leu Pro Tyr Thr
1 5

<210> 45

<211> 5

<212> PRT

<213> Mus musculus

<400> 45

Asp Cys Tyr Met Asn
1 5

<210> 46

<211> 17

<212> PRT

<213> Mus musculus

<400> 46

Asp Ile Asn Pro Phe Asn Gly Gly Thr Thr Tyr Asn Gln Lys Phe Lys
1 5 10 15
Gly

<210> 47

<211> 16

<212> PRT

<213> Mus musculus

<400> 47

Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp Asp Ala Met Asp Tyr
 1 5 10 15

<210> 48

<211> 15

<212> PRT

<213> Mus musculus

<400> 48

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn
 1 5 10 15

<210> 49

<211> 7

<212> PRT

<213> Mus musculus

<400> 40

Ala Ala Ser Asn Leu Gln Ser
 1 5

<210> 50

<211> 9

<212> PRT

<213> Mus musculus

<400> 50

Gln Gln Ser Asn Gln Asp Pro Trp Thr
 1 5

<210> 51

<211> 5

<212> PRT

<213> Rabbit-Mouse Chimera

<400> 51

Ser Tyr Trp Met Asn
 1 5

<210> 52

<211> 16

<212> PRT

<213> Rabbit-Mouse chimera

<400> 52

Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser Trp Ala Lys Gly
 1 5 10 15

<210> 53

<211> 4

<212> PRT

<213> Rabbit-Mouse chimera

<400> 53

Asn Trp Asn Leu
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<210> 54

<211> 13

<212> PRT

<213> Rabbit-Mouse chimera

<400> 54

Gln Ser Ser Gln Ser Val Tyr Asp Asn Asn Trp Leu Ala
1 5 10

<210> 55

<211> 7

<212> PRT

<213> Rabbit-Mouse chimera

<400> 55

Asp Ala Ser Asp Leu Ala Ser
1 5

<210> 56

<211> 10

<212> PRT

<213> Rabbit-Mouse Chimera

<400> 56

Gln Gly Ala Tyr Asn Asp Val Ile Tyr Ala
1 5 10

<210> 57

<211> 7

<212> PRT

<213> Mus musculus

<400> 57

Thr Ser Gly Met Gly Val Gly
1 5

<210> 58

<211> 16

<212> PRT

<213> Mus musculus

<400> 58

His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Val Leu Lys Ser
1 5 10 15

<210> 59

<211> 14

<212> PRT

<213> Mus musculus

<400> 59

Glu Asp Phe Asp Tyr Asp Glu Glu Tyr Tyr Ala Met Asp Tyr
1 5 10

<210> 60

<211> 10

<212> PRT

<213> Mus musculus

<400> 60

Ser Ala Ser Ser Ser Val Ser Phe Val Asp
1 5 10

<210> 61

<211> 7

<212> PRT

<213> Mus musculus

<400> 61

Arg Thr Ser Asn Leu Gly Phe
1 5

<210> 62

<211> 9

<212> PRT

<213> Mus musculus

<400> 62

Gln Gln Arg Ser Thr Tyr Pro Pro Thr
 1 5

<210> 63

<211> 20

<212> PRT

<213> Homo sapiens

<400> 63

Cys Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp
 1 5 10 15
 Trp Arg Pro Ser
 20

<210> 64

<211> 20

<212> PRT

<213> Homo sapiens

<400> 64

Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp
 1 5 10 15
 Arg Pro Ser Gly
 20

<210> 65

<211> 20

<212> PRT

<213> Homo sapiens

<400> 65

Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg
 1 5 10 15
 Pro Ser Gly Pro
 20

<210> 66

<211> 20

<212> PRT

<213> Homo sapiens

<400> 66

Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro
 1 5 10 15

Ser Gly Pro Asp
 20

<210> 67

<211> 20

<212> PRT

<213> Homo sapiens

<400> 67

Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser
 1 5 10 15
 Gly Pro Asp Phe
 20

<210> 68

<211> 20

<212> PRT

<213> Homo sapiens

<400> 68

Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser Gly
 1 5 10 15
 Pro Asp Phe Arg
 20

<210> 69

<211> 20

<212> PRT

<213> Homo sapiens

<400> 69

Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser Gly Pro
 1 5 10 15
 Asp Phe Arg Cys
 20

<210> 70

<211> 14

<212> PRT

<213> Homo sapiens

<400> 70

Ser Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys
 1 5 10

<210> 71

<211> 7

<212> PRT

<213> Homo sapiens

<400> 71

Leu Val Ala Ser Cys Lys Cys
 1 5

<210> 72

<211> 8

<212> PRT

<213> Homo sapiens

<400> 72

Cys Arg Glu Leu His Phe Thr Arg
 1 5

<210> 73

<211> 7

<212> PRT

<213> Homo sapiens

<400> 73

Cys Ile Pro Asp Arg Tyr Arg
 1 5

<210> 74

<211> 399

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 74

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 gtgactatta cctgtcaatc tagtcagagc gtgtatgata acaattggct ggcgtggtac 180
 cagcaaaaac cgggcaaagc cccgaagctg ctcatctatg acgcgtccga tctggctagc 240
 ggtgtgccaa gccgtttcag tggcagtggc agcggtagtg actttaccct cacaatttcg 300
 tctctccagc cgggaagatt cgccacttac tattgtcaag gtgcttacaa cgatgtgatt 360
 tatgccttcg gtcagggcac taaagtagaa atcaaacyt 399

<210> 75

<211> 133

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 75

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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Trp
 1      5      10      15
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
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 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
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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<210> 76

<211> 393

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 76

atggagactg ggcctgcctg gcttctctct gtcgctgtgc tcaaagggtg ccactgtgag 60

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gtgcagctgt tggagctctg aggcgggctt gtccagcctg gagggagcct gcgtctctct 120
tgtgcagcaa gcggttcag ctatcctct tactggatga attgggtgcg gcaggcacct 180
gggaagggcc tggagtgggt gggcaccatt gattccggag gccgtacaga ctacgcgtct 240
tggcaaaagg gccgttcac cattcccg cacaactcca aaaataccat gtacctccag 300
atgaactctc tccgcgcaga ggacacagca cgttattact gtgcacgcaa ctggaatctg 360
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393

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<210> 77

<211> 131

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 77

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
 1      5      10      15
Val His Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
 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
115      120      125
Val Ser Ser
130

```

<210> 78

<211> 11

<212> PRT

<213> Mus musculus

<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

<211> 7

<212> PRT

<213> Mus musculus

<400> 79

Tyr Thr Ser Arg Leu Leu Ser
 1 5

<210> 80

<211> 9

<212> PRT

<213> Mus musculus

<400> 80

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1 5

<210> 81

<211> 11

<212> PRT

<213> Mus musculus

<400> 81

Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
 1 5 10

<210> 82

<211> 24

<212> PRT

<213> Rattus norvegicus

<400> 82

Gln Gly Trp Gln Ala Phe Lys Asn Asp Ala Thr Glu Ile Ile Pro Gly
 1 5 10 15
 Leu Arg Glu Tyr Pro Glu Pro Pro
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<210> 83

<213> 20

<212> PRT

<213> Rattus norvegicus

<400> 63

Thr Glu Ile Ile Pro Gly Leu Arg Glu Tyr Pro Glu Pro Pro Gln Glu
 1 5 10 15
 Leu Glu Asn Asn
 20

<210> 84

<211> 20

<212> PRT

<213> Rattus norvegicus

<400> 84

Pro Glu Pro Pro Gln Glu Leu Glu Asn Asn Gln Thr Met Asn Arg Ala
 1 5 10 15
 Glu Asn Gly Gly
 20

<210> 85

<211> 20

<212> PRT

<213> Rattus norvegicus

<400> 85

Glu Asn Gly Gly Arg Pro Pro His His Pro Tyr Asp Thr Lys Asp Val
 1 5 10 15
 Ser Glu Tyr Ser
 20

<210> 86

<211> 14

<212> PRT

<213> Rattus norvegicus

<400> 86

Cys Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro
 1 5 10

<210> 87

<211> 25

<212> PRT

<213> Rattus norvegicus

<400> 87

Cys Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro Ser Arg
 1 5 10 15
 Ser Ala Lys Pro Val Thr Glu Leu Val
 20 25

<210> 88

<211> 23

<212> PRT

<213> Rattus norvegicus

<400> 88

Cys Arg Ser Ala Lys Pro Val Thr Glu Leu Val Ser Ser Gly Gln Ser
 1 5 10 15
 Gly Pro Arg Ala Arg Leu Leu
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<210> 89

<211> 25

<212> PRT

<213> Rattus norvegicus

<400> 89

Cys Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Val Lys Trp
 1 5 10 15
 Trp Arg Pro Asn Gly Pro Asp Phe Arg
 20 25

<210> 90

<211> 20

<212> PRT

<213> Rattus norvegicus

<400> 90

Arg Ala Gln Arg Val Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg
 1 5 10 15
 Ser Arg Lys Val
 20

<210> 91

<211> 16

<212> PRT

<213> Rattus norvegicus

<400> 91

Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val Ala Ser
 1 5 10 15

<210> 92

<211> 23

<212> PRT

<213> Rattus norvegicus

<400> 92

Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu Leu Lys Asp Phe Gly
 1 5 10 15
 Pro Glu Thr Ala Arg Pro Gln
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<210> 93

<211> 16

<212> PRT

<213> Rattus norvegicus

<400> 93

Ile Pro Asp Arg Tyr Ala Gln Arg Val Gln Leu Leu Ser Pro Gly Gly
 1 5 10 15

<210> 94

<211> 24

<212> PRT

<213> Rattus norvegicus

<400> 94

Ser Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly
 1 5 10 15
 Arg Lys Pro Arg Pro Arg Ala Arg
 20

<210> 95

<211> 23

<212> PRT

<213> Rattus norvegicus

<400> 95

Lys Gly Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln
 1 5 10 15
 Ala Glu Leu Glu Asn Ala Tyr
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<210> 96

<211> 18

<212> PRT

<213> Rattus norvegicus

<400> 96

Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro Asp
 1 5 10 15
 Phe Arg

<210> 97

<211> 22

<212> PRT

<213> Rattus norvegicus

<400> 97

Lys Trp Trp Arg Pro Asn Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg
 1 5 10 15
 Tyr Arg Ala Gln Arg Val
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<210> 98

<211> 213

<212> PRT

<213> Rattus norvegicus

<400> 98

Met Gln Leu Ser Leu Ala Pro Cys Leu Ala Cys Leu Leu Val His Ala
 1 5 10 15
 Ala Phe Val Ala Val Glu Ser Gln Gly Trp Gln Ala Phe Lys Asn Asp
 20 25 30

Ala Thr Glu Ile Ile Pro Gly Leu Arg Glu Tyr Pro Glu Pro Pro Gln
 35 40 45
 Glu Leu Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
 50 55 60
 Pro Pro His His Pro Tyr Asp Thr Lys Asp Val Ser Glu Tyr Ser Cys
 65 70 75 80
 Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro Cys Arg Ser
 85 90 95
 Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala
 100 105 110
 Arg Leu Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn
 115 120 125
 Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
 130 135 140
 Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg
 145 150 155 160
 Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln
 165 170 175
 Ser Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly
 180 185 190
 Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu
 195 200 205
 Leu Glu Asn Ala Tyr
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<210> 99

<211> 7

<212> PRT

<213> Mus musculus

<400> 99

Tyr Thr Ser Arg Leu His Ser
 1 5

<210> 100

<211> 9

<212> PRT

<213> Mus musculus

<400> 100

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1 5

<210> 101

<211> 11

<212> PRT

<213> Mus musculus

<400> 101

Arg Ala Ser Gln Val Ile Thr Asn Tyr Leu Tyr
 1 5 10

<210> 102

<211> 7

<212> PRT

<213> Mus musculus

<400> 102

Tyr Thr Ser Arg Leu His Ser
 1 5

<210> 103

<211> 9

<212> PRT

<213> Mus musculus

<400> 103

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1 5

<210> 104

<211> 11

<212> PRT

<213> Mus musculus

<400> 104

Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 105

<211> 7

<212> PRT

<213> Mus musculus

<400> 105

Tyr Thr Ser Arg Leu Leu Ser
1 5

<210> 106

<211> 9

<212> PRT

<213> Mus musculus

<400> 106

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 107

<211> 11

<212> PRT

<213> Mus musculus

<400> 107

Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 108

<211> 7

<212> PRT

<213> Mus musculus

<400> 108

Tyr Thr Ser Arg Leu Phe Ser
1 5

<210> 109

<211> 9

<212> PRT

<213> Mus musculus

<400> 109

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 110

<211> 11

<212> PRT

<213> Mus musculus

<400> 110

Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 111

<211> 7

<212> PRT

<213> Mus musculus

<400> 111

Tyr Thr Ser Arg Leu Leu Ser
1 5

<210> 112

<211> 9

<212> PRT

<213> Mus musculus

<400> 112

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 113

<211> 11

<212> PRT

<213> Mus musculus

<400> 113

Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 114

<211> 7

<212> PRT

<213> Mus musculus

<400> 114

Tyr Thr Ser Thr Leu Gln Ser
1 5

<210> 115

<211> 9

<212> PRT

<213> Mus musculus

<400> 115

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 116

<211> 12

<212> PRT

<213> Mus musculus

<400> 116

Ser Val Ser Ser Ser Ile Ser Ser Ser Asn Leu His
1 5 10

<210> 117

<211> 213

<212> PRT

<213> Mus musculus

<400> 117

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Thr Ser Pro Gly
1 5 10 15
Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Tyr Met
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp 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
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 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
210

<210> 118

<211> 642

<212> DNA

<213> Mus musculus

<400> 118

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caaattgttc tctcccagtc tccagcaatc ctgtctacat ctccagggga gaaggtcaca 60
atgacttgca gggccagctc aagtgtatat tacatgcact ggtaccagca gaagccagga 120
tctcccccca aaccttgat ttatgccaca tccaacctgg cttctggagt cctcttccgc 180
ttcagtgcca gtgggtctgg gacctcttac tctctcaca tcaccagagt ggaggctgaa 240
gatgctgcca ctattactg ccagcagtg agtagtgacc cactcacgtt cgggtctggg 300
accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 360
agtgaagcag taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480
agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg 540
accaaggacg agtatgaacg acataacagc tatacctgtg aggccactca caagacatca 600
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<210> 119

<211> 235

<212> PRT

<213> Mus musculus

<400> 119

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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 Ile
20      25      30
Leu Ser Thr Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
35      40      45

```

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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 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
195      200      205
Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
210      215      220
Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225      230      235

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<210> 120

<211> 708

<212> DNA

<213> Mus musculus

<400> 120

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aggggacaaa ttgttctctc ccagcttcca gcaatcctgt ctacatctcc aggggagaag 120
gtcacaaatga cttgcagggc cagctcaagt gtatattaca tgcactggta ccagcagaag 180
ccaggatcct cccccaacc ctggatttat gccacatcca acctggcttc tggagtccct 240
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gctgaagatg ctgccactta ttactgccag cagtggagta gtgacctact cacgttcggg 360
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ccatccagtg agcagttaac atctggagggt gcctcagtcg tgtgcttctt gaacaacttc 480
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ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccttc 600
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggg cactcacaag 660
acatcaactt cacccttatt caagagcttc aacaggaatg agtggttag 708

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<210> 121

<211> 445

<212> PRT

<213> Mus musculus

<400> 121

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

<210> 122

<211> 1338

<212> DNA

<213> Mus musculus

<400> 122

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 cctgaacagg gcttgagggt gattggaagg cttgatcctg aggatgggtg aagtgattat 180
 gccccgaagt tccaggacaa ggccattatg acagcagaca catcatccaa cacagcctat 240
 cttcagctca gaagctgac aictgaggac actgccatct attattgtga gagagaggac 300
 tacgatggta cctacacctt ttttccttac tggggccaag ggactctggt cactgtctct 360
 gcagcccaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcctcaact 420
 aactccatgg tgacctggg atgacctggc aagggctatt tccctgagcc agtgacagt 480
 acctggaact ctggatccct gtccagcggg gtgcacacct tcccagctgt cctgcagct 540
 gacctctaca ctctgagcag ctccagtact gtcccctcca gcacctggcc cagegagacc 600
 gtcacctgca acgttgccca cccggccagc agcaccagg tggacaagaa aattgtgccc 660
 agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcac 720
 ttcccccaaa agcccaagga ttgtctcacc attactctga ctctaaagt cactgtgtgt 780
 gtggttagaa tcagcaagga tgatcccag gtccagtcca gctggtttgt agatgatgtg 840
 gagggtgaca cagctcagac gcaacccgg gaggagcagt tcaacagcac ttccgctca 900
 gtcagtgaac ttccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960
 gtcaacagtg cagctttccc tgccccatc gagaaaacca tctccaaac caaaggcaga 1020
 ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080
 gtcagcttga cctgcatgat aacagacttc ttccctgaag acatctactt ggagtgagcag 1140
 tgggaatggg agccagcggg gaactacaag aacactcagc ccatcatgga cacagatggc 1200
 tcttacttca tctacagcaa gctcaatgtg cagaagagca actggggaggc aggaataact 1260

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320
 cactctctg gtaaatga 1338

<210> 123

<211> 464

<212> PRT

<213> Mus musculus

<400> 123

Met Lys Cys Ser Trp Val Ile Phe Phe Leu Met Ala Val Val Thr Gly
 1 Val Asn Ser Glu Val Gln Val Gln Gln Ser Gly Pro Glu Leu Val Lys
 20 Pro Gly Ala Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
 35 Lys Asp Tyr Phe Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
 50 Glu Trp Ile Gly Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala
 65 Pro Lys Phe Gln Asp Lys Ala Ile Met Thr Ala Asp Thr Ser Ser Asn
 85 Thr Ala Tyr Leu Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Ile
 100 Tyr Tyr Cys Glu Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Phe Phe Pro
 115 Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr
 130 Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
 145 Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
 165 Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
 180 Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Val
 195 Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
 210 Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
 225 Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
 245 Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
 260 Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
 275 Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
 290 Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
 305 Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
 325 Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
 340 Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
 355 Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
 370 Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
 385 Asn Gly Gln Pro Ala 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 Thr Cys Ser Val Leu His Glu Gly
 435 Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
 450 455 460

<210> 124

<211> 1395

<212> DNA

<213> Mus musculus

<400> 124

atgaaatgca gctgggtcat cttcttcctg atggcagfgg ttacaggggt caattcagag 60
 gttcaggtgc agcaggtctgg gccagaactt gtgaagccag gggcctcagt caagttgtcc 120
 tgcacagctt ctggcttcaa cattaaagac tactttatcac actgggtgaa gcagaggcct 180
 gaacagggcc tggagtggat tggaaaggct gatcctgagg atgggtgaaag tgattatgcc 240
 ccgaagtcc aggaacaaggc cattatgaca gcagacacat catccaacac agcctatctt 300
 cagctcagaa gcccgacatc tgaggacact gccatctatt attgtgagag agaggactac 360
 gatggtaact acactttttt tccttactgg ggccaaggga ctctgtgtcac tgtctctgca 420
 gccaaaacga caccctccatc tgtctatcca ctggcccctg gatctgtctc ccaactaac 480
 tccatgggtga cctctgggatg cctgggtcaag ggctatttcc ctgagccagt gacagtgacc 540
 tggaaactctg gatcctctgc cagcgggtgtg cacaccttcc cagctgtcct gcagctgtac 600
 ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 660
 acctgcaacg ttgccacccc ggccagcagc accaagggtgg acaagaaaat tgtgccagg 720
 gattgtgggt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780
 cccccaaagc ccaaggatgt gctcaccatt actctgactc.ctaaggctcac gtgtgtgtg 840
 gtgacacacg ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 900
 agtgaacttc ccacatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 1020
 aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 1080
 aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1140
 agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtg 1200
 aatgggcagc cagcgagaa ctacaagaac actcagccca tcatggacac agatggctct 1260
 tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatacttct 1320
 acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380
 tctcttggtg aatga 1395

<210> 125

<211> 215

<212> PRT

<213> Mus musculus

<400> 125

Glu Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ala Ala Ser Pro Gly
 1 5 10 15
 Glu Lys 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 Ser Asp Thr Ser Pro Lys Pro Trp
 35 40 45
 Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
 65 70 75 80
 Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
 85 90 95
 Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg Arg Ala Asp Ala
 100 105 110
 Ala Pro Thr Val Ser Ile Phe 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
 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
 195 200 205
 Ser Phe Asn Arg Asn Glu Cys
 210 215

<210> 126

<211> 648

<212> DNA

<213> Mus musculus

<400> 126

gaaattgtgc tcaccagtc tccagcactc atggctgcat ctccggggga gaaggtcacc 60
 atcacctgca gtgtcagttc aactataagt tccaaccact tgcactggtt ccagcagaag 120
 tcagacacct ccccaaac ctggatttat ggcacatcca acctggcttc tggagtcctt 180
 gttcgtctca gtggcagtg atctgggacc tcttattctc tcacaatcag cagcattggag 240
 gctgaggatg ctgccactta ttactgtcaa cagtggagta gttaccact cactgtcggc 300
 gctgggacca agctggagct gagacgggct gatgctgcac caactgtatc catcttccca 360
 ccattccagt agcagttaac atctggaggt gcctcagtcg tgtgctctt gaacaacttc 420
 taccctaaag acatcaatgt caagtgggaag attgatggca gtgaacgaca aaatggcgctc 480
 ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 540
 acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactacaag 600
 acatcaactt caccctatgt caagagcttc aacaggaatg agtggttag 648

<210> 127

<211> 237

<212> PRT

<213> Mus musculus

<400> 127

Met Asp Phe His Val Gln Ile Phe Ser Phe Met Leu Ile Ser Val Thr
 1 5 10 15
 Val Ile Leu Ser Ser Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Leu
 20 25 30
 Met Ala Ala Ser Pro Gly Glu Lys 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 Ser Asp
 50 55 60
 Thr Ser Pro Lys Pro 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
 100 105 110
 Gln Trp Ser Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu
 115 120 125
 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 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

<210> 128

<211> 714

<212> DNA

<213> Mus musculus

<400> 128

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atggattttc atgtgcagat tttcagcttc atgctaataca gtgtcacagt cattttgtcc 60
agtggagaaa ttgtgctcac ccagctctca gcactcatgg ctgcatctcc gggggagaag 120
gtcaccatca cctgcagtggt cagtccaact ataagttcca accacttgca ctggttccag 180
cagaagtcag acacctctccc caaacctctgg atttatggca catccaacct ggcttctgga 240
gtccctgttc gcttcagtggt cagtggatct gggacctctt attctctcac aatcagcagc 300
atggaggctg aggatgctgc cacttattac tgtcaacagt ggagtagtta cccactcacg 360

```

```

ttcggcgctg ggaccaagct ggagctgaga cgggctgatg ctgcaccaac tgtatccatc 420
ttcccaccat ccagtgcagca gttaacatct ggaggtgcct cagtcgtgtg ctctctgaac 480
aacttctacc ccaaagacat caatgtcaag tggagattg atggcagtga acgacaaaat 540
ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc 600
accctcacgt tgaccaagga cgagtatgaa cgacataaca gctataacct tgaggccact 660
cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg ttag 714

```

<210> 129

<211> 449

<212> PRT

<213> Mus musculus

<400> 129

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Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15
Leu Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Phe
20 25 30
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
50 55 60
Gln Asp Lys Ala Thr Leu Thr Thr Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80
Leu Gln Leu Ser Gly Leu Thr Ser Glu Thr Thr Ala Val Tyr Tyr Cys
85 90 95
Ser Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe
100 105 110
Asp Val Trp Gly Ala Gly Thr Thr Ile Thr Val Ser Ser Ala Lys Thr
115 120 125
Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
130 135 140
Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
180 185 190
Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
195 200 205
Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
210 215 220
Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
225 230 235 240
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
Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
275 280 285
Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
290 295 300
Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
325 330 335
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
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
Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
420 425 430
Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly

```

Lys 435 440 445

<210> 130

<211> 1350

<212> DNA

<213> Mus musculus

<400> 130

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gaggttcagc tgcagcagtc tggggctgaa cttgtgaggg caggggacctt agtcaagttg 60
tcctgcacag cttctgactt caacattaaa gacttctatc taacttggtt gaggcagcgg 120
cctgaacagg gccctgactg gattggaagg attgatcctg agaattggtg tactttatat 180
gaccgcaagt tcaggacaaa ggccactctt acaacagaca catctcccaa cacagctac 240
ctgcagctca cgggctgac atctgagacc actgcccgtt attactgttc tagagaggcg 300
gattatttcc acgatgggtac ctctacttgg tacttccgat tctggggcgc agggaccaca 360
atcacccgtc cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct 420
gctgcccata ctaactccat ggtgaccctg ggtgacctgg tcaagggtta ttcccttgag 480
ccagtgcacg tgacctgga cctctggatc ctgtccagcg gtgtgcacac cttcccagct 540
gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccttc cagcacctgg 600
cccagcgaga cgtgcacctg caacgttgcc caccggccca gcagcaccac ggtggacaag 660
aaaattgtgc ccagggtatt tgggtgttaag ctttgcata gtacagtccc agaagatca 720
tctgtcttca tcttccccc aaagcccaag gatgtgtcca ccattactct gactcctaag 780
gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctgggtt 840
gtagatgatg tggagggtga cacagctcag acgcaacccc gggaggagca gttcaacagc 900
actttccgtc cgttcactga acttcccatc atgcaccagg actggctcaa tggcaaggag 960
ttcaaatgca gggtaacag tgcagctttc cctgcccaca tcgagaaaac catctccaaa 1020
accaaaggca gaccgaagc tccacaggtg tacaccattc cactcccaa ggagcagatg 1080
gccaaaggata aagtcagctt gacttgcagt ataacagact tcttccctga agacattact 1140
gtggagtggc agtgggaatg gcagccagcg gagaactaca agaactaca gcccatcatg 1200
gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag 1260
gcaggaaata ctttccactg cctgtgttta catgagggcc tgcaacaaca ccatactgag 1320
aagagcctct cccactctcc tggtaaatga 1350

```

<210> 131

<211> 468

<212> PRT

<213> Mus musculus

<400> 131

```

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 Glu Leu Val Arg
20 25 30
Pro Gly Ala Leu Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile
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

```

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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
245 250 255
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
260 265 270
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
275 280 285
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
340 345 350
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
355 360 365
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
370 375 380
Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
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
435 440 445
Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
450 455 460
Ser Pro Gly Lys
465

```

<210> 132

<211> 1407

<212> DNA

<213> Mus musculus

<400> 132

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atgaaatgca gctgggtcat cttcttctctg atggcagtggt ttacaggggt caattcagag 60
gttcagctgc agcagctctgg ggctgaactt gtgaggccag gggccttagt caagttgtcc 120
tgacacgctt ctgacttcaa cattaaagac ttctatctac actggatgag gcagcggcct 180
gaacaggggc ttgacttggt ttggaaggatt gatcctgaga atgggtgatac tttatatgac 240
ccgaagtctc aggaacaaggc cactcttaca acagacacat cctccaacac agcctacctg 300
cagctcagcg gccctgacatc tgagaccact gccgtctatt actgttctag agagggcggat 360
tatttcacg atggtaacctc ctactgggtac ttcgatgtct ggggcgcagg gaccacaatc 420
accgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc ttgactctgct 480
gcccaacta actccatggt gacctggga tgcctgggtca agggctattt ccctgagcca 540
gtgacagtga cctggaactc tggatccctg tccagcgggtg tgcacacctt cccagctgtc 600
ctgcagtctg accctcacac tctgagcagc tcagtgtactg tcccctccag cacctggccc 660
agcgagacgg tcacctgcaa cgttgcccac ccggccagca gcaccaaggt ggacaagaaa 720
attgtgcccc gggattgtgg ttgtaagcct tgcataatga cagtcccaga agtatcatct 780
gtcttcatct tcccccaaaa gcccaaggat gtgctcacca ttactctgac tcctaaggctc 840
acgtgtgttg tggtagacat cagcaaggat gatcccgagg tccagttcag ctggtttgta 900
gatgatgtgg aggtgcacac agctcagacg caaccccggg aggagcagtt caacagcact 960
ttccgctcag tcagtgaact tcccattcat caccaggact ggctcaatgg caaggagttc 1020
aaatgcaggg tcaacagtgc agctttccct gcccccatcg agaaaacat ctccaaaacc 1080
aaaggcagac cgaaggctcc acaggtgtac accattccac ctcccaagga gcagatggcc 1140
aaggataaag tcaactgtgac ctgcatgata acagacttct tccctgaaga cattactgtg 1200
gagtgggcagt ggaatgggca gccagcggag aactacaaga acactcagcc catcatggac 1260
acagatggct ctacttcat ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca 1320
ggaaatactt tcacctgtct tgtgttcat gagggcctgc acaaccacca tactgagaag 1380
agcctctccc actctcctgg taaatga 1407

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<210> 133

<211> 214

<212> PRT

<213> Mus musculus

<400> 133

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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 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
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
80     85     90
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
95     100    105
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
110    115    120
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
125    130    135
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
140    145    150
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
155    160    165
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
170    175    180
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
185    190    195
Phe Asn Arg Asn Glu Cys
200    205    210

```

<210> 134

<211> 645

<212> DNA

<213> Mus musculus

<400> 134

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gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120
gatggaactt ttaactcct tatcttctac acatcaagat tactctcagg agtcccacat 180
agggtcagtg gcagtgggtc tggaaacagat tattctctca ccatttacaa cctggagcaa 240
gaagattttg ccacttact ttgccaacag ggagatacgc ttccgtacac ttcggagggg 300
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttccacca 360
tccagtggac agttaacatc tggagggtcc tcagtcgtgt gcttctgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagtggga ctgacaggga cagcaagac agcacctaca gcagtgcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gtttag 645

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<210> 135

<211> 234

<212> PRT

<213> Mus musculus

<400> 135

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 Ile Thr Ser Ser Leu Ser
 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
 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> 136

<211> 705

<212> DNA

<213> Mus musculus

<400> 136

atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
 gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 120
 atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 180
 gatggaaactt ttaaaactcct tatctttctac acatcaagat tactctcagg agtcccatca 240
 aggttcagtg gcagtgggctc tgggaacagat tattctctca ccatttacaa cctggagcaa 300
 gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 360
 gggaccaagc tggaaataaa acggggtgat gctgcaccaa ctgtatccat cttcccacca 420
 tccagtgaac agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caactttctac 480
 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaa tggcgctcctg 540
 aacagttgga ctgattcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
 ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gtttag 705

<210> 137

<211> 447

<212> PRT

<213> Mus musculus

<400> 137

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
 1 5 10 15
 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 Ser 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
 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 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
 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 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
Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
240      245      250
Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
255      260      265
Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
270      275      280
Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
285      290      295
Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
300      305      310
Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
315      320      325
Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Thr Ile Pro
330      335      340
Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
345      350      355
Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
360      365      370
Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
375      380      385
Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
390      395      400
Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
405      410      415
His Asn His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
420      425      430
435      440      445

```

<210> 138

<211> 1344

<212> DNA

<213> Mus musculus

<400> 138

```

gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcttgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac 120
caaggaaaga ccttagagtg gataggagaa attaatccta acagtgggtg tgctggctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtccctcac cacagcctac 240
atggagcttc gcagctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tacgatgata tctacagcga ctggctatct gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccttgg atctgctgcc 420
caaaactaact ccatggtgac cctgggatgc ctgggtcaagg gctatttccc tgagccagtg 480
acagtgcact ggaactctgg atccctgtcc agcgggtgtg acaccttccc agctgtcctg 540
cagcttgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtgggtg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgtttgtg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtcg gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaacctctc caaaaccaa 1020
ggcagaccga aggtccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gttcgaacct catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtggg atgggcagcc agcggagaac tacaagaaca ctaccccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggctgcaca accaccatac tgagaagagc 1320
ctctcccaact ctccctggtaa atga 1344

```

<210> 139

<211> 466

<212> PRT

<213> Mus musculus

<400> 139

```

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 Ser Gly Pro Glu Leu Met Lys
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 Ala Gly Tyr Asn
65 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
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
145 150 155 160
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
165 170 175
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
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
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
305 310 315 320
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
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> 140

<211> 1401

<212> DNA

<213> Mus musculus

<400> 140

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atgggatgga gctggacatt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccaactgc aacagttctg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa 180
ggaaagaccc tagagtggat aggagaaatt aatcctaaca gtgggtgtgc tggctacaac 240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
gagctccgca gcttgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
gatgatactc acgacgactg gtacttcgat gtctggggcg caggggaccac ggtcaccgtc 420
tctccagcca aaacgacacc ccatctgtc tatccactgg cccctggatc tgcctgccaa 480
actaactcca tggtagacct gggatgcctg gtcaagggtc atttccctga gccagtgaac 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgcctcgagc 600
tctgacctct acactctgag cagctcagtg actgtccctc ccagcacctg gccacgcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggtat gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggaatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtgtag acatcagcaa ggaatgtccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
aggggtcaaca gtgcagcttt ccctgcccc atcgagaaaa ccatctccaa aaccaaaagg 1080
agaccgaagg ctccacaggt gtacaccatt ccaactccca aggagcagat ggccaaggat 1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatttcag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaatg a
1401

```

<210> 141

<211> 214

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 141

```

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 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 Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100    105    110
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
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    195
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
200    205
Phe Asn Arg Gly Glu Cys
210

```

<210> 142

<211> 642

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 142

```

gacatccaga tgaccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc 60
ataacatgta gagcatctca agatatattcc aactatttga attggtacca acaaaaaccc 120
ggcaaaagcac ctaaactcct catttactat acatcaagac tcctctccgg cgttccatca 180
cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca 240
gaagattttg caacctatta ctgtcaacaa ggcgatacac tccatacac attcggcggc 300
ggcacaaaag ttgaaattaa acgtacgggtg gctgcacccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt
642

```

<210> 143

<211> 236

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 143

```

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 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      225
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225      230      235

```

<210> 144

<211> 708

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 144

```

atggacatga ggggtcccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc 60
agatgtgaca tccagatgac ccagtctcca tcctccctct ccgcatacgt aggcgaccgc 120
gtaaccataa catgtagagc atctcaagat atttccaact atttgaattg gtaccaacaa 180
aaacccggca aagcacctaa actcctcatt tactatacat caagactcct ctccggcggtt 240
ccatcacgat tctcaggctc cggctccggc acagatttca cactcactat ttgctccctc 300
caaccagaag attttgcaac ctattactgt caacaaggcg atacactccc atacacattc 360
ggcggcggca caaaagttga aattaaactg acggtggctg caccatctgt cttcatcttc 420
ccgccatctg atgagcagtt gaaatcttga actgcctctg ttgtgtgctt gctgaataac 480
ttctatccca gagaggccaa agtacagtgg aaggtggata acgcccctcca atcgggtaac 540
tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600
ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660
cagggcctga gctcgcccggt cacaagagac ttcaacaggg gagagtgt 708

```

<210> 145

<211> 449

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 145

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 Gly Glu Ile Asn Pro Asn Ser Gly Ala Gly Tyr Asn Gln Lys Phe
 50 Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 80 Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 95 Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
 110 Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
 125 Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
 140 Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
 155 Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
 170 Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
 185 Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
 200 Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
 215 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 230 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 245 Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 260 Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
 275 Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
 290 Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
 305 310 315 320 325 330 335

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 355 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
 385 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 400 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 415 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 430 435 440 445

<210> 146

<211> 1347

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 146

gaggtgcagc tgggtgcagag cggcgccgag gtaaaaaaac caggagcaag cggttaaagtt 60
 tcttgtaaaag caagcgggata tacatttaca gattacaaca tgcattgggtt aagacaagcg 120
 ccagggaacag gattggaatg gatggggcgaa attaacctta atagtggagg agcaggctac 180
 aatcaaaaat tcaaaaggag agttacaatg acaacagaca caagcacttc aacagcatat 240
 atggaaactgc gatcacttag aagcgcagat acagctgtat actattgcgc acgacttggg 300
 tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc 360
 gtctctagtg cctccaccaa gggcccatcg gtcttccccg tggcgccctg ctccaggagc 420
 acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccgggtg 480
 acggtgtcgt ggaactcagg cgctctgacc agcggcgctgc acaccttccc agctgtccta 540
 cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccttccag caacttcggc 600
 acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 660
 gttgagcgca aatgttgtgt cgagtgcaca ccgtgccagc caccacctgt ggcaggaccg 720
 tcagtcttcc tcttcccccc aaaaaccacg gacacctca tgatctcccc gacccctgag 780
 gtcacgtgcg tgggtgtgga cgtgagccac gaagaccctg aggtccagtt caactgttac 840
 gtggacggcg tggaggtgca taatgccaa gacaagccac gggaggagca gttcaacagc 900
 acgttcctgt tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 960
 tacaagtgcg aggtctccaa caaaggcctc ccagccccca tcgagaaaaa catctccaaa 1020
 accaaagggc agccccgaga accacaggtg tacaccttgc ccccatcccc ggaggagatg 1080
 accaaagacc aggtcagcct gacctgcttg gtcaaaggct tctacccccg cgacatcgcc 1140
 gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1200
 gactccgagc gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1260
 caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1320
 aagagcctct cctctgtctc ggtgtaaa 1347

<210> 147

<211> 468

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 147

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Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala 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 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

```

```

Glu Trp Met Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65      70      75      80
Gln Lys Phe Lys 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 Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
115      120      125
Phe Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
130      135      140
Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
145      150      155      160
Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
165      170      175
Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
180      185      190
His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
195      200      205
Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
210      215      220
Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
225      230      235      240
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
245      250      255
Ala Gly Pro Ser Val Phe Leu Phe Pro Lys Pro Lys Asp Thr Leu
260      265      270
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
275      280      285
His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
290      295      300
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
305      310      315      320
Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
325      330      335
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
340      345      350
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
355      360      365
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
370      375      380
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385      390      395      400
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
405      410      415
Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
420      425      430
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
435      440      445
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
450      455      460
Ser Pro Gly Lys
465

```

<210> 148

<211> 1404

<212> DNA

<213> Mus musculus

<400> 148

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atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccaactccgag 60
gtgcagctgg tgcagagcgg cgccgaggtg aaaaaaccag gagcaagcgt taaagtctct 120
tgtaaaagcaa gtcgatatac atttacagat tacaacatgc attgggtaag acaagcgcca 180
ggacaaggat tggaatggat gggcgaaatt aaccctaata gtggaggagc aggtacaat 240
caaaaattca aagggagagt tacaatgaca acagacacaa gcacttcaac agcatatag 300
gaactgcgat cacttagaag cgacgataca gctgtatact attgcgcacg acttgggtat 360
gatgatatat atgatgactg gtatttcgat gtttggggcc agggaaacaac agttaccgctc 420
tctagtgcct ccaccaaggg cccatcggtc ttcccccttg cgccctgctc caggagcacc 480

```

```

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 tcccccaaaa acccaaggac accctcatga tctcccggac ccttgaggtc 840
acgtgcgtgg tgggtggacgt gagccacgaa gaccccagg tccagttcaa ctggtacgtg 900
gacggcgtgg aggtgcataa tgccaagaca aagccacggg aggagcagtt caacagcagc 960
ttcgtgtggg tcagctcctt caccgttgtg caccaggact ggcgtgaacg caaggagtag 1020
aagtgcaggg tctccaaaca aggcctccca gcccccctcg agaaaacat ctccaaaacc 1080
aaaggggcag cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc 1140
aagaaccagg tcagcctgac ctgcctgggc aaaggcttct accccagcga catcgccgtg 1200
gagtgaggaga gcaatgggca gccggagaac aactacaaga ccacacctcc catgctggac 1260
tccgacggct ccttcttctt ctacagcaag ctaccctggg acaagagcag gtggcagcag 1320
gggaacgtct tctcatgtct cgtgatgcat gaggtctctg acaaccacta cacycagaag 1380
agcctctccc tgtctccggg taaa

```

<210> 149

<211> 214

<212> PRT

<213> Mus musculus

<400> 149

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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 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 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

```

<210> 150

<211> 645

<212> DNA

<213> Mus musculus

<400> 150

```

gatattccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60
atcagttgca gggcaagtca ggacattagc aattatttaa actggtttca gcagaaacca 120
gatggaactc ttaaaactct gatctttctac acatcaagat tacactcagg agttccatca 180
aggttcagtg gcagtgggctc tggaaacagat tattctctca ccattagcaa cctggagcaa 240
gaagatatgg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcgggggg 300
gggaccaagc tggaaataag acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
tccagtgaac agttaacatc tggagggtgc tcagtcgtgt gcttcttgaa caactttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtctctg 480
aacagttgga ctgatcagga cagcaaaagc 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

```

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 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 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 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

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atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 120
atcagttgca gggcaagtca ggacattagc aattatttaa actggtttca gcagaaacca 180
gatggaactc ttaaaactct gatcttctac acatcaagat tacactcagg agttccatca 240
aggttcagtg gcagtgggtc tggaaacagat tattctctca ccattagcaa cctggagcaa 300
gaagataatt ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcgggggg 360
gggaccaagc tggaaataag acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgaac agttaacatc tggaggtgcc tcagtcgtgt gcctcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaa tggcgtcctg 540
aacagtggga ctgatcagga cagcaaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccaattgtcaa gagcttcaac aggaatgagt gtttag 705

```

<210> 153

<211> 447

<212> PRT

<213> Mus musculus

<400> 153

```

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

```

```

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
Asn Met His 20 Trp Val Lys Gln Asn 25 Gln Gly Lys Ser Leu 30 Glu Trp Ile
Gly Glu 35 Ile Asn Pro Asn Ser 40 Gly Ser Gly Tyr 45 Asn Gln Lys Phe
Lys 50 Gly Lys Ala Thr Leu 55 Val Asp Lys Ser 60 Ser Thr Ala Tyr
Met 65 Glu Leu Arg Ser 70 Leu Thr Ser Glu Asp 75 Ser Ala Val Tyr Tyr Cys
Ala Arg Leu 85 Val Tyr Asp Gly Ser Tyr 90 Glu Asp Trp Tyr Phe Asp Val
Trp Gly Ala 100 Gly Thr Thr Val Thr 105 Val Ser Ser Ala Lys 110 Thr Thr Pro
Pro Ser Val 115 Tyr Pro Leu Ala 120 Pro Gly Ser Ala Ala 125 Gln Thr Asn Ser
Met 130 Val Thr Leu Gly Cys 135 Leu Val Lys Gly Tyr 140 Phe Pro Glu Pro Val
Thr 145 Val Thr Trp Asn Ser 150 Gly Ser Leu Ser 155 Ser Gly Val His Thr Phe
Pro Ala Val 160 Leu Gln Ser Asp Leu Tyr 165 Thr Leu Ser Ser 170 Ser Val Thr
Val Pro Ser 175 Ser Thr Trp Pro Ser 180 Glu Thr Val Thr Cys 185 Asn Val Ala
His 190 Pro Ala Ser Ser Thr Lys 195 Val Asp Lys Lys Ile Val Pro Arg Asp
Cys 200 Gly Cys Lys Pro Cys 205 Ile Cys Thr Val Pro Glu Val Ser Ser Val
Phe 210 Ile Phe Pro Pro Lys Pro Lys Asp Val 215 Leu Thr Ile Thr Leu Thr
Pro Lys Val 220 Thr Cys Val Val Val Asp 225 Ile Ser Lys Asp Asp 230 Pro Glu
Val Gln Phe 235 Ser Trp Phe Val Asp 240 Asp Val Glu Val His 245 Thr Ala Gln
Thr 250 Gln Pro Arg Glu Glu Gln 255 Phe Asn Ser Thr Phe Arg Ser Val Ser
Glu 260 Leu Pro Ile Met His 265 Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
Cys 270 Arg Val Asn Ser 275 Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
Ser Lys Thr 280 Lys Gly Arg Pro Lys Ala 285 Pro Gln Val Tyr Thr Ile Pro
Pro Pro Lys 290 Glu Gln Met Ala Lys 295 Asp Lys Val Ser Leu Thr Cys Met
Ile Thr Asp 300 Phe Phe Pro Glu 305 Asp Ile Thr Val Glu Trp Gln Trp Asn
Gly 310 Gln Pro Ala Glu Asn Tyr Lys 315 Asn Thr Gln Pro Ile Met Asp Thr
Asp 320 Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
Trp Glu Ala 325 Gly Asn Thr Phe Thr Cys 330 Ser Val Leu His Glu Gly Leu
His Asn His 335 Thr Glu Lys Ser 340 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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gaggtccagc tgcaacagtc tggacctgaa ctaatgaagc ctggggccttc agtgaagatg 60
tcctgcaagg cttctgggata cacattcact gactacaaca tgcactgggt gaaacagaac 120
caaggaaaga gacctagagt gataggagaa attaatccta acagtgggtg tagtggctac 180
aaccaaaagt tcaaaaggcaa ggccacattg actgtagaca agtcttcacg cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattggtc 300
tacgatggca gctacgagga ctggtacttc gatgtctggg gcgcaggagc cacggtcacc 360

```

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gtctcctcag caaaaacgac acccccattc gtctatccac tggccctggg atctgctgcc 420
caaaactaact ccattggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgaact ggaactcttg atccctgtcc agcgggtgtg acaccttccc agctgtcctg 540
cagttgacct tctacactct gacgagctca gtgactgtcc cctccagcac ctggccagtc 600
gagaccgtca cctgcaacgt tgccccccg gccagcagca ccaagtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctccaccatta ctctgactcc taaggtcacg 780
tgtgtgtgtg tagacatcag caaggatgat cccgaggtcc agttcagctg gttgttagat 840
gatgtgagg tgcaacagc tcagacgcaa ccccgaggag agcagtcca cagcactttc 900
cgctcagtc gtgaacttcc catcatgcac caggactggc tcaatggcaa ggaattcaaa 960
tgcaagggtca acagtgcagc ttccctgtcc cccatcgaga aaacctctc caaaaccaa 1020
ggcagaccga aggtctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctgagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaaggagga 1260
aatactttca ctgtctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccaact ctcttggtaa atga 1344

```

<210> 155

<211> 466

<212> PRT

<213> Mus musculus

<400> 155

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
 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 Ser Leu
 50 55 60
 Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn
 65 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 Val Tyr Asp Gly Ser Tyr Glu 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
 Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
 145 150 155 160
 Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
 165 170 175
 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
 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
 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
 305 310 315 320
 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
 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

atgggatgga gctggacatt tctcttctc ctgtcaggaa ctgcaggtgt cctctctgag 60
 gtccagctgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
 tgcaaggctt ctggatacac attcactgac tacaacatgc actgggtgaa acagaacca 180
 ggaagagagc tagagtggat aggagaaatt aatcctaaca gtggtggtag tggctacaac 240
 caaaagtcca aaggcaaggc cacattgact gttagacaagt ctccagcac agcctacatg 300
 gagctccgca gctgacatc tgaggactct gcagtctatt actgtgcaag attggtctac 360
 gatggcagct acgaggactg gtacttcgat gtctggggcg caggggaccac ggtcaccgctc 420
 tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgcctgccaa 480
 actaactcca tggtagacct gggatgcctg gtcaagggtc atttccctga gccagtaca 540
 gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttccagc tgcctgcag 600
 tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gccagcgag 660
 accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
 cccagggatt gtggttataa gccttgcata gtacagtc cagaagtatc atctgtcttc 780
 atcttcccc caaagcccaa ggtgtgtctc accattactc tgactcctaa ggtcacgtgt 840
 gttgtgttag acatcagcaa ggtatgtccc gaggtccagt tcagctggtt tgtagatgat 900
 gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cacttccgc 960
 tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagg gttcaaatgc 1020
 agggtaaca gtgcagcttt ccctgcccc atcgagaaaa ccatctccaa aaccaaggc 1080
 agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
 aaagtacgtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggatgg 1200
 cagtggaaatg ggcagccagc ggagaaactac aagaacactc agcccatcat ggacacagat 1260
 ggctcttact tcattctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
 actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
 tcccactctc ctggtaaatg a 1401

<210> 157

<211> 214

<212> PRT

<213> Mus musculus

<400> 157

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
 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

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
 130 135 140 145
 Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
 150 155 160 165
 Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
 170 175 180 185
 Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
 190 195 200 205
 Phe Asn Arg Asn Glu Cys
 210

<210> 158

<211> 642

<212> DNA

<213> Mus musculus

<400> 158

gataaccaga tgacacagac tacatctccc ctgtctgcct ctctgggaga cagagtcacc 60
 atctgttgca gggcaagtca ggtcattacc aattatttat actggtatca gcagaaacca 120
 gatggaaactt ttaaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180
 aggttcagtg gcagtgggtc tggaaacagat tattctctca ccattagcaa cctgggaacag 240
 gaagatatgt ccacttactt ttgccacag ggtgatacgc ttccgtacac gttcggaggg 300
 gggaccaagc tggaaaataaa acgggctgat gctgcaccaa ctgtatccat ctcccccacca 360
 tccagtgaagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
 aacagtggga ctgatcagga cagcaaaagac agcacctaca gcatgagcag caccctcacg 540
 ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 159

<211> 234

<212> PRT

<213> Mus musculus

<400> 159

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 Thr Thr Ser Ser Leu Ser
 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 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
 130 135 140 145
 Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
 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

```

atgatgtcct ctgctcagtt ccttgggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 120
atctgttgca gggcaagtca ggtcattacc aattatttat actggtatca gcagaaacca 180
gatgggaactt taaactcct gatctactac acatcaagat tacactcagg agtcccatca 240
aggttcagtg gcagtggggtc tggaaacagat tattctctca ccattagcaa cctgggaacag 300
gaagatatgg ccacttactt ttgcccaacag ggtgatacgc ttccgtacac gttcggagggg 360
gggaccaagc tggaaataaa acggggtgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgaac agttaacatc tgggggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagttgga ctgatcagga cagcaaaagac agcacctaca gcattgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 702

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<210> 161

<211> 447

<212> PRT

<213> Mus musculus

<400> 161

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Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
1      5      10      15
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 Ala Gly Tyr Asn Gln Gln Phe
50     55     60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg Thr Ala Tyr
65     70     75
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85     90     95
Ala Arg Leu Gly Tyr Val Gly Asn 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
Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
160    165    170
Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
175    180    185
Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
190    195    200
His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
205    210    215
Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
220    225    230
Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
235    240    245
Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
250    255    260
Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
265    270    275
Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
280    285    290

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Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
305    310    315
Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
320    325    330
Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
335    340    345
Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
350    355    360
Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
365    370    375
Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
380    385    390
Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
395    400    405
Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
410    415    420
His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
425    430    435

```

<210> 162

<211> 1341

<212> DNA

<213> Mus musculus

<400> 162

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gaggtccagc tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcttgcagg ctcttggata cacattcact gactacaaca tgcactggat gaagcagaac 120
caaggaaaga gcttagaatg gataggagaa attaatccta acagtgggtg tgctggctac 180
aaccagcagt tcaaaaggcaa ggccacattg actgtagaca agtctctccag gacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tacgttggtg attacgagga ctgggtacttc gatgtctggg gcgcaggagac cacggtcacc 360
gtctcttcag ccaaaacgac acccccatct gtctatccac tggccctggg atctgtctgcc 420
caactaact ccatgggtgac cctgggtatgc ctgttcaagg gctatttccc tgagccagt 480
acagtgaact ggaactctgg atccctgtcc agcgggtgtc acaccttccc agctgtcctg 540
cagcttgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaactg tgcaccccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc cccaaagcc caaggatgtg ctaccatta ctctgactcc taaggtcacg 780
tgtgtgtgg tagacatcag caaggatgat cccgagggtcc agttcagctg gttgttagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgaggagg agcagttcaa cagcactttc 900
cgctcagtc gtgaacttcc catcatgcac caggactggg tcaatggcaa ggagtccaaa 960
tgcagggtca acagtgcagc ttcccttccc cccatcgaga aaacatcttc caaaaccaa 1020
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gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctgagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgtctgtg gttacatgag ggctgcaca accaccatac tgagaagagc 1320
ctctcccaact ctctggtaa a 1341

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<210> 163

<211> 466

<212> PRT

<213> Mus musculus

<400> 163

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

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

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<210> 164

<211> 1398

<212> DNA

<213> Mus musculus

<400> 164

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atggggtgga gctggacatt tctcttcttc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccagctgc aacagctctg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatacac attcactgac tacaacatgc actggatgaa gcagaaccaa 180
ggaaagagcc tagaatggat aggagaaatt aatcctaaca gtgggtggtgc tggctacaac 240
cagcagttca aaggcaaggc cacattgact gttagacaagt cctccaggac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagctctatt actgtgcaag attgggctac 360
gttggtaatt acgaggactg gtacttcgat gtctggggcg cagggaaccac ggtcaccgtc 420
tcctcagcca aaacgacacc cccattctgc tatccactgg cccctggatc tgcctgccaa 480
actaacctca tggtagcttg gggatgcctg gtcgaaggct atttccctga gccagtga 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttccagc tgcctctgag 600
tctgacctct acactctgag cagctcagtg actgtccctt ccagcacctg gccagcgag 660
accgtcacct gcaacgttgc ccaccgggc agcagcaca aggtggacaa gaaaattgtg 720

```

```

cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttcccc caaagcccaa ggaatgtgct accattactc tgactcctaa ggtcacgtgt 840
gttgtgtagt acatcagcaa ggaatgatcc gaggtccagt tcagctggtt ttagatgat 900
gtggaggtgc acacagttca gacgcaacc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca tggtagcttg ccttgccttc atcgagaaaa ccatctccaa aaccaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacttccca aggagcagat ggccaaggat 1140
aaagtctagt tgacttgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggatgt ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatctacag caagtcaat gtgcagaaga gcaactggga ggaggagaa 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaa 1398

```

<210> 165

<211> 214

<212> PRT

<213> Mus musculus

<400> 165

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Asp Ile Gln Met Thr Gln Thr 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 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
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
80     85     90
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
95    100    105
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
110   115   120
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
125   130   135
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
140   145   150
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
155   160   165
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
170   175   180
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
185   190   195
Phe Asn Arg Asn Glu Cys
200  205  210

```

<210> 166

<211> 645

<212> DNA

<213> Mus musculus

<400> 166

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gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaacca 120
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccata 180
agggttcagt gcagtgggtc tggaaacagat tattctctca ccatttcaaa cctggagcaa 240
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac ttctggagg 300
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat ctccacca 360
tccagtgaac agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caactctac 420
ccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagttgga ctgatcagga cagcaaaagc agcacctaca gcatgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

```

<210> 167

<211> 234

<212> PRT

<213> Mus musculus

<400> 167

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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 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 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
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> 168

<211> 705

<212> DNA

<213> Mus musculus

<400> 168

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atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatctctc ctgtctgcct ctctgggaga cagggtctcc 120
atcagttgca gggcaagtca agacattagc aattatttaa actgggtatca gcagaaacca 180
gatggaaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 240
aggttcagtg gcagtgggtc tggaaacagat tattctctca ccatttacaa cctggagcaa 300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac ttccggaggg 360
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttccacca 420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaa tggcgtcctg 540
aacagttgga ctgacagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gtttag 705

```

<210> 169

<211> 447

<212> PRT

<213> Mus musculus

<400> 169

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Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
1 5 10 15
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 Thr Leu Asp Trp Ile
35 40 45

```

Gly Glu Ile Asn Pro. Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
 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 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
 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 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
 420 425 430 440
 His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
 435 445

<210> 170

<211> 1344

<212> DNA

<213> Mus musculus

<400> 170

gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
 tcctgcaagg ctctgggata tacattcact gactacaaca tgcactgggt gaagcagaac 120
 caagggaaga ccctagactg gataggagaa attaatccta acagtgtggg tgctggctac 180
 aaccagaagt tcaaggggcaa ggccacattg actgtagaca agtctctcac cacagcctac 240
 atggagctcc gcagctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
 tacgatgata tctacgacga ctgggtacttc gatgtctggg gcgcaggggac cacggtcacc 360
 gtctctctcag ccaaaacgac acccccatct gtctatccac tggccctctg atctgctgcc 420
 caaactaact ccatggtagc cctgggatgc ctggtcaagg gctatctccc tgagccagtg 480
 acagtgaacct ggaactctgg atccctgtcc agcgggtgtc acaccttccc agctgtcctg 540
 cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
 gtgcccaggg attgtgggtg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
 ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taagggtcacg 780
 tgtgtgtggg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
 gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
 cgctcagttca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
 tgcagggtca acagtgcagc ttcccttgcc cccatcgaga aaacatctc caaaaccaa 1020
 ggagaccga aggtccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
 gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
 tggcagtgga atgggacgcc agcgagaac tacaagaaca ctcagcccat catggacaca 1200
 gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
 aatactttca cctgtctgt gtacatgag ggcctgcaca accaccatac tgagaagagc 1320
 ctctccact ctctggttaa atga 1344

<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
 20 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 Thr Leu
 50 Asp Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
 65 Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
 80 Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
 95 Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Trp Tyr
 110 Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
 125 Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
 140 Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
 155 Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
 170 His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
 185 Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
 200 Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
 215 Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
 230 Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
 245 Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
 260 Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
 275 Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
 290 Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
 305 Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
 320 Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
 335 Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
 350

Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
 365 Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
 380 Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
 395 Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
 410 Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
 425 Gly Lys
 440

<210> 172

<211> 1401

<212> DNA

<213> Mus musculus

<400> 172

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 gtccaactgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
 tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaactcaa 180
 ggaagacccc tagactggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
 cagaagtcca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
 gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
 gatgatactc acgacgactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420
 tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgcgtcccaa 480
 actaactcca tggtagacct gggatgcctg gtcaagggtc atttccctga gccagtga 540
 gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttccagc tgcctgcag 600
 tctgacctct acactctgag cagctcagtg actgtccctc ccagcacctg gccagcgag 660
 accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
 cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
 atcttccccc caaagcccaa ggtatgtgct accattactc tgactcctaa ggtcacgtgt 840
 gttgtgtag acatcagcaa ggtatgcc cagggtccagt tcagctggtt tgtatgatgt 900
 gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
 tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagg gttcaaatgc 1020
 agggtaaca gtgcagcttt cctgcccc atcgagaaaa ccatctccaa aaccaaaggc 1080
 agaccgaagg ctccacaggt gtacaccatt ccacttccca aggagcagat ggccaaggat 1140
 aaagtacgtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
 cagtggaaat ggcagccagc ggagaaactc aagaacactc agcccatcat ggacacagat 1260
 ggctcttact tcattcacag caagctcaat gtgcagaaga gcaactggga ggcaggaat 1320
 actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
 tcccactctc ctggtaaatg a

<210> 173

<211> 214

<212> PRT

<213> Mus musculus

<400> 173

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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 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
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
Pro Thr Val Ser Ile Phe 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

```

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130      135      140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145      150      155
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
160      165      170
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
175      180      185
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
190      195      200
Phe Asn Arg Asn Glu Cys
205      210

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<210> 174

<211> 642

<212> DNA

<213> Mus musculus

<400> 174

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gatattcaga tgacacagat tacatctctc ctgtctgcct ctctgggaga cagggtctcc 60
atcagttgca gggcaagtc agacattagc aattatttaa attggtatca gcagaaacca 120
gatggaactt ttaaacctct tatcttctac acatcaagat tattttcagg agtcccatca 180
aggttcagtg gcagtgggtc tggaaacagat tattctctca ccatttacia cctggagcaa 240
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac ttctggaggg 300
gggaccaagg tggaaataaa acgggctgat gctgcaccaa ctgtatccat ctctccacca 360
tccagtgaagc agttaacatc tggagggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgctcctg 480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt

```

<210> 175

<211> 234

<212> PRT

<213> Mus musculus

<400> 175

```

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 Ile Thr Ser Ser Leu Ser
 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 Phe 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 Val 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
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
160      165      170
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
175      180      185
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
190      195      200
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
205      210      215      220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225      230

```

<210> 176

<211> 702

<212> DNA

<213> Mus musculus

<400> 176

```

atgatgtcct ctgttcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga caggggtctcc 120
atcagttgca gggcaagtca agacattagc aattatttaa attggtatca gcagaaacca 180
gatggaaactt ttaaacctct tatcttctac acatcaagat tattttcagg agtcccatca 240
aggttcagtg gcagtgggtc tggaaacagat tattctctca ccatttaca cctggagcaa 300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac ttccggaggg 360
gggaccaagg tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgaac agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagtggga ctgatcagga cagcaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 702

```

<210> 177

<211> 450

<212> PRT

<213> Mus musculus

<400> 177

```

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Thr
1 5 10 15
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
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
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
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
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
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
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

```

```

Arg Thr Ile Ser Lys Pro Lys Gly Pro Val Arg Ala Pro Gln Val Tyr
340 345 350
Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
355 360 365
Thr Cys Met Ile Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp
370 375 380
Thr Asn Asn Gly Gln Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val
385 390 395 400
Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
405 410 415
Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
420 425 430
Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
435 440 445
Gly Lys
450

```

<210> 178

<211> 1350

<212> DNA

<213> Mus musculus

<400> 178

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gaggtccaac tgaacagtc tggacctgaa ctaatgaagc ctgggacttc agtgaagatg 60
tcctgcaagg ctctctggata tacattcact gactacaaca tgcactgggt gaagcagacc 120
caagggaaga cccatagagt gataggagaa attaatccta acagtgggtg tgctgggtac 180
aaccagaaat tcaagggcaa ggccacattg actgtagaca agtctctcac cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aaaaattgggc 300
tacgatgata tctacagcga ctgggtatttc gatgtctggg gcgcagggaac caccggtcacc 360
gtctctccag ccaaaacaac agcccatcgc gtctatccac tggccctgtg gtgtggagat 420
acaactggct cctcggtagc tctaggatgc ctgggtcaagg gttatttccc tgagccagtg 480
accttgacct ggaactcttg atccctgttc agtgaatgac acaccttccc agctctcctg 540
cagtctggcc tctacacctt cagcagctca gtgactgtaa ccacctggcc cagccagacc 600
atcactgca atgtggccca cccggcaagc agcaccaaag tggacaagaa aattgagccc 660
agagggtccc caacacataa acctgtctct ccatgccagc ctctaaactc cttgggtgga 720
ccatccgtct tcatcttccc tccaaagatc aaggatgtac tcatgatctc cctgagcccc 780
atggtcacgt gtgtgggtgt ggatgtgagc gaggatgacc cagatgtcca tgtcagctgg 840
ttcgtgaaca acgtggaagt acacacagct cagacacaaa cccatagaga ggattacaac 900
agtactatcc ggtgtgtagc tgcctcccc atccagcacc aggactggat gagtggcaag 960
gagttcaaat gcaagggtcaa caacaaagcc ctcccagcgc ccatcgagag aaccatctca 1020
aaacccaaag gccaggttaag agctccacag gtatatgtct tgcctccacc agaagaagag 1080
atgactaaga aacagggtcac tctgacctgc atgatcacag acttcatgcc tgaagacatt 1140
tacgtggagt ggaccaacaa cgggcaaaac gagctaaact acaagaacac tgaaccagtc 1200
ctggactctg atggttctta ctctcatgtac agcaagctga gagtggaaaa gaagaactgg 1260
gtggaagaaa atagctactc ctgttcagtg gtccacgagg gtctgcacaa tcaccacacg 1320
actaagagct tctcccgac tccgggtaaa 1350

```

<210> 179

<211> 469

<212> PRT

<213> Mus musculus

<400> 179

```

Met Gly Trp Ser Trp Thr Phe Leu Phe 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
20 25 30
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
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
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
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
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
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
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 Pro Glu Glu Glu Met Thr Lys Lys Gln
370 375 380
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
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

<213> Mus musculus

<400> 180

```

atgggagtgga gctggacctt tctcttcttc ctgtcaggaa ctgcagggtg cctctctgag 60
gtccaactgc aacagctctg acctgaacta atgaagcctg ggacttcagt gaagatgtcc 120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagacccaa 180
ggaaagaccc tagagtggtg agggagaaatt aatcctaaca gtgggtggtg tgggtacaac 240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaaa attgggttac 360
gatgatactt agacgactg gtatttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcttcagcca aacaacacgc cccatcggtc tatccactgg cccctgtgtg tggagataca 480
actggctctt cgggtactct aggatgcctg gtcaagggtt atttccctga gccagtggac 540
ttgacctgga actctggatc cctgtccagt gatgtgcaca ccttcccagc tctcctgcag 600
tctggcctct acacccctag cagctcagtg actgtaacca cctggcccag ccagaccatc 660
acctgcaatg tggcccaccc ggcaagcagc accaaagtgg acaagaaaaa tgagcccgag 720
gggtcccca cacaataacc ctgtcttcca tggccagctc ctaacctctt ggggtggacca 780
tccgtcttca tcttccctcc aaagatcaag gatgtactca tgatctccct gagcccatg 840

```

```

gtcacgtgtg tgggtgggga tgtgagcgag gatgaccag atgtccatgt cagctgggtc 900
gtgaacaacg tggaaagtaca cacagctcag acacaaaccc atagagagga ttacaacagt 960
actatccggg tgggtcagtg cctccccatc cagcaccagg actggatgag tggcaaggag 1020
ttcaaatgca aggtcaacaa caaagccctc ccagcgccca tcgagagaa cactcaaaa 1080
cccaaggggc cagtaagagc tccacaggta tatgtcttgc ctccaccaga agaagagatg 1140
actaagaaac aggtcactct gacctgcagt atcacagatg tcagtcttga agacatttac 1200
gtggagtggg ccaacaacgg gcaaacagag ctaaaactaca agaactactga accagctcgt 1260
gactctgatg gttcttactt catgtacagc aagctgagag tggaaaagaa gaactgggtg 1320
gaaagaaata gttactctct ttcatgtggtc cagcagggtc tgcacaatca ccacacgact 1380
aagagcttct cccggactcc gggtaaa 1407

```

<210> 181

<211> 214

<212> PRT

<213> Mus musculus

<400> 181

```

Asp Ile Gln Met Thr Gln Thr 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 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 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
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

```

<210> 182

<217> 645

<212> DNA

<213> Mus musculus

<400> 182

```

gatattcaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120
gatggaaact ttaaactctt tatcttctac acatcaagat tactctcagg agtcccatca 180
aggttcagtt gcaagtgggtc ttgaacagat tattcttcca ccatctacaa cctggagcaa 240
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac ttctggaggg 300
gggacaaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttccacta 360
tccagtgagc agttaacatc tggagggtgcc tcagtcgtgt gcttctttaa caacttctac 420
cccaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgctcgt 480
aacagttgga ctgatcagga cagcaagac agcacctaca gcattgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

```

<210> 183

<211> 234

<212> PRT

<213> Mus musculus

<400> 183

```

Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Cys Phe Gln
1 1 5 10 15
Gly Thr Arg Cys Asp Ile Gln Met Thr Thr Thr Ser Ser Leu Ser
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 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
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> 184

<211> 705

<212> DNA

<213> Mus musculus

<400> 184

```

atgatgtcct ctgttcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 120
atcagttgca gggcaagtc agacattagc aattatttaa actggtatca gcagaaacca 180
gatggaaactt ttaaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 240
aggttcagtg gcagtgggtc tggaaacagat tattctctca ccatttacaa cctggagcaa 300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac ttccggaggg 360
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttccacta 420
tccagtgagc agttaacatc tggagggtgcc tcagtctgtt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagttgga ctgatacagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gtttag 705

```

<210> 185

<211> 447

<212> PRT

<213> Mus musculus

<400> 185

```

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
1 5 10 15
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 Thr Leu Glu Trp Ile
35 40 45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
50 55 60

```

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr
 65 Met Glu Leu Arg Ser 70 Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 100 Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Pro
 115 Pro Ser Val Tyr Pro Leu Ala 120 Pro Gly Ser Ala Ala Gln Thr Asn Ser
 130 Met Val Thr Leu Gly Cys 135 Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
 145 Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
 165 Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
 180 Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
 195 His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
 210 Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
 225 Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
 245 Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
 260 Val Gln Phe Ser Trp Phe Val Asp Val Glu Val His Thr Ala Gln
 275 Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
 290 Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
 305 Cys Arg Val Asn Ser 310 Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
 325 Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
 340 Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
 355 Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
 370 Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
 385 Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
 405 Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
 420 His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
 435 440 445

<210> 186

<211> 1344

<212> DNA

<213> Mus musculus

<400> 186

gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcctc agtgaagatg 60
 tcctgcaagg ctctgggata tacattcact gactacaaca tgcactgggt gaagcagaac 120
 caaggaaaga ccttagaatg gataggagaa attaatccta acagtgggtg tgctgggtac 180
 aaccagaaat tcaaggggcaa ggccacattg actgtagaca agtccctccac cacagcctac 240
 atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
 tacgatgata tctacagcga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360
 gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
 caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
 acagtgaact ggaactctgg atccctgtcc agcgggtgtc acaccttccc agctgtcctg 540
 cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
 gagaccgtca cctgcaacgt tgcccaccg gccagcagca ccaaggtgga caagaaaatt 660
 gtgcccaggg attgtggttg taagccttgc atatgtacag tccagaagat atcatctgtc 720

ttcatcttcc ccccaaagcc caaggatgtg ctaccatta ctctgactcc taaggtcacg 780
 tgtgtttgtg tagacatcag caaggatgat cccgaggtcc agttcagctg gttttagat 840
 gatgtggagg tgacacagc tcagacgcaa cccgggagg agcagttcaa cagcactttc 900
 cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
 tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaacatctc caaaaccaa 1020
 ggagagccga aggtccaca ggtgtacacc attccactc ccaaggagca gatggccaag 1080
 gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
 tggcagtgga atgggcagcc agcggagaac tacaagaaca ctgagcccat catggacaca 1200
 gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
 aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
 ctctccact ctctggttaa atga 1344

<210> 187

<211> 466

<212> PRT

<213> Mus musculus

<400> 187

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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
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
65 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 Trp Tyr
115 120 125
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
145 150 155 160
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
165 170 175
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
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
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
305 310 315 320
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
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

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```

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

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<210> 188

<211> 1401

<212> DNA

<213> Mus musculus

<400> 188

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atgggatgga gctggacctt tctcttcttc ctgtcaggaa ctgcagggtgt cctctctgag 60
gtccaactgc aacagtcttg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaagcctt ctggatatat attcactgac tacaacatgc actgggtgaa gcagaaccaa 180
ggaagacccc tagaatggat aggagaaatt aatcctaaca gtgggtgtgc tggctacaac 240
cagaagtcca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
gagctccgca gcttgacatc tgaggactct gcagttctatt actgtgcaag attgggtac 360
gatgatactt acgacgactg gtacttcgat gtctggggcg cagggaaccac ggtcaccgtc 420
tcctcagcca aaacgacacc ccatctgtc tatccactgg cccctggatc tgcctgctaa 480
actaactcca tggatgacct gggatgacct gtcaaaggct atttccctga gccagtga 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttccagc tgcctgag 600
tctgacctct acactctgag cagctcagtg actgtccctt ccagcacctg gccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagg gttcaaatgc 1020
agggtcaaca gtgcagcttt cctgcccc atcagaaaaa ccattcccaa aaccaaaggc 1080
agaccgaagg ctccacagtg gtacaccatt ccacttccca aggagcagat ggccaaggat 1140
aaagtcaagt tgacctgcat gataacagac ttcttccctg aagacattac tgtggtgagg 1200
cagtggaatg ggcagccagc ggagaactac aagaacatc agcccatcat ggacacagat 1260
ggctcttact tcattcacag caagctcaat gtgcagaaga gcaactggga ggcaggaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tccactctc ctggtaaatg a

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<210> 189

<211> 213

<212> PRT

<213> Mus musculus

<400> 189

Gln Ile Val Leu Ser Gln Ser Pro Ala Phe Leu Ser Val Ser Pro Gly
 1 5 10 15
 Asp Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ile Ser Tyr Ile
 20 25 30
 His Trp Phe Gln Lys Pro Gly Ser Ser Pro Arg Ser Trp Ile Tyr
 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
 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 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
 210

<210> 190

<211> 642

<212> DNA

<213> Mus musculus

<400> 190

caaattgttc tctccagtc tccagcattc ctgtctgtat ctccagggga taaggtcaca 60
 atgacttgca gggccagctc aagtataagt tacatacact ggtttcagca gaagccagga 120
 tcctcccccga gatcctggat ttatgccaca tccaacctgg ctctggaggt ccctggtcgc 180
 ttcatgggga gtgggtctgg gacctcttac tctctcaca tcagcagagt ggaggctgag 240
 gatgctgcca ctattactg ccagcagtggt agtagtgacc cactcacgtt cgggtgctggg 300
 accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt ccaccatcc 360
 agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
 aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480
 agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg 540
 accaaggacg agtatgaacg acataacagc tatacctgtg aggcactca caagacatca 600
 acttcaccca ttgtcaagag ctccaacagg aatgagtgtt ag 642

<210> 191

<217> 235

<212> PRT

<213> Mus musculus

<400> 191

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
 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 Thr Ser Tyr Ser Leu Thr Ile
 85 90 95
 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 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
 195 200 205
 Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
 210 215 220
 Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
 225 230 235

<210> 192

<211> 708

<212> DNA

<213> Mus musculus

<400> 192

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atggattttc aagtgcagat ttccagcttc ctgctaataca gtgcttcagt cataatgtcc 60
agaggacaaa ttgttctctc ccagtcctcca gcattcctgt ctgtatctcc aggggataag 120
gtcacaaatga cttgcagggc cagctcaagt ataagttaca tacactgggt tcagcagaag 180
ccaggatcct cccccagatc ctggatttat gccacatcca acctggcttc tggagtcctc 240
ggtcgcttca gtggcagtggt gtctgggacc tcttactctc tcacaatcag cagagtggag 300
gctgaggatg ctgccactta ttactgccag cagtggagta gtgaccact cagcttcggt 360
gctgggacca agctggagct gaaacgggct gatgctgcac caactgtatc catcttccca 420
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgtctctt gaacaaacttc 480
taccctaaag acatcaatgt caagtggag attgatggca gtgaacgaca aaatggcgtc 540
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 600
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660
acatcaactt caccattgt caagagcttc aacaggaatg agtggttag 708

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<210> 193

<211> 445

<212> PRT

<213> Mus musculus

<400> 193

```

Glu Val Gln Leu Gln Gln Ser Gly Ala Asp Leu Val Gln Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Thr Ala Ser Gly Phe Asp Ile Lys Asp Tyr
20 25 30
Tyr Ile His Trp Met Lys Gln Arg Pro Asp 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 Ala Thr Phe Thr Thr Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80
Leu Gln Leu Arg Gly Leu Thr Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95
Gly 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 Ala Ala Lys Thr Thr Pro Pro Ser
115 120 125
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
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
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
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
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

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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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gaagttcagc tgcaacagtc tggggcagac cttgtgcagc caggggcctc agtcaagggtg 60
tcctgcacag ctcttggtct cgacattaag gactactata tacactggat gaaacagagg 120
cctgaccagg gcttgagggt gattggaagg gttgatcctg acaatggtga gactgaattt 180
gccccgaagt tcccggtcaa ggccactttt acaacagaca catcctccaa cacagcctac 240
ctacaactca gaggcctgac atctgaggac actgcatctt attactgtgg gagagaagac 300
tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt cactgtctct 360
gcagccaaaa acgttgcccc atctgtctat ccactggccc ctggatctgc tgcccaaaact 420
aactccatgg tgacctgggt atgctgtgtc aagggtatct tccctgagcc agtgacagtg 480
acctggaact ctggatccct gtccagcggg gtgcacacct tcccagctgt cctgcagtct 540
gacctctaca ctctgagcag ctacagtact gtcccttcca gcacctggcc cagcgagacc 600
gtcacctgca acgttgcccc cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
agggattgtg gtgtgaagcc ttgcatatgt acagtcccag aagtatcatc tgttcttcatc 720
ttcccccaaa agcccaagga tgtgtctacc attactctga ctctaaaggt cactgtgtgt 780
gtggtagaca tcagcaagga tgatcccgag gtccagtcca gctggtttgt agatgatgtg 840
gaggtgcaca cagctcagac gcaacccctg gaggagcagt tcaacagcac ttctcgctca 900
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960
gtcaacagtg cagctttccc tgccccctac gagaaaacca tctccaaaac caaaggcaga 1020
ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080
gtcagtctga cctgcatgat aacagacttc tccctgaag acattactgt ggagtggcag 1140
tggaaatgggc agccagcggg gaactacaag aacactcagc ccatcatgga cacagatggc 1200
tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1260
ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320
cactctctcg gtaaatga 1338

```

<210> 195

<211> 464

<212> PRT

<213> Mus musculus

<400> 195

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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

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Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145 150 155
Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
160 165 170
Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
175 180 185
Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Val
190 195 200
Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
205 210 215
Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
220 225 230
Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
235 240 245
Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
250 255 260
Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
265 270 275
Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
280 285 290
Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
295 300 305
Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
310 315 320
Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
325 330 335
Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
340 345 350
Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
355 360 365
Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
370 375 380
Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
385 390 395
Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
400 405 410
Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
415 420 425
Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
430 435 440 445 450 455 460

```

<210> 196

<211> 1395

<212> DNA

<213> Mus musculus

<400> 196

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atgaaatgca gctgggtcat cttcttcctg atggcagtgg ttacaggggt caattcagaa 60
gttcagctgc aacagtctgg ggcagacctt gtgcagccag gggcctcagt caagggtgcc 120
tgacacagctt ctggcttcga cattaaggac tactatatac actggatgaa acagaggcct 180
gaccaggggct tggagtggat tgggaagggt gatcctgaca atggtgagac tgaatttgcc 240
ccgaagtctc cgggcaaggc cacttttaca acagacacat cctccaacac agcctaccta 300
caactcagag gctgacatc tgaggacact gccatctatt actgtgggag agaagactac 360
gatggtagctt acacctgggt tccttattgg ggccaaggga ctctggtcac tgtctctgca 420
gccaaaacga ccccccatc tgcttatcca ctggccccct gatctgctgc ccaactaac 480
tccatgggtga cctgggatg cctgggtcaag ggctatttcc ctgagccagt gacagtgacc 540
tggaaactctg gatcctgtgc cagcgggtgt cacaccttcc cagctgtcct gcagtctgac 600
ctctacactc tgagcagctc agtgactgtc cctccagca cctggcccag cgagaccgtc 660
acctgcaacg ttgccacccc ggccagcagc accaagggtg acaagaaaat tgtgccagg 720
gattgtgggt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780
ccccaaagc ccaaggatgt gctcaccatt actctgactc ctaagggtcac gtgtgtgtg 840
gtgacacagc gcaaggatga tcccagggtc cagttcagct ggtttgtaga tgatgtggag 900
gtgacacagc ctacagcaga accccgggag gagcagttca acagcacttt ccgctcagtc 960
agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttaa atgcagggtc 1020
aacagtgcag ctttccctgc ccccatcgag aaaaccatc ccaaaaccaa aggcagaccg 1080
aaggctcac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1140
agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 1200

```

```

aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1260
tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1320
acctgtctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380
tctctggta aatga 1395

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<210> 197

<211> 214

<212> PRT

<213> Mus musculus

<400> 197

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Asp Leu Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1      5      10      15
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
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
Asp Asp Ala 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
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

```

<210> 198

<211> 645

<212> DNA

<213> Mus musculus

<400> 198

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gatctccaga tgacacagac tacttctcct ctgtctgcct ctctgggaga cagagtcacc 60
atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120
gatggaactg taaagctcct gatcttctac acatcaacat tacagtcagg agtcccatcg 180
aggttcagtg gcagtgggtc tggaaacaat tattctctca ccattaccac cctggagcaa 240
gatgatctg ccaactactt ttgccacagc ggtgatacgc ttccgtacac gttcggaggg 300
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatcatc cttccacca 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
ccccaaagca tcaatgtcaa tgggaagatt gatggcagtg aacgacaaaa tggcgctcctg 480
aacagtggga ctgatcagga cagcaagac 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

<400> 199

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Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Cys Phe Gln
1      5      10      15
Gly Ser Arg Cys Asp Leu 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 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 Thr Lys Leu Glu Ile Lys Arg
 115 120 125
 Ala Asp 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 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> 200

<211> 705

<212> DNA

<213> Mus musculus

<400> 200

atgatgtcct ctgtcagtt ccttggtctc ctgttgctct gttttcaagg ttccagatgt 60
 gatctccaga tgacacagac tacttctctc ctgtctgcct ctctgggaga cagagtcacc 120
 atcagttgca gggcaagtcg ggacattagc aattatttaa actgggtatca gcagaaacca 180
 gatggaaactg ttaagctcct gatcttctac acatcaacat tacagtcagg agtcccatcg 240
 aggttcagtg gcagtgggtc tggaaacaaat tattctctca ccattaccaa cctggagcaa 300
 gatgatgctg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg 360
 gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
 tccagtgaac agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgctcctg 540
 aacagtggga ctgacagga cagcaaaagac agcacctaca gcatgagcag caccctcacg 600
 ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
 tcaacttcac ccatgtgcaa gagcttcaac aggaatgagt gtttag 705

<210> 201

<211> 447

<212> PRT

<213> Mus musculus

<400> 201

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
 1 5 10 15
 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
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys 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

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 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> 202

<211> 1344

<212> DNA

<213> Mus musculus

<400> 202

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 caaggaaaga gcctagagtg gataggagag attaatccta acagtgtgtg ttctgggtac 180
 aaccagaagt tcaaaggcaa ggccacattg actgtagaca agtcctccag cacagcctac 240
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 tactatggtt actacgagga ctgggtatttc gatgtctggg gcgcaggagc caggttcacc 360
 gtctctcttg ccaaaacgac acccccatct gtctatccac tggcccttgg atctgtctgc 420
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 tgtgtttggg tagacatcag caaggatgat cccgaggtcc agttcagctg gttttagatg 840
 gatgtggagg tgcacacagc tcagacgcaa ccccgaggag agcagttcaa cagcactttc 900
 cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
 tgcagggtca acagtgcagc ttccctgtcc cccatcgaga aaaccatctc caaaacaaa 1020
 ggacagaccg aggtccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
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 gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
 aatactttca cctgtctgtg gttacatgag ggcctgcaca accacatac tgagaagagc 1320
 ctctcccaact ctctgggtaa atga 1344

<210> 203

<211> 466

<212> PRT

<213> Mus musculus

<400> 203

Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ser Gly
 1 Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
 20 Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
 35 Thr Asp Tyr Asn Met His Trp Met 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
 80 Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
 100 Tyr Tyr Cys Ala Arg Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr
 115 Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser 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
 160 Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
 175 His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
 190 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
 240 Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
 255 Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
 270 Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
 285 Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
 300 Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
 315 Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
 330 Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
 345 Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
 360 Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
 375 Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
 390 Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
 405 Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
 420 435 440 445

Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
 450 455 460
 Gly Lys
 465

<210> 204

<211> 1401

<212> DNA

<213> Mus musculus

<400> 204

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 tgcaaggctt ctggatacac attcactgac tacaacatgc actggatgaa gcagaaccaa 180
 ggaagagacc tagagtggat aggagagatt aatcctaaca gtggtggttc tggttacaac 240
 cagaagtcca aaggcaagcc cacattgact gtacacaagt cctccagcac agcctacatg 300
 gagctccgac gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
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 tctcttgcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgcctgccaa 480
 actaactcca tgggtgacct gggatgcctg gtcaagggtc atttccctga gccagtgcag 540
 gtgacctgga actctggatc cctgtccagc ggtgtgcaca ctttccagc tgcctgcag 600
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 agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
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 cagtggaatg ggcagccagc ggagaactac agcccatcat ggacacagat 1260
 ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
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<210> 205

<211> 215

<212> PRT

<213> Mus musculus

<400> 205

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
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 Glu Lys Val Thr Met Thr Cys Arg Ala 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
 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
 Ala Pro Thr Val Ser Ile Phe 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
 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

195 200 205
 Ser Phe Asn Arg Asn Glu Cys
 210 215

<210> 206

<211> 645

<212> DNA

<213> Mus musculus

<400> 206

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 ccaggatctt ccccaaaact ctggatttat agcacatcca acctggcttc aggagtcca 180
 gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagtgtggag 240
 gctgaggatg ctgccactta ttactgccag cagtatgatt ttttccatc gacgttcggt 300
 ggaggcacca agctggaaat caagcgggct gatgctgcac caactgtatc catcttcca 360
 ccattccagt agcagtttaac atctggagggt gcctcagtcg tgtgcttctt gaacaacttc 420
 taccaccaag acatcaatgt caagtggaaag attgatggca gtgaacgaca aaatggcgctc 480
 ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccttc 540
 acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 600
 acatcaactt caccatcgt caagagcttc aacaggaatg agtgt 645

<210> 207

<211> 237

<212> PRT

<213> Mus musculus

<400> 207

Met Asp Ser Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Leu
 1 5 10 15
 Val Lys Met Ser Arg Gly Gln Ile Val Leu Thr Gln Ser Pro Ala Ile
 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 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

<210> 208

<211> 711

<212> DNA

<213> Mus musculus

<400> 208

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gtcaccatga cctgcagggc cagctcaagt gtaacttcca gttacttgaa ctggtaccag 180
cagaagccag gatcttcccc caaactctgg atttatagca catccaacct ggcttcagga 240
gtccagctgc gcttcagtgg cagtgggtct gggacctctt actctctcac aatcagcagt 300
gtggaggctg aggatgctgc cacttattac tggcagcagt atgatttttt cccatcgacg 360
ttcgggtggag gcaccaagct ggaaatcaag cgggctgatg ctgcaccaac tgtatccatc 420
ttcccaccat ccagtgcagca gttaacatct ggaggcgctt cagtcgtgtg cttcttgaac 480
aacttctacc ccaaagacat caatgtcaag tggagagatt atggcagtag acgacaaaat 540
ggcgtcctga acagtggac tgatcaggac agcaaagaca gcacctacag catgagcagc 600
accttcacgt tgaccaagga cgagtatgaa cgacataaca gctataacct tgaggccact 660
cacaagacat caacttcacc catcgtcaag agcttcaaca ggaatgagtg t 711

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<210> 209

<211> 445

<212> PRT

<213> Mus musculus

<400> 209

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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 Tyr Thr Phe Thr Asp Tyr
20      25      30
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
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 Ala Lys Thr Thr Pro Pro Ser
115      120      125
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
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
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
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
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
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

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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

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<210> 210

<211> 1335

<212> DNA

<213> Mus musculus

<400> 210

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catggagaga gcccttgatg gattggagat attaatcctt acaacgatga tactacctac 180
aaccacaagt tcaagggcaa ggccacattg actgtagaca aatcctccaa cacagcctac 240
atgcagctca acagcctgac atctgaggac tctgcagtct attactgtgc aagagagacg 300
gccgttatta ctacgaatgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360
tcagccaaaa cgacaccccc atctgtctat ccaactggccc ctggatctgc tgcccaaact 420
aactccatgg tgacctcggg atgccttggtc aagggctatt tccttgagcc agtgacagtg 480
acctggaaat ctggatccct gtccagcggg gtgcacacct tccagctgt cctgcagtct 540
gacctctaca ctctgagcag ctacgtgact gtcccctcca gcacctggcc cagcgagacc 600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
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ttcccccata agcccaagga tgtgctcacc attactctga ctctaaagt cactgtgtgt 780
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tcttacttca tctacagcaa gctcaatgtg cagaagagca actggggaggc aggaataact 1260
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<210> 211

<211> 464

<212> PRT

<213> Mus musculus

<400> 211

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20     25     30     35
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
40     45     50     55
Thr Asp Tyr Tyr Met Asn Trp Val Lys Gln Ser His Gly Glu Ser Leu
60     65     70     75
Glu Trp Ile Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn
80     85     90     95
His Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asn
100    105    110    115
Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val
120    125    130    135
Tyr Tyr Cys Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp
140    145    150    155
Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr
160    165    170    175
Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
180    185    190    195
Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
200    205    210    215
Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
220    225    230    235
Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Val
240    245    250    255
Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
260    265    270    275
Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
280    285    290    295
Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
300    305    310    315
Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
320    325    330    335
Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
340    345    350    355
Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
360    365    370    375
Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
380    385    390    395
Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Gly
400    405    410    415
Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
420    425    430    435
Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
440    445    450    455
Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
460    465    470    475
Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
480    485    490    495
Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
500    505    510    515
Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
520    525    530    535
Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
540    545    550    555
Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
560    565    570    575

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<210> 212

<211> 1392

<212> DNA

<213> Mus musculus

<400> 212

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tgtaaggctt ctggatacac attcactgac tactacatga actgggtgaa gcagagccat 180
ggagagagcc ttgagtggaat tggagatatt aatccttaca acgatgatac tacctacaac 240
cacaaagttca agggcaaggc cacattgact gtagacaaat cctccaacac agcctacatg 300
cagctcaaca gccctgacatc tgaggactct gcagctctatt actgtgcaag agagacggcc 360
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tacttcatct acagcaagct caatgtgcag aagagcaact gggagggcagg aaatactttc 1320
acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380
tctctggta aa 1392

```

<210> 213

<211> 215

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 213

```

Asp Ile Gln Leu Thr 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
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Phe Phe Pro
80     85     90
Ser Thr Phe 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
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
160    165    170
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
175    180    185
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
190    195    200
Ser Phe Asn Arg Gly Glu Cys
205    210    215

```

<210> 214

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 214

```

gacatccagc tgaccagag cccagcttc ctttccgcat ccgttggtga ccgagtaaca 60
atcacatgcc gcgcctcctc ttccagttaca tcttcttctc ttaattggta tcaacaaaaa 120
ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatc aggagttccc 180
tctcgatttt caggtacttg atcaggcaca gaatttacac ttactatata atcactccaa 240
ccagaagact tcgccactta ttactgccaa caatacgatt tttttccaag cacattcggg 300
ggaggtacaa aagtagaat caagcgtacg gtggctgcac catctgtctt catcttccc 360
ccatctgatg agcagttgaa atctggaact gccctctgtg tgtgctctgt gaataacttc 420
tatcccagag agggcaaaat acagtggag gtggataacg cctccaatc gggtaactcc 480
caggagagtg tcacagagca ggacagcaag gacagcactt acagcctcag cagcaccctg 540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 600
ggcctgagct cgccgtcac aaagagcttc aacaggggag agtgt 645

```

<210> 215

<211> 237

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 215

```

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly 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 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
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 Tyr Asp 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
Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
145     150     155
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> 216

<211> 711

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 216

```

atggacatga ggggtccctc tcagctcctg ggggtccctg tactctggct cccaggtgcc 60
agatgtgaca tccagctgac ccagagcccc agcttccttt ccgcatccgt tggtagcga 120
gtaaacatca catgccgcgc ctcatcttca gttacatctt ctatcttaa ttggatcaa 180
caaaaaccag gaaaagcacc taaacttctt atatactcta catctaactc cgcacagga 240
gttcctcttc gattttcagg atctggatca ggcacagaat ttacacttac tatatcatca 300
ctccaaccag aagacttcgc cacttattac tgccaacaat acgatttttt tccaagcaca 360
ttcggaggag gtacaaaagt agaaatcaag cgtacgggtg ctgcaccatc tgtcttcac 420
ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgtttgtgt cctgctgaat 480
aacttctatc ccagagaggg caaagtacag tggaaagggtg ataacgccct ccaatcgggt 540
aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 600
accctgacgc tgagcaaaag agactacgag aaacacaaag tctacgcctg cgaagtcacc 660
catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t 711

```

<210> 217

<211> 447

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 217

```

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
Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85
Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
100
Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420
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

```

gaggtgcagc tgggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaagggt 60
agttgcaaa gactctggata cacatttacc gactactaca tgaattgggt acgacaagcc 120
cctggacaaa gacttgaatg gatggggagac attaacccctt ataacgacga cactacatcac 180
aatcataaat ttaaagggaag agttacaatt acaagagata catccgcatc aaccgcctat 240
atggaaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact 300
gccgttatta ctactaacgc tatggattac tggggtcaag gaaccactgt taccgtctct 360

```

```

agtgcctcca ccaagggccc atcgggtcttc cccctggcgc cctgctccag gaggacctcc 420
gagagcacag cggccctggg ctgcctgggtc aaggactact tcccgaacc ggtgacgggt 480
tcgtggaaat caggcgctct gaccagcggc gtgcacacct tccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtgggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagt gcccacgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggaacac ctcagtatct cccggacccc tgaggtcacg 780
tgctgtgtgg tggacgtgag caagcaaaag ccacgggagg agcagttaa cagcacgttc 840
ggcgtggagg tgcataatgc caagcaaaag ccacgggagg agcagttaa cagcacgttc 900
cgtgtgggtc cgtctctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaacatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctgggtcaaa ggcttctacc ccagcgacat cgcctgggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca caccctccat gctggactcc 1200
gacgggtctc tcttctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgtctcgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa a

```

<210> 219

<211> 466

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 219

```

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala 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 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 Thr Thr Tyr Asn
65      70      75      80
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
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
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
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
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
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys

```

```

Glu Tyr Lys Cys 325 Lys Val Ser Asn Lys 330 Gly Leu Pro Ala 335 Ile Glu
340      345      350
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
385      390      395      400
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
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
450      455      460
Gly Lys
465

```

<210> 220

<211> 1398

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 220

```

atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccaactccgag 60
gtgcagctgg tgcagagcgg cgccgaggtc aagaaacctg gagcaagcgt aaaggttagt 120
tgcaaaagcat ctggatacac atttaccgac tactacatga attgggtacg acaagcccct 180
ggcaaaagac ttgaatggat gggagacatt aacccttata acgacgacac tacatacaat 240
cataaaattta aaggaagagt tacaattaca agagatacat cgcacacac cgcctatatg 300
gaactttcct cattgagatc tgaagacact gctgtttatt actgtgcaag agaaactgcc 360
gttattacta ctaacgctat ggattactgg ggtcaaggaa ccactgttac cgtctctagt 420
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cactcccgag 480
agcacagcgg cctctgggctg cctgggtcaag gactacttcc ccgaaccggg gacgggtgtc 540
tggaactcag gcgctctgac cagcggcggtg cacaccttcc cagctgtcct acagtctctc 600
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg caccagacc 660
tacacctgca acgtagatca caagcccgagc aacaccaagg tggacaagac agttgagcgc 720
aaatgttgtg tcgagtgccc acctgtccca gcaccacctg tggcaggacc gtcagctctc 780
ctcttcccc caaaacccaa ggacaccttc atgatctccc ggacctctga ggtcacgtgc 840
gtggtgtgtg acgtgagcca cgaagacccc gaggtccagt tcaactggtc cgtggagcgc 900
gtggaggtgc ataattgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 960
gtggtcagcg tcctcacctg tgtgcaccag gactggctga acggcaagga gtacaagtgc 1020
aaggtctcca acaaaggcct ccagccccc atcgagaaaa ccactctcaa aaccaaggg 1080
cagccccgag aaccacaggt gtacacctgt ccccatccc gggaggagat gaccaagaac 1140
caggtcagcc tgacctgctt ggtcaaaaggc ttctacccca gcgacatcgc cgtggagtgg 1200
gagagcaatg ggcagccgga gaacaaactac aagaccacac ctccatgctt ggactccgac 1260
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1320
gtcttctcat gctcgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380
tcctgtctc cgggtaaa

```

<210> 221

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 221

```

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 Gln Trp Ser Ser Tyr Pro
 85      90      95
Leu Thr Phe 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 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

```

<210> 222

<211> 645

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 222

```

gacatccaga tgacccagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca 60
ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcatgggtt ccaacagaaa 120
cccggaagag cacttaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct 180
tcaagatttt caggctctgg ctgaggcacc gactttactc ttacaatata ctccttccaa 240
ccggaagact tcgcaacctt ttactgtcaa caatggtcct catatccact cacattggc 300
ggcggcacaa aagtagaaat taaacgtacg gtggctgcac catctgtctt catcttccg 360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgctgtct gaataacttc 420
tatccagag aggcctaaag acagtgggaag gtggataacg cctccaatc gggtactcc 480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcactctg 540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 600
ggcctgagct cgccgtcac aaagagcttc aacaggggag agtggt 645

```

<210> 223

<211> 237

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 223

```

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly 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

```

atggacatga ggggtccccg tcagctcctg ggggtcctgc tactctggct ccgaggtgcc 60
agatgtgaca tccagatgac ccagttctcca tctctcctct cagcatccgt aggcgataga 120
gttacaataa catgcagcgt atcatcaact atatcatcaa atcatcttca ttggttccaa 180
cagaaacccg gcaaagcacc taaatcactt atatacggca catcaaatct cgcacaggcc 240
gttctttcaa gattttcagg ctctggctca gccaccgact ttactcttac aatatcctcc 300
ctccaacccg aagacttcgc aacctattac tgtcaacaat ggtcctcata tccactcaca 360
tttggcggcg gcacaaaagt agaaattaaa cgtacgggtg ctgcaccatc tgtcttcac 420
ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttggtg cctgctgaat 480
aactttctat ccagagaggg caaagtacag tgggaagggtg ataacyccct ccaatcgggt 540
aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 600
acctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc 660
catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtgt t 711

```

<210> 225

<217> 451

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 225

```

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 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 Ala Ser Thr
115 120 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser

```

130	Glu	Ser	Thr	Ala	Ala	Leu	135	Gly	Cys	Leu	Val	Lys	140	Asp	Tyr	Phe	Pro	Glu
145	Pro	Val	Thr	Val	Ser	Trp	150	Asn	Ser	Gly	Ala	Leu	155	Thr	Ser	Gly	Val	His
	Thr	Phe	Pro	Ala	Val	Leu	165	Gln	Ser	Ser	Gly	Leu	170	Tyr	Ser	Leu	Ser	Ser
	Val	Val	Thr	Val	Pro	Ser	180	Asn	Phe	Gly	Thr	Gln	185	Thr	Tyr	Thr	Cys	
	Asn	Val	Asp	His	Lys	Pro	195	Ser	Asn	Thr	Lys	Val	200	Asp	Lys	Thr	Val	Glu
	Arg	Lys	Cys	Cys	Val	Glu	210	Cys	Pro	Pro	Cys	Pro	215	Ala	Pro	Pro	Val	Ala
225	Gly	Pro	Ser	Val	Phe	Leu	230	Phe	Pro	Pro	Lys	Pro	235	Lys	Asp	Thr	Leu	Met
	Ile	Ser	Arg	Thr	Pro	Glu	245	Val	Thr	Cys	Val	Val	250	Val	Asp	Val	Ser	His
	Glu	Asp	Pro	Glu	Val	Gln	260	Phe	Asn	Trp	Tyr	Val	265	Asp	Gly	Val	Glu	Val
	His	Asn	Ala	Lys	Thr	Lys	275	Pro	Arg	Glu	Glu	Gln	280	Phe	Asn	Ser	Thr	Phe
	Arg	Val	Val	Ser	Val	Leu	290	Thr	Val	Val	His	Gln	295	Asp	Trp	Leu	Asn	Gly
305	Lys	Glu	Tyr	Lys	Cys	Lys	310	Val	Ser	Asn	Lys	Gly	315	Leu	Pro	Ala	Pro	Ile
	Glu	Lys	Thr	Ile	Ser	Lys	325	Thr	Lys	Gly	Gln	Pro	330	Arg	Glu	Pro	Gln	Val
	Tyr	Thr	Leu	Pro	Pro	Ser	340	Arg	Glu	Glu	Met	Thr	345	Lys	Asn	Gln	Val	Ser
	Leu	Thr	Cys	Leu	Val	Lys	355	Gly	Phe	Tyr	Pro	Ser	360	Asp	Ile	Ala	Val	Glu
	Trp	Glu	Ser	Asn	Gly	Gln	370	Pro	Glu	Asn	Asn	Tyr	375	Lys	Thr	Thr	Pro	Pro
385	Met	Leu	Asp	Ser	Asp	Gly	380	Ser	Phe	Phe	Leu	Tyr	385	Ser	Lys	Leu	Thr	Val
	Asp	Lys	Ser	Arg	Trp	Gln	390	Gln	Gly	Asn	Val	Phe	395	Ser	Cys	Ser	Val	Met
	His	Glu	Ala	Leu	His	Asn	405	His	Tyr	Thr	Gln	Lys	410	Ser	Leu	Ser	Leu	Ser
	Pro	Gly	Lys				420						425					
							435						440					
							450						455					

<210> 226

<211> 1353

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 226

```

gagggtgcagc tgggtgcagtc tgggggctgag gtgaagaagc ctgggggcctc agtgaaggctc 60
tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gattggaagg attgatcctg agaattggta tactttatat 180
gaccggaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg 300
gattatttcc acgatgttac ctctactggg tacttcgatg tctggggccg tggcaccctg 360
gtcaccgtct ctagtgcctc caccaagggc ccattcggtc tcccccctggc gccctgctcc 420
aggagacact ccgagagcac agcggccctg ggctgctctg tcaaggacta cttcccga 480
ccggtgacgg tgcgtggaa ctacggcgct ctgaccagcg gcgtgcacac cttcccagct 540
gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcaac 600
ttcggcacc agacctacac ctgcaacgta gatcacaagc ccagcaacac caagggtggac 660
aagacagttg agcgcaaatg ttgtgtcag tgcccaccgt gccagcacc acctgtggca 720
ggaccgctcag tcttctctt ccccccacaa cccaaggaca cctcatgat ctcccggacc 780
cctgaggtca cgtgcgtggt ggtggacgtg agccacgaag accccgaggt ccagttcaac 840
tggtacgtgg acggcgtgga ggtgcataat gccaaagaca agcccagggg ggagcagttc 900
aacagcacgt tccgtgtggt cagcgtcctc accgttgtgc accaggactg gctgaacggc 960

```

```

aaggagtaca agtgaaggct ctccaacaaa ggccctccag ccccatcga gaaaaccatc 1020
tccaaaacca aagggcagcc ccgagaacca cagggtgtaca ccctgcccc atcccgggag 1080
gagatgacca agaaccaggt cagcctgacc tgcctgggtca aaggcttcta ccccagcgac 1140
atcgccgtgg agtgggagag caatgggag ccggagaaca actacaagac cacacctccc 1200
atgctggact ccgacggctc cttcttctc tacagcaagc tcaccgtgga caagagcagg 1260
tggcagcagg ggaacgtctt ctcattgctc gtgatgcatg aggcctgca caaccactac 1320
acgcagaaga gcctctcctt gtctccgggt aaa 1353

```

<210> 227

<211> 470

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 227

```

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala 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 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
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
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
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
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
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 Phe Asn
305 310 315 320
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
Pro Gln Val Tyr Thr Leu Pro 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
385 390 395 400
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr

```

```

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
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
465 470

```

<210> 228

<211> 1410

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 228

```

atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg gggccctcagt gaagggtctcc 120
tgcaaggctt ctgacttcaa cattaaagac ttctatctac actgggtgcg acaggcccct 180
ggacaagggc ttgagtggat tggaggatt gatcctgaga atgggtgatac ttatatgac 240
ccgaagtccc aggacaaggt caccatgacc acagacacgt ccaccagcac agcctacatg 300
gagctgagga gcctgagatc tgacgacacg gccgtgtatt actgtgcgag agaggcggat 360
tatttcacg atggtacctc ctactggtac ttcgatgtct ggggcccgtg caccctggtc 420
accgtctcta gtgctccac caagggccca tcggtcttcc ccctggcgc ctgctccagg 480
agcacctccg agagcacagc ggccctgggc tgcctggtca aggactactt ccccgaaacc 540
gtgacgggtg ctgggaactc aggcgtctcg accagcggcg tgcacacctt cccagctgtc 600
ctacagtcct caggactcta ctccctcagc agcgtgggtg ccgtgccctc cagcaacttc 660
ggcaccacga ctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag 720
acagttgagc gcaaatgttg tgtcagatgc ccaccgtgcc cagcaccacc tgtggcagga 780
ccgtcagctc tctcttctcc cccaaaacc aaggacaccc tcatgatctc ccggaccctc 840
gaggtcacgt gcgtgggtgg ggcgtgagc cacgaagacc ccgaggtcca gttcaactgg 900
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc caggggagga gcagttcaac 960
agcacgttcc gtgtgggtcag cgtcctcacc gttgtgcacc aggactggct gaacggcaag 1020
gagtacaagt gcaagggtctc caacaaagc ctcccagccc ccatcgagaa aaccatctcc 1080
aaaaccaag ggcagccccc agaaccacag gtgtacaccc tgcctccatc ccgggaggag 1140
atgaccaaga accaggtcag cctgacctgc ctgggtcaag gcttctaccc cagcgacatc 1200
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac acctcccatg 1260
ctggactccg acggctcctt ctctctctac agcaagctca ccgtggacaa gagcaggtgg 1320
cagcagggga acgtctctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1380
cagaagagcc tctccctgtc tccgggtaaa

```

<210> 229

<211> 213

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 229

```

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 Ile Ser Tyr Ile
20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys 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

```

```

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> 230

<211> 639

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 230

```

gacatccagt tgaccagctc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg 120
aaagccctta agctcctgat ctatgccaca tccaacctgg cttctggggt cccatcaagg 180
ttcagcggca gtggatctgg gacagaattc actctcaca tcagcagcct gcagcctgaa 240
gattttgcaa cttattactg tcagcagtgg agtagtgacc cactcacgtt cggcggaggg 300
accaaggtgg agatcaaacg tacggtggct gcaccatctg tcttcattct cccgccatct 360
gatgagcagt tgaatctgga aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
agagaggcca aagtacagtg gaagggtgat aacgcctccc aatcgggtaa ctcccaggag 480
agtgctcagc agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540
agcaaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600
agctcgcccg tcacaaagag cttcaacagg ggagagtgt

```

<210> 231

<211> 235

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 231

```

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 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 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 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

```

atggacatga ggggtcccg ctagctcctg gggctcctgc tgctctggct cccaggtgcc 60
agatgtgaca tccagttgac ccagctctcca tccttctctgt ctgcatctgt aggagacaga 120
gtcaccatca cttgcagggc cagctcaagt ataagttaca tacactggta tcagcaaaaa 180
ccagggaag cccctaagct cctgatctat gccacatcca acctggcttc tggggtccca 240
tcaaggttca gcggcagtg atctgggaca gaattcactc tcacaatcag cagcctgcag 300
cctgaagatt ttgcaactta ttactgtcag cagtggagta gtgacccact cagcttcggc 360
ggagggacca aggtggagat caaacgtacg gtggctgcac catctgtctt catcttcccg 420
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgctgtct gaataacttc 480
tatccagag aggcctaaat acagtggag gtggataacg cctccaatc gggtactcc 540
caggagagt tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 600
acgtgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 660
ggcctgagct cgccgtcac aagagagcttc aacaggggag agtgt 705

```

<210> 233

<211> 447

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 233

```

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 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
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
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210     215     220

```

210	Val	Glu	Cys	Pro	Pro	Cys	215	Pro	Ala	Pro	Pro	Val	220	Ala	Gly	Pro	Ser	Val
225	Phe	Leu	Phe	Pro	Pro	Lys	230	Pro	Lys	Asp	Thr	235	Leu	Met	Ile	Ser	Arg	Thr
	Pro	Glu	Val	Thr	Cys	Val	245	Val	Val	Asp	Val	250	Ser	His	Glu	Asp	Pro	Glu
	Val	Gln	Phe	Asn	Trp	Tyr	260	Val	Asp	Gly	Val	265	Glu	Val	His	Asn	Ala	Lys
	Thr	Lys	Pro	Arg	Glu	Glu	275	Gln	Phe	Asn	Ser	280	Phe	Arg	Val	Val	Ser	
	Val	Leu	Thr	Val	Val	His	290	Gln	Asp	Trp	Leu	300	Gly	Lys	Glu	Tyr	Lys	
305	Cys	Lys	Val	Ser	Asn	Lys	310	Gly	Leu	Pro	Ala	315	Pro	Ile	Glu	Lys	Thr	Ile
	Ser	Lys	Thr	Lys	Gly	Gln	325	Pro	Arg	Glu	Pro	330	Gln	Val	Tyr	Thr	Leu	Pro
	Pro	Ser	Arg	Glu	Glu	Met	340	Lys	Asn	Gln	Val	345	Ser	Leu	Thr	Cys	Leu	
	Val	Lys	Gly	Phe	Tyr	Pro	355	Ser	Asp	Ile	Ala	360	Glu	Trp	Glu	Ser	Asn	
	Gly	Gln	Pro	Glu	Asn	Asn	370	Lys	Thr	Thr	Pro	375	Pro	Met	Leu	Asp	Ser	
385	Asp	Gly	Ser	Phe	Phe	Leu	390	Ser	Lys	Leu	Thr	395	Val	Asp	Lys	Ser	Arg	
	Trp	Gln	Gln	Gly	Asn	Val	405	Phe	Ser	Cys	Ser	410	Met	His	Glu	Ala	Leu	
	His	Asn	His	Tyr	Thr	Gln	420	Lys	Ser	Leu	Ser	425	Pro	Gly	Lys			
							435					440						

<210> 234

<211> 1341

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 234

gaggtgcagc	tggtgcagtc	tggtgcagtc	gtgaagaagc	ctggggcctc	agtgaaggtc	60
tcctgcaagg	cttctggatt	cgacattaag	gactactata	tacactgggt	gcgacaggcc	120
cctggacaag	ggcttgagtg	gacgggaagg	gttgatcctg	acaatgggtg	gactgaattt	180
gccccgaagt	tccccggcaa	ggtcaccatg	accacagaca	cgctccatcg	cacagcctac	240
atggagctga	gcaggctgag	atctgacgac	acggccgtgt	attactgtgc	gagagaagac	300
tacgatggta	ctacaccttg	gtttccttat	tggggccaag	ggactctggt	caccgtctct	360
agtgcctcca	ccaagggccc	atcggctctc	ccccctggcg	cctgctccag	gagcacttcc	420
gagagcacag	cggcctctgg	ctgcctgggt	aaggactact	tccccgaacc	ggtgacgggt	480
tcgtggaact	caggcgctct	gaccagcggt	gtgcacacct	tcccagctgt	cctacagtcc	540
tcaggactct	actccctcag	cagcgtgggt	accgtgccct	ccagcaactt	cggcacccag	600
acctacacct	gcaacgtaga	tcacaagccc	agcaacacca	agggtggaca	gacagttag	660
cgcaaatggt	gtgtcgagtg	cccaccgtgc	ccagcaccac	ctgtggcagg	accgtcagtc	720
tctctcttcc	ccccaaaacc	caaggacacc	ctcatgatct	cccggacccc	tgaggtcacg	780
tgctgtgtgg	tggaagtgag	ccacgaagac	cccaggtccc	agttcaactg	gtacgtggac	840
ggcgtggagg	tgcatatgac	caagacaagg	ccacgggagg	agcagttcaa	cagcacgttc	900
cgtgtgtgtca	cgtrctctac	cgttgtgcac	caggactggc	tgaacggcaa	ggagtacaag	960
tgcaaggtct	ccaacaaagg	cctcccagcc	cccatcgaga	aaacctcttc	caaaaccaaa	1020
gggcagcccc	gagaaccaca	ggtgtacacc	ctgcccccat	cccgggagga	gatgaccaag	1080
aaccaggtca	gcctgacctg	cctgggtcaa	ggcttctacc	ccagcgacat	cgccgtggag	1140
tgggagagca	atgggcagcc	ggagaacaac	tacaagacca	cacctcccat	gctggactcc	1200
gacggctcct	tcttctctta	cagcaagctc	accgtggaca	agagcagggt	gcagcagggg	1260
aacgtcttct	catgtccgtg	gatgcatgag	gctctgcaca	accactacac	gcagaagagc	1320
ctctccctgt	ctccgggtaa	a				1341

<210> 235

<211> 466

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 235

```

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala 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 Asp Ile
35 40 45
Lys Asp Tyr Trp Ile His Trp Val Arg Gln Ala Pro Gly 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 Val Thr Met Thr Thr Asp Thr Ser Ile Ser
85 90 95
Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Ala 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 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
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
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
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
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
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
385 390 395 400
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
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
450 455 460
Gly Lys
465

```

<210> 236

<211> 1398

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 236

```

atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccaactccgag 60
gtgcagctgg tgcagctctg ggctgagggt aagaagcctg gggccctcagt gaaggtctcc 120
tgcaaggctt ctgattcgaa cattaaggac tactatatac actgggtgagc acaggcccct 180
ggacaagggt ttgagttgat cggaagggtt gatcctgaca atggtgagac tgaatttgcc 240
ccgaagtctc cgggcaaggt caccatgacc acagacacgt ccatcagcac agcctacatg 300
gagctgagca ggcctgagat tgacgacacg gccgtgtatt actgtgagag agaagactac 360
gatggtaact acacctgggt tccttattgg ggccaaggga ctctggtcac cgtctctagt 420
gccctccaca agggcccacc ggtcttcccc ctggcgccct gctccaggag cactcccgag 480
agcacagcgg cctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 540
tggaactcag gcgctctgac cagcggcggt cacaccttcc cagctgtcct acagtcttca 600
ggactctact cctcagcag cgtgggtgacc gtgccctcca gcaacttcgg caccagacc 660
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 720
aaatgtttgt tcgagtgccc accgtgcccc gcaccacctg tggcaggacc gtcagtcttc 780
ctcttcccc caaaaccaca ggacaccctc atgatctccc ggaccctga ggtcacgtgc 840
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 900
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacttccgt 960
gtgtcagcgg tcctaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 1020
aaggtctcca acaaaggcct ccagccccc atcgagaaaa ccatctccaa aaccaaagg 1080
cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac 1140
caggtcagcc tgacctgcct ggtcaaggcc ttctacccca gcgacatcgc cgtggagtgg 1200
gagagcaatg gccagccgga gaacacacac ctccatgct ggactccgac 1260
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1320
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tcctgtcttc cgggtaaa
1398

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<210> 237

<211> 7

<212> PRT

<213> Mus musculus

<400> 237

Gly Thr Ser Asn Leu Ala Ser
1 5

<210> 238

<211> 8

<212> PRT

<213> Mus musculus

<400> 238

Gln Gln Trp Thr Thr Thr Tyr Thr
1 5

<210> 239

<211> 11

<212> PRT

<213> Mus musculus

<400> 239

Arg Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 240

<211> 7

<212> PRT

<213> Mus musculus

<400> 240

Ser Thr Ser Arg Leu Asn Ser
1 5

<210> 241

<211> 8

<212> PRT

<213> Mus musculus

<400> 241

Gln Gln Asp Ile Lys His Pro Thr
1 5

<210> 242

<211> 11

<212> PRT

<213> Mus musculus

<400> 242

Lys Ala Ser Gln Asp Val Phe Thr Ala Val Ala
1 5 10

<210> 243

<211> 7

<212> PRT

<213> Mus musculus

<400> 243

Trp Ala Ser Thr Arg His Thr
1 5

<210> 244

<211> 9

<212> PRT

<213> Mus musculus

<400> 244

Gln Gln Tyr Ser Ser Tyr Pro Leu Thr
1 5

<210> 245

<211> 5

<212> PRT

<213> Mus musculus

<400> 245

Asp Tyr Asn Met His
 1 5

<210> 246

<211> 17

<212> PRT

<213> Mus musculus

<400> 246

Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
 1 5 10 15
 Gly

<210> 247

<211> 14

<212> PRT

<213> Mus musculus

<400> 247

Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 1 5 10

<210> 248

<211> 5

<212> PRT

<213> Mus musculus

<400> 248

Asp Tyr Asn Met His
 1 5

<210> 249

<211> 17

<212> PRT

<213> Mus musculus

<400> 249

Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe Lys
 1 5 10 15
 Gly

<210> 250

<211> 14

<212> PRT

<213> Mus musculus

<400> 250

Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr Phe Asp Val
 1 5 10

<210> 251

<211> 5

<212> PRT

<213> Mus musculus

<400> 251

Asp Tyr Asn Met His
 1 5

<210> 252

<211> 17

<212> PRT

<213> Mus musculus

<400> 252

Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Gln Phe Lys
1 5 10 15
Gly

<210> 253

<211> 14

<212> PRT

<213> Mus musculus

<400> 253

Leu Gly Tyr Val Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
1 5 10
Gly

<210> 254

<211> 5

<212> PRT

<213> Mus musculus

<400> 254

Asp Tyr Asn Met His
1 5
Gly

<210> 255

<211> 17

<212> PRT

<213> Mus musculus

<400> 255

Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1 5 10 15
Gly

<210> 256

<211> 14

<212> PRT

<213> Mus musculus

<400> 256

Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1 5 10
Gly

<210> 257

<211> 5

<212> PRT

<213> Mus musculus

<400> 257

Asp Tyr Asn Met His
1 5
Gly

<210> 258

<211> 17

<212> PRT

<213> Mus musculus

<400> 258

Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1 5 10 15
Gly

<210> 259

<211> 14

<212> PRT

<213> Mus musculus

<400> 259

Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 1 5 10

<210> 260

<211> 5

<212> PRT

<213> Mus musculus

<400> 260

Asp Tyr Asn Met His
 1 5

<210> 261

<211> 17

<212> PRT

<213> Mus musculus

<400> 261

Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
 1 5 10 15
 Gly

<210> 262

<211> 14

<212> PRT

<213> Mus musculus

<400> 262

Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 1 5 10

<210> 263

<211> 5

<212> PRT

<213> Mus musculus

<400> 263

Asp Tyr Asn Met His
 1 5

<210> 264

<211> 17

<212> PRT

<213> Mus musculus

<400> 264

Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe Lys
 1 5 10 15
 Gly

<210> 265

<211> 14

<212> PRT

<213> Mus musculus

<400> 265

Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
 1 5 10

<210> 266

<211> 5

<212> PRT

<213> Mus musculus

<400> 266

Asp Tyr Tyr Ile His
 1 5

<210> 267

<211> 17

<212> PRT

<213> Mus musculus

<400> 267

Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val Pro Lys Phe Gln
 1 5 10 15
 Gly

<210> 268

<211> 13

<212> PRT

<213> Mus musculus

<400> 268

Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val Asp Tyr
 1 5 10
 Gly

<210> 269

<211> 5

<212> PRT

<213> Mus musculus

<400> 269

Asp Tyr Ile Met His
 1 5
 Gly

<210> 270

<211> 17

<212> PRT

<213> Mus musculus

<400> 270

Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe Lys
 1 5 10 15
 Gly

<210> 271

<211> 11

<212> PRT

<213> Mus musculus

<400> 271

Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
 1 5 10
 Gly

<210> 272

<211> 5

<212> PRT

<213> Mus musculus

<400> 272

Asp Tyr Tyr Met His
 1 5
 Gly

1 5
 Gly

<210> 273

<211> 17

<212> PRT

<213> Mus musculus

<400> 273

Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe Gln
 1 5 10 15
 Gly

<210> 274

<211> 10

<212> PRT

<213> Mus musculus

<400> 274

Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr
1 5 10

<210> 275

<211> 10

<212> PRT

<213> Mus musculus

<400> 275

Arg Ala Ser Ser Ser Val Tyr Tyr Met His
1 5 10

<210> 276

<211> 7

<212> PRT

<213> Mus musculus

<400> 276

Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 277

<211> 9

<212> PRT

<213> Mus musculus

<400> 277

Gln Gln Trp Ser Ser Asp Pro Leu Thr
1 5

<210> 278

<211> 12

<212> PRT

<213> Mus musculus

<400> 278

Ser Val Ser Ser Thr Ile Ser Ser Asn His Leu His
1 5 10

<210> 279

<211> 7

<212> PRT

<213> Mus musculus

<400> 279

Gly Thr Ser Asn Leu Ala Ser
1 5

<210> 280

<211> 9

<212> PRT

<213> Mus musculus

<400> 280

Gln Gln Trp Ser Ser Tyr Pro Leu Thr
1 5

<210> 281

<211> 10

<212> PRT

<213> Mus musculus

<400> 281

Arg Ala Ser Ser Ser Ile Ser Tyr Ile His
1 5 10

<210> 282

<211> 7

<212> PRT

<213> Mus musculus

<400> 282

Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 283

<211> 9

<212> PRT

<213> Mus musculus

<400> 283

Gln Gln Trp Ser Ser Asp Pro Leu Thr
1 5

<210> 284

<211> 12

<212> PRT

<213> Mus musculus

<400> 284

Arg Ala Ser Ser Ser Val Thr Ser Ser Tyr Leu Asn
1 5 10

<210> 285

<211> 7

<212> PRT

<213> Mus musculus

<400> 285

Ser Thr Ser Asn Leu Ala Ser
1 5

<210> 286

<211> 9

<212> PRT

<213> Mus musculus

<400> 286

Gln Gln Tyr Asp Phe Phe Pro Ser Thr
1 5

<210> 287

<211> 5

<212> PRT

<213> Mus musculus

<400> 287

Asp Tyr Phe Ile His
1 5

<210> 288

<211> 17

<212> PRT

<213> Mus musculus

<400> 288

Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala Pro Lys Phe Gln
1 5 10 15
Asp

<210> 289

<211> 12

<212> PRT

<213> Mus musculus

<400> 289

Glu Asp Tyr Asp Gly Thr Tyr Thr Phe Phe Pro Tyr
 1 5 10

<210> 290

<211> 5

<212> PRT

<213> Mus musculus

<400> 290

Asp Phe Tyr Leu His
 1 5

<210> 291

<211> 17

<212> PRT

<213> Mus musculus

<400> 291

Arg Ile Asp Pro Gly Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe Gln
 1 5 10 15
 Asp

<210> 292

<211> 16

<212> PRT

<213> Mus musculus

<400> 292

Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe Asp Val
 1 5 10 15

<210> 293

<211> 5

<212> PRT

<213> Mus musculus

<400> 293

Asp Tyr Tyr Ile His
 1 5

<210> 294

<211> 17

<212> PRT

<213> Mus musculus

<400> 294

Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe Pro
 1 5 10 15
 Gly

<210> 295

<211> 12

<212> PRT

<213> Mus musculus

<400> 295

Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr
 1 5 10

<210> 296

<211> 5

<212> PRT

<213> Mus musculus

<400> 296

Asp Tyr Tyr Met Asn
1 5

<210> 297

<211> 17

<212> PRT

<213> Mus musculus

<400> 297

Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe Lys
1 5 10 15
Gly

<210> 298

<211> 11

<212> PRT

<213> Mus musculus

<400> 298

Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp
1 5 10

<210> 299

<211> 130

<212> PRT

<213> Mus musculus

<400> 299

Met Asp Phe Gln Val Gln Ile Phe Ser Phe Met Leu Ile Ser Val Thr
1 5 10 15
Val Ile Leu Ser Ser Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Leu
20 25 30
Met Ala Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Val Ser
35 40 45
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
100 105 110
Gln Trp Thr Thr Thr Tyr Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu
115 120 125
Lys Arg
130

<210> 300

<211> 390

<212> DNA

<213> Mus musculus

<400> 300

atggattttc aggtgcagat tttcagcttc atgctaataca gtgtcacagt catattgtcc 60
agtggagaaa ttgtgctcac ccagtctcca gactcatgg ctgcatctcc aggggagaag 120
gtcaccatca cctgcagtgt cagctcgagt ataagttcca gcaacttaca ctggtccag 180
cagaagtcag gaacctccc caaactctgg atttatggca catccaacct tgcttctgga 240
gtccctgttc gcttcagtgg cagtggatct gggacctctt attctctcac aatcagcagc 300
atggaggctg aagatgctgc cacttattac tgtcaacagt ggactactac gtatacgttc 360
ggatcgggga 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 Trp 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

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atgggatgga actggatcat ctcttcctg atggcagtg ttacaggggt caattcagag 60
gtgcagttgc ggcagtcctg ggcagacct gtgaagccag gggcctcagt caagttgtcc 120
tgacacagctt ctggcttcaa cattaaagac tactatatac actgggtgaa gcagaggcct 180
gaacagggcc tggagtggat tggaggaggt gatcctgata atgggtgaaag tacatatgtc 240
ccgaagtcc agggcaaggc cactataaca gcagacacat catccaacac agcctaccta 300
caactcagaa gcctgacatc tggagacact gccatctatt attgtgggag agaggggctc 360
gactatggtg actactatgc tgtggactac tggggtaag gaacctcggg cacagtctcg 420
aggc
423

```

<210> 303

<211> 130

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 303

```

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly 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 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

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atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gccgggctcg 60
cgctgcgata ttcagctgac ccagagcccg agctttctga gcgcgagcgt gggcgatcgc 120
gtgaccatta cctgcagcgt gagcagcagc attagcagca gcaacctgca ttggtatcag 180
cagaaaccgg gcaaacgccc gaaactgctg atttatggca ccagcaacct ggcgagcggc 240
gtgccgagcc gctttagcgg cagcggcagc ggcaccgaat ttacctgac cattagcagc 300
ctgcagccgg aagattttgc gacctattat tgccagcagt ggaccaccac ctatactttt 360
ggccagggca ccaactgga aattaaactg
390

```

<210> 305

<211> 141

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 305

```

Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Pro Thr Gly
 1      5      10
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 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
Pro Lys Phe Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
 80     85     90
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

```

<210> 306

<211> 423

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 306

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atggattgga cctggagcat tctgtttctg gtggcggcgc cgaccggcgc gcatagcgaa 60
gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc 120
tgcaaaagcga gcggctttaa cattaaagat tattatattc attgggtgcg ccaggcgccg 180
ggccaggggcc tgggaatggat gggccgcatt gatccggata acggcgaaag caccctatgtg 240
ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg 300
gaactcgca gcctgcgcag cgatgatacc gcggtgtatt attgcgcgcg cgaaggcctg 360
gattatggcg attattatgc ggtggattat tggggccagg gcaccctggt gaccgtctcg 423
agc

```

<210> 307

<211> 127

<212> PRT

<213> Mus musculus

<400> 307

```

Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
 1      5      10
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
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser
 80     85     90
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 ctgtcagtt ccttgggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcaac 120
atcagctgca gggcaagtca ggacattagc agttatttaa actggtatca gcagaaacca 180
gatggaaactg ttaactcctc gatctactcc acatcaagat taaactcagg agtcccatca 240
aggttcagtg gcagtgggtc tgggacagat tattctctca ctattagcaa cctggcacaa 300
gaagatatgt ccacttactt ttgccaacag gatattaagc atccgacgtt cgggtggaggc 360
accaagttgg agctgaaacg t

```

<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

<400> 310

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atggaatgga tctggatatt tctcttcctc ctgtcaggaa ctgcagggtg ccactctgag 60
gtccagctgc agcagctctgg acctgagctg gtaaaagctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctgggttcac attcactgac tacattatgc actgggtgaa gcagaagcct 180
gggcagggcc ttgagtggat tggatatatt aatccttaca atgatgatac tgaatacaat 240
gagaagttca aaggcaaggc cacactgact tcagacaaat cctccagcac agcctacatg 300
gatctcagca gtctgacctc tgagggtctt gcggtctatt actgtgcaag atcgatttat 360
tactacgatg ccccgtttgc ttactggggc caagggactc tggtcacagt ctcgagc 417

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<210> 311

<211> 127

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 311

```

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
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

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
Lys His Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
115      120      125

```

<210> 312

<211> 381

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 312

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atgatgtcct ctgctcagtt ccttggtctc ctggtgctct gttttcaagg taccagatgt 60
gatatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtagggtg ccgtgtcacc 120
atcacttgcc gcgcaagtc ggatattagc agctatttaa attggtatca gcagaaacca 180
gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca 240
cgcttcagtg gcagtyggctc tgggacagat ttcaacttca ccatcagcag tctgcaacct 300
gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cgtcaaggc 360
accaaggtgg agatcaaacg t
381

```

<210> 313

<211> 139

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<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
Glu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser
 80      85      90
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

```

<210> 314

<211> 107

<212> PRT

<213> Mus musculus

<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
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile Lys His Pro Thr
 80      85      90
Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg
100      105

```

<210> 315

<211> 128

<212> PRT

<213> Mus musculus

<400> 315

```

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
Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
 80      85      90
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 cttgtatcac atgttgctgt ggttgctctg tgttgaagga 60
gacattgtga tgaccagtc tcacaaattc atgtccacgt cagtaggaga cagggtcacc 120
atcaccctgca aggcagtcga ggatgtcttt actgctgtag cctggtatca acagaaacca 180
ggacaattctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccctgat 240
cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct 300
gaagacttgg cagattattt ctgtcaacaa tatagcagct atccctctac 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 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

<212> DNA

<213> Mus musculus

<400> 318

```

atgggatgga actggatcat cttcttcctg atggcagtgg ttacaggggt caattcagag 60
gttcagctgc agcagctctgg ggctgagcct gtgaggccag gggccttagt caagttgtcc 120
tgcaaaagctt ctggcttcaa tattaaagac tactatatgc actgggtgaa gcagaggcct 180
gaacagggcc tggagtggat tggaaaggatt gatcctgaga atggtgatat tatatatgac 240
ccgaagtcc agggcaaggc cagtataaca acagacacat cctccaacac agcctacctg 300
cagctcagca gctgacgtc tgaggacact gccgtctatt actgtgctta cgtgctggt 360
gaccccgctt ggtttactta ctggggccaa gggactctgg tcaccgtctc g 411

```

<210> 319

<211> 130

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 319

```

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly 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

```

<210> 320

<211> 390

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 320

```

atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gcgcggcgcg 60
cgctgcgata tccagatgac ccagagcccg agcagcctga gcgcgagcgt gggcgatcgc 120
gtgaccatta cctgcaaagc gagccaggat gtgtttaccg cggtggcggtg gtatcagcag 180
aaaccgggca aagcgccgaa actgctgatt tattggcgga gcaccggcca taccggcggtg 240
ccagtcgctc tttagcggcag cggcagcggc accgatttta ccctgacct tagcagcctg 300
cagccggaag attttgcgac ctattattgc cagcagtata gcagctatcc gctgaccttt 360
ggcggcgga ccaaagtga aattaaacgt

```

<210> 321

<211> 138

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 321

```

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

```

<210> 322

<211> 414

<212> DNA

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 322

```

atggattgga cctggagcat tctgtttctg gtggcggcgc cgaccggcgc gcatagcgaa 60
gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc 120
tgcaaaagcga cgggcttttaa cattaagat tattatatgc attgggtgcg ccaggcgccg 180
ggccagggcc tggaaatgat cggccgcatt gatccggaaa acggcgatat tatttatgat 240
ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg 300
gaactgcgca gcctgcgcag cgatgatacc gcggtgtatt attgcgcgta tgatgcgggc 360
gatccgcgt ggttacctt ttggggccag ggcaccctgg tgaccgtctc gagc 414

```

<210> 323

<211> 106

<212> PRT

<213> Mus musculus

<400> 323

```

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
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
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

```

<210> 324

<211> 324

<212> PRT

<213> Mus musculus

<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
 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
 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 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
 Ser Pro Gly Lys

<210> 325

<211> 106

<212> PRT

<213> Homo sapiens

<400> 325

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1 5 10 15
 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
 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

<210> 326

<211> 327

<212> PRT

<213> Homo sapiens

<400> 326

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
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 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
 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
 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
 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
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
 225 230 235 240
 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
 Thr Thr 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
 305 310 315 320
 Leu Ser Leu Ser Leu Gly Lys 325

<210> 327

<211> 120

<212> PRT

<213> Mus musculus

<400> 327

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 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
 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
 Gly Thr Leu Val Thr Val Ser Ser 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 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
 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
 Gly Thr Leu Val Thr Val Ser Ser 120

<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 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
Gly Thr Leu Val Thr Val Ser Ser
115      120

```

<210> 330

<211> 226

<212> PRT

<213> Mus musculus

<400> 330

```

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 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
Gly Thr Leu Val Thr Val Ser Ser Thr Val Ala Ala Pro Ser Val Phe
115      120      125
Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
130      135      140
Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
145      150      155      160
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
165      170      175
Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
180      185      190
Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
195      200      205
Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
210      215      220
Glu Cys
225

```

<210> 331

<211> 447

<212> PRT

<213> Mus musculus

<400> 331

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 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 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
 Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly 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 Gln 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 Tyr Arg Val Val Ser
 290 295 300

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
 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
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 395 400
 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
 420 425 430 435
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
 440 445

<210> 332

<211> 107

<212> PRT

<213> Mus musculus

<400> 332

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 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

<210> 333

<211> 324

<212> PRT

<213> Mus musculus

<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      145
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
150      155      160

```

```

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
210

```

<210> 335

<211> 444

<212> PRT

<213> Mus musculus

<400> 335

```

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
 Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
 Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
 Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
 Met Asp Leu Ser Ser Leu Thr Ser Glu Gly Ser Ala Val Tyr Tyr Cys
 Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr 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 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 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 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 Ala Gln Thr Gln Pro
 Arg Glu 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 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 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 Ser
 Tyr Phe Val 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 His
 His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys

<210> 336

<211> 108

<212> PRT

<213> Mus musculus

<400> 336

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Phe Thr Ala
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Leu
 Thr Phe Gly Gly Thr Lys Val Glu Ile Lys Arg

<210> 337

<211> 324

<212> DNA

<213> Mus musculus

<400> 337

gatattccaga tgaccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60
 attacctgca aagcgagcca ggatgtgtt accgcggtgg cgtggtatca gcagaaaccg 120
 ggcaaagcgc cgaaactgct gatttattgg gcgagcacc ccataaccgg cgtgccgagt 180
 cgcttttagcg gcagcggcag cggcaccgat ttaccctga ccattagcag cctgcagccg 240
 gaagattttg cgacctatta ttgccagcag tatagcagct atccgctgac ctttggcggc 300
 ggcaccaaag tggaaattaa acgt

<210> 338

<211> 119

<212> PRT

<213> Mus musculus

<400> 338

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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 Phe Asn Ile Lys Asp Tyr
 20     25     30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu 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

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<210> 339

<211> 357

<212> DNA

<213> Mus musculus

<400> 339

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gaagtgcagc ttgtgcagag cggcgcgga gtgaaaaaac cggcgcgag cgtgaaagt 60
agctgcaaa cgagcggctt taacattaaa gattattata tgcattgggt gcgccaggcg 120
ccgggccagg gcttgggaat gatcggccgc attgatccgg aaaacggcga tattatttat 180
gatccgaaat ttcaggggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat 240
atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gtatgatgcg 300
ggcgatccgg cgtgttttac ctattggggc cagggcaccc ttgtgacctg ctcgagc 357

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<210> 340

<211> 1395

<212> DNA

<213> Mus musculus

<400> 340

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atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc cactccgag 60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc 120

```

```

tgcaaggctt ctggttttac cttaccgcac tatattatgc actgggtgctg tcaggccccc 180
gggtcaaggc ttgagtgagt gggctatatc aacccttata atgatgacac cgaatacaac 240
gagaagtcca agggcgtgt cagcattacc gcggacaaat ccacgagcac agcctacatg 300
gagctgagca gcttgcgttc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat 360
tactacgatg cccgttttgc ttactggggc caagggactc ttgtcaccgt ctctagtgcc 420
tccaccaagg gcccatcggt cttccccctg gcgccctgct ccaggagcac ctccgagagc 480
acagcggccc tgggtgcctt ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 540
aactcaggcg ctctgaccag cggcgtgcac accttcccag ctgtcttaca gtcttcagga 600
cttactccc tcagcagcgt ggtgacctgt ccttccagca acttcggcac ccagacctac 660
acctgcaacg tagatcacaa gccacgcaac accaaggctg acaagacagt tgagcgcaaa 720
tgttgtgtcg agtgcccacc gtgcccagca ccacctgtgg caggaccgtc agtcttcttc 780
ttcccccaa aacccaagga caccctcatg atctccccga ccctgaggt cactgtcgtg 840
gtggtggagc tgagccacga agaccccgag gtccagtcca actggtacgt ggacggcggtg 900
gaggtgcata atgccaagac aaagccacgg gaggagcagt tcaacagcac gttccgtgtg 960
gtcagcgtcc tcaccgttgt gcaccaggac tggctgaacg gcaaggagta caagtgaag 1020
gtctccaaca aaggcctccc agcccccatc gagaaaacca tctccaaaac caaagggcag 1080
ccccgagaac cacaggtgta caccctgccc ccattcccgg aggagatgac caagaaccag 1140
gtcagcctga cctgcttgtt caaaggcttc taccacagcg acatcgccgt ggagtgggag 1200
agcaatgggc agccggagaa caactacaag accacacctc ccatgctgga ctccgacggc 1260
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1320
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ctgtctccgg gtaaa
1395

```

<210> 341

<211> 213

<211> PRT

<213> Mus musculus

<400> 341

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 Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys 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
 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

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtag ccgtgtcacc 60
 atcacttgcc gcgcaagtc ggatattagc agctatttaa attggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtag ggtcccatca 180

cgcttcagtg gcagtggttc tgggacagat ttcactctca ccatacagcag tctgcaacct 240
 gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtaaggc 300
 accaaggtgg agatcaaacg tacggtggct gcaccatctg tcttcatctt cccgcatct 360
 gatgagcagt tgaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
 agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480
 agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540
 agcaagcag actacgagaa acacaaagtc tacgcctgag aagtcaccca tcagggcctg 600
 agctcgcccc tcacaaagag ctccaacagg ggagagtgt 639

<210> 343

<231> 235

<212> PRT

<213> Mus musculus

<400> 343

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly 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 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 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 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> 344

<211> 705

<212> DNA

<213> Mus musculus

<400> 344

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atggacatga ggggtgccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcc 60
agatgtgaca tccagatgac ccagtcctca tcctccctgt ctgcatctgt aggtgaccgt 120
gtcaccatca cttgccgcgc aagtcaggat attagcagct atttaaattg gtatcagcag 180
aaaccaggga aagcccttaa gctcctgac tattctactt cccgtttgaa tagtggggtc 240
ccatcacgct tcagtggcag tggctctggg acagatttca ctctcaccat cagcagtcctg 300
caacctgaag attttgcaac ttactactgt caacaggata ttaaacaccc tacgttcggt 360
caaggcacca aggtggagat caaacgtacy gtggctgcac catctgtctt catcttccc 420
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtcctgtct gaataacttc 480
tatccagag aggccaaagt acagtggaa gtggataacg ccctccaatc gggttaactcc 540
caggagagtg tcacagagca ggacagcaag gacagcacct acagctcag cagcaccctg 600
acgtgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 660
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 705

```

<210> 345

<211> 446

<212> PRT

<213> Mus musculus

<400> 345

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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 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
340 345 350
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
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 Lys
435 440 445

```

<210> 346

<211> 1338

<212> DNA

<213> Mus musculus

<400> 346

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gaggtgcagc tgggtcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggttt taccttcacc gactatatta tgcactgggt gcgtcaggcc 120
cctggtcaag ggcttgagtg gatgggctat atcaaccctt ataattgatg caccgaatac 180
aacgagaagt tcaaggccg tgtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgct ctctgaggac acggccgtgt attactgtgc gcgttcgatt 300
tattactacg atgccccgtt tgcttactgg ggccaaggga ctctggtcac cgtctctagt 360
gctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cactcccgag 420
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggg gacgggtctg 480
tggaaactag gcgctctgac cagcggcggt caccacttcc cagctgtcct acagtctcca 540
ggactctact ccctcagcag cgtgggtacc gtgcctcca gcaacttcgg caccagacc 600
tacacctgca acgtagatca caagccagc aacaccaagg tggacaagac agttgagcgc 660
aaatgttgtg tcgagtgccc accgtgcccc gcaccacctg tggcaggacc gtcagtcttc 720
ctcttcccc caaaacccaa ggacacccct atgatctccc ggacctctga ggtcacgtgc 780
gtggtgggtg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 840
gtggagggtg ataattgcaa gacaaagcca cyggaggagc agttcaacag cactgtccgt 900
gtggtcagcg tcttcaccgt tcttcaccgt gactggctga acggcaagga gtacaagtgc 960
aaggtctcca acaaaaggct cccagccccc atcgagaaaa ccatctccaa aaccaagggt 1020
cagcccgag aaccacagtg gtacacccct ccccatccc gggaggagat gaccaagaac 1080
caggtcagcc tgacctgcct ggtcaaaagg ttctacccca gcgacatcgc cgtggagtgg 1140
gagagcaatg ggacgcgga gaacaaactac aagaccacac ctcccatgct ggactccgac 1200
ggctctctct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
tcctgtcttc cgggtaaa 1338

```

<210> 347

<211> 465

<212> PRT

<213> Mus musculus

<400> 347

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Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala 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     35
Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
40     45     50     55
Thr Asp Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
60     65     70     75
Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn
80     85     90     95
Glu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser
100    105    110    115
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
120    125    130    135
Tyr Tyr Cys Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
140    145    150    155
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
160    165    170    175
Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
180    185    190    195
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
200    205    210    215
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
220    225    230    235
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
240    245    250    255
Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
260    265    270    275
Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
280    285    290    295
Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
300    305    310    315
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
320    325    330    335
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
340    345    350    355
Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
360    365    370    375
Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
380    385    390    395
Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
400    405    410    415
Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
420    425    430    435
Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
440    445    450    455
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
460    465    470    475
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
480    485    490    495
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
500    505    510    515
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
520    525    530    535
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
540    545    550    555
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
560    565    570    575
Lys
580
465

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<210> 348

<211> 1395

<212> DNA

<213> Mus musculus

<400> 348

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atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60
gtgcagctgg tgcagtcctg ggctgaggtg aagaagcctg ggtcctcggg gaaggtctcc 120
tgcaaggctt ctgggttttac cttcaccgac tatattatgc actgggtgcg tcaggccctc 180
gggcaagggc ttgagtggtat gggctatatc aacccttata atgatgacac cgaatacaac 240
gagaagttca agggccgtgt caccgattacc gcggacaaat ccacgagcac agcctacatg 300
gagctgagca gctcgcgttc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat 360
tactacgatg ccccgcttgc ttactggggc caagggactc tggtcaccgt ctctagtgcc 420
tccaccaagg gcccatcggt cttccccctg gcgccctgct ccaggagcac ctccgagagc 480
acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 540
aactcaggcg ctctgaccag cggcgtgcac accctccag ctgtcctaca gtcctcagga 600
ctctactccc tcagcagcgt ggtgaccgtg cctccagca acttcggcac ccagacctac 660
acctgcaacg tagatcaca gccccagcaac accaaggtgg acaagacagt tgagcgcaaa 720
tggtgtgtcg agtgcccacc gtgccagca ccactgtgg caggaccgtc agtcttcctc 780
ttcccccaa aacccaagga caccctcatg atctcccgga cctctgaggt cactgtcggtg 840
gtggtggagc tgagccacga agaccccag gtccagtcca actggtacgt ggacggcggtg 900
gaggtgcata atgccaagac aaagccacgg gagggagcag tcaacagcac gttccgtgtg 960
gtcagcttcc tcaccgttgt gcaccaggag tggctgaacg gcaaggagta caagtgcag 1020
gtctccaaca aaggcctccc agcccccatt gagaaaacca tctccaaaac caaagggcag 1080
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag 1140
gtcagctctg cctgcctggt caaaggcttc tacccagcg acatcgccgt ggagtgaggag 1200
agcaatgggc agccggagaa caactacaag accacacctc ccatgtcggg ctccgacggc 1260
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1320
ttctcatgct cgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1380
ctgtctccg gtaaa 1395

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<210> 349

<211> 417

<212> DNA

<213> Mus musculus

<400> 349

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gtgcagctgg tgcagtcctg ggctgaggtg aagaagcctg ggtcctcggg gaaggtctcc 120
tgcaaggctt ctgggttttac cttcaccgac tatattatgc actgggtgcg tcaggccctc 180
gggcaagggc ttgagtggtat gggctatatc aacccttata atgatgacac cgaatacaac 240
gagaagttca agggccgtgt caccgattacc gcggacaaat ccacgagcac agcctacatg 300
gagctgagca gctcgcgttc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat 360
tactacgatg ccccgcttgc ttactggggc caagggactc tggtcacagt ctccgagc 417

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<210> 350

<211> 218

<212> PRT

<213> Mus musculus

<400> 350

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Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ala Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20     25     30     35
Gly Thr Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
40     45     50     55
Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Glu Ile Pro Ala
60     65     70     75
Arg Phe Ser Gly Thr Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
80     85     90     95
Pro Val Glu Glu Glu Asp Ile Thr Thr Tyr Tyr Cys Gln Gln Ser Asn
100    105    110    115
Glu Asp Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
120    125    130    135
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
140    145    150    155
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
160    165    170    175
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
180    185    190    195
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
200    205    210
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
215

```

<210> 351

<211> 15

<212> PRT

<213> Mus musculus

<400> 351

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Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Thr Ser Tyr Met Asn
1      5      10      15

```

<210> 352

<211> 7

<212> PRT

<213> Mus musculus

<400> 352

Ala Ala Ser Asn Leu Glu Ser
1 5

<210> 353

<211> 9

<212> PRT

<213> Mus musculus

<400> 353

Gln Gln Ser Asn Glu Asp Pro Phe Thr
1 5

<210> 354

<211> 657

<212> DNA

<213> Mus musculus

<400> 354

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atcgccctgca aggccagcca aagtgttgat tatgatggta ctagtatat gaattggtac 120
caacagaaac caggacagcc acccaaatc ctcactctat ctgcatccaa tctagaatct 180
gagatcccag ccaggttttag tggcactggg tctgggacag acttcaccct caacatccat 240
cctgtggagg agggagatat cacaaacctat tactgtcagc aaagtaatga ggatccgttc 300
acgttcggag gggggaccaa gttggaata aaacgggctg atgctgcacc aactgtatcc 360
atcttccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420
aacaacttct accccaaga catcaatgtc aagtggaaaga ttgatggcag tgaacgacaa 480
aatggctcc tgaacagttg gactgatcag gacagcaaa acagcaccta cagcatgagc 540
agcacctcca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600
actcacaaga catcaacttc acccatgtgc aagagcttca acaggaatga gtgttag 657

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<210> 355

<211> 238

<212> PRT

<213> Mus musculus

<400> 355

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Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15
Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
20 25 30
Val Ser Leu Gly Gln Arg Ala Thr Ile Ala Cys Lys Ala Ser Gln Ser
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 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 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 Ser Thr Leu Thr Leu Thr Lys Asp
195 200 205
Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr
210 215 220
Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230 235

```

<210> 356

<211> 717

<212> DNA

<213> Mus musculus

<400> 356

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atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60
gacattgtgt tgaccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 120
atcgccctgca aggccagcca aagtgttgat tatgatggta ctagtatat gaattggtac 180
caacagaaac caggacagcc acccaaatc ctcactctat ctgcatccaa tctagaatct 240
gagatcccag ccaggttttag tggcactggg tctgggacag acttcaccct caacatccat 300
cctgtggagg agggagatat cacaaacctat tactgtcagc aaagtaatga ggatccgttc 360
acgttcggag gggggaccaa gttggaata aaacgggctg atgctgcacc aactgtatcc 420

```

```

atcttccac catccagtga gcagttaaca tctggagggtg cctcagtcgt gtgcttcttg 480
aacaacttct accccaaga catcaatgtc aagtgggaaga ttgatggcag tgaacgacaa 540
aatggcgctcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 600
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 660
actcacaaga catcaacttc acccatgttc aagagcttca acaggaatga gtgttag 717

```

<210> 357

<211> 442

<212> PRT

<213> Mus musculus

<400> 357

```

Gln Val Gln Leu Gln Gln Pro Gly Thr Glu Leu Val Arg Pro Gly Thr
1      5      10      15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Thr Tyr
20      25      30
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Leu Asp Lys Ser Ser Thr Ala Tyr
65      70      75
Met His Leu Ser Gly Pro Thr Ser Val Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Ser Gly Glu Trp Gly Ser Met Asp Tyr Trp Gly Gln Gly Thr
100     105     110
Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro
115     120     125
Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly
130     135     140
Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn
145     150     155
Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165     170     175
Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr
180     185     190
Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser
195     200     205
Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro
210     215     220
Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro
225     230     235
Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys
245     250     255
Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp
260     265     270
Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu
275     280     285
Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met
290     295     300
His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser
305     310     315
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
Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu
370     375     380
Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe
385     390     395
Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn
400     405     410
Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr
415     420     425
Glu Lys Ser Leu Ser His Ser Pro Gly Lys
435     440

```

<210> 358

<211> 5

<212> PRT

<213> Mus musculus

<400> 358

```

Thr Tyr Trp Met Asn
1      5

```

<210> 359

<211> 17

<212> PRT

<213> Mus musculus

<400> 359

```

Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp Gln Lys Phe Lys
1      5      10      15
Asp

```

<210> 360

<211> 9

<212> PRT

<213> Mus musculus

<400> 360

Ser Gly Glu Trp Gly Ser Met Asp Tyr
 1 5

<210> 361

<211> 1329

<212> DNA

<213> Mus musculus

<400> 361

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cagggtccaac tacagcagcc tgggactgag ctggtgaggg ctggaacttc agtgaagttg 60
tcctgtaagg cttctggcta catcttcacc acctactgga tgaactgggt gaaacagagg 120
cctggacaag gccttgagtg gattggcatg attcatcctt ccgcaagtga aattaggttg 180
gatcagaaat tcaaggacaa ggccacattg actcttgaca aatcctccag cacagcctat 240
atgcacctca gcggcccgaac atctgtggat tctgcggtct attactgtgc aagatcaggg 300
gaatgggggt ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctcagccaaa 360
acgacacccc catctgtcta tccactggcc cctggatctg ctgccc aaac taactccatg 420
gtgacccctg gatgctgggt caagggttat ttccctgagc cagtgcagat gacctggaac 480
tctggatccc tgtccagcgg tgtgcacacc ttcccgatg tcctgcagtc tgacctctac 540
actctgagca gctcagtgac tgtccctccc agcacctggc ccagcgagac cgtcacctgc 600
aacgttgccc acccgccag cagcaccaag gtggacaaga aaattgtgcc cagggtattg 660
gggtgtaagc ctgcatatg tacagtccca gaagtatcat ctgtcttcat cttcccccca 720
aagcccaagg atgtgtcac cattactctg actcctaagg tcacgtgtgt tgtggtagac 780
atcagcaagg atgattccga ggtccagttc agctggtttg tagatgatgt ggaggtgcac 840
acagctcaga cgacaccccg ggaggagcag ttcaacagca ctttccgctc agtcagtgaa 900
cttcccatca tgcaccagga ctggctcaat ggcaaggagt tcaaatgcag ggtcaacagt 960
gcagctttcc ctgcccccat cgagaaaacc atctccaaaa ccaaggcgag accgaaggct 1020
ccacaggtgt acactattcc acctcccaag gagcagatgg ccaaggataa agtcagtctg 1080
acctgcatga taacagactt cttccctgaa gacattactg tggagtgcca gtggaatggg 1140
cagccagcgg agaactacaa gaacactcag cccatcatgg acacagatgg ctcttacttc 1200
atctacagca agctcaatgt gcagaagagc aactgggagg caggaaatac tttcacctgc 1260
tctgtgttac atgagggcct gcacaaccac catactgaga agagcctctc ccactctcct 1320
ggtaaatga

```

<210> 362

<211> 461

<212> PRT

<213> Mus musculus

<400> 362

Met Gly Trp Ser Ser Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
 1 5 10 15
 Val His Ser Gln Val Gln Leu Gln Gln Pro Gly Thr Glu Leu Val Arg
 20 25 30
 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
 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
 Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser
 130 135 140
 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
 Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
 180 185 190
 Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
 195 200 205
 Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
 210 215 220
 Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
 225 230 235 240
 Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
 245 250 255
 Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
 260 265 270
 Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
 275 280 285
 Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
 290 295 300
 Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
 305 310 315 320
 Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
 325 330 335
 Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 340 345 350
 Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
 355 360 365
 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
 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
 435 440 445
 His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
 450 455 460

<210> 363

<211> 1386

<212> DNA

<213> Mus musculus

<400> 363

atgggatgga gctctatcat cctcttcttg gtagcaacag ctacaggtgt ccactcccag 60
 gtccaactac agcagcctgg gactgagctg gtgaggcctg gaacttcagt gaagttgtcc 120
 tgaaggcttt ctggctacat cttcaccacc tactggatga actgggtgaa acagaggcct 180
 ggacaaggcc ttgagtggat tggcatgatt catccttcgg caagtgaat taggttggat 240
 cagaaattca aggaagaagg caccattgact ctgacaaat cctccagcac agcctatatg 300
 cactcagcgg gcccgacatc tgtggattct gcggtctatt actgtgcaag atcaggggaa 360
 tgggggtcta tggactactg gggtaagga acctcagtc cgtctcctc agccaaaacg 420
 acactcccat ctgtctatcc actggcccct ggatctgctg cccaaactaa ctccatgggt 480
 acctggggat gcttggtcaa gggctatttc cctgagccag tgacagtgaac ctggaactct 540
 ggatccctgt ccagggtgtg gcacaccctc ccagctgtcc tgacagtga cctctacact 600
 ctgagcagct cagtactgt cccctccagc acctggccca gcgagaccgt cacctgcaac 660
 gttgcccacc cggccagcag caccaagggt gacaagaaa ttgtgcccag ggattgtgtg 720
 tgaagcctt gcatatgtac agtcccagaa gtatcatctg tcttcatct cccccaaag 780
 cccaaggatg tgcctacat tactctgact cctaagggtc cgtgtgtgt ggtgacacac 840
 agcaaggatg atcctgaggt ccagttcagc tggttgttag atgatgtgga ggtgcacaca 900
 gctcagacgc aaccccgga ggagcagttc aacagcactt tccgtcagt cagtgaactt 960
 cccatcatgc accaggactg gctcaatggc aaggagtcca aatgcagggt caacagtga 1020
 gctttccctg ccccatcga gaaaaccatc tccaaaacca aaggcagacc gaaggctcca 1080
 cagggtgaca ccattccacc tcccaaggag cagatggcca aggataaagt cagtctgacc 1140
 tgcagataaa cagacttctt ccctgaagac attactgtgg agtggcagtg gaatgggcag 1200
 ccagcggaga actacaagaa cactcagccc atcatggaca cagatggctc ttacttcac 1260
 tacagcaagc tcaatgtgca gaagagcaac tgggaggcag gaaatacttt cacctgtctc 1320
 gtgttacatg agggcctgca caaccaccat actgagaaga gcctctccca ctctcctggt 1386
 aaatga

<210> 364

<211> 106

<212> PRT

<213> Mus musculus

<400> 364

```

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 Ser Tyr
20      25      30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys 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
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
100      105

```

<210> 365

<211> 318

<212> DNA

<213> Mus musculus

<400> 365

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gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gcgcaagtc ggatattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctct gatctattct acttcccgtt tgaatagtg ggtcccatca 180
cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtaagggc 300
accaggttg agatcaaa 318

```

<210> 366

<211> 120

<212> PRT

<213> Mus musculus

<400> 366

```

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
Gly Thr Leu Val Thr Val Ser Ser
115      120

```

<210> 367

<211> 360

<212> DNA

<213> Mus musculus

<400> 367

```

gaggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tctgcaagg ctctgggtt taccttcacc gactatatta tgcactgggt gcgtcaggcc 120
ctgggtcaag ggcttgagtg gatgggctat atcaaccctt ataagatga caccgaatac 180
aacgagaagt tcaagggccg tgtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgcg ctctgaggac acggccgtgt attactgtgc gcgttcgatt 300
tattactacg atgccccgtt tgcttactgg ggccaaggga ctctgggtcac cgtctctagt 360

```

<210> 368

<211> 108

<212> PRT

<213> Mus musculus

<400> 368

```

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> 369
 <211> 324
 <212> DNA
 <213> Mus musculus

<400> 369
 gataatccaga tgaccacagag cccgagcagc ctgagcgcga gcgtgggcca tcgctgacc 60
 attacctgca aagcgagcca ggatgtgttt accgcggtgg cgtggtatca gcagaaaccg 120
 ggcaaaagcgc cgaactgct gatttattgg gcgagcaccg gccataccgg cgtgccgagt 180
 cgcttttagcg gcagcggcag cggcaccgat ttaccctga ccattagcag cctgcagccg 240
 gaagattttg cgacctatta ttgccagcag tatagcagct atccgctgac ctttggcggc 300
 ggcaccaaag tggaaattaa acgt 324

<210> 370
 <211> 119
 <212> PRT
 <213> Mus musculus

<400> 370
 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 Trp Ile
 35 40 45
 Gly Arg Ile Asp Pro Gln 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> 371
 <211> 357
 <212> DNA
 <213> Mus musculus

<400> 371
 gaagtgcagc tgggtgcagag cggcgccggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60
 agctgcaaag cgagcgctt taacattaaa gattattata tgcattgggt gcgccaggcg 120
 ccgggccagg gcttggatg gatcgccgc attgatccgg aaaacggcga tattatttat 180
 gatccgaat ttcaaggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat 240
 atggaaatgc gcagcctgc cagcgatgat accgcggtgt attattgcgc gtatgatgcg 300
 ggcgatccgg cgtggtttac ctattggggc cagggcaccc tggtgaccgt ctgcagc 357

<210> 372
 <211> 108
 <212> PRT
 <213> Mus musculus

<400> 372
 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 Ser Val Ser Ser Ser Ile Ser Ser Ser
 20 25 30
 Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu 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 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 Trp Thr Thr Thr Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

<210> 373
 <211> 324
 <212> DNA
 <213> Mus musculus

<400> 373

```

gatattcagc tgaccagag cccgagcttt ctgagcgcga gcgtgggcga tcgctgacc 60
attacctgca gcgtgagcag cagcattagc agcagcaacc tgcattggta tcagcagaaa 120
ccgggcaaaag cgcggaaact gctgatttat ggcaccaagca acctggcgag cggcgtgccg 180
agccgcttta cggcgagcgg cagcggcacc gaatttacc tgaccattag cagcctgcag 240
ccggaagatt ttgcgacctt ttattgccag cagtggacca ccacctatac ctttggccag 300
ggcaccaaac tggaaattaa acgt

```

<210> 374

<211> 122

<212> PRT

<213> Mus musculus

<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 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

```

<210> 375

<211> 366

<212> DNA

<213> Mus musculus

<400> 375

```

gaagtgcagc tgggtgcagag cggcgcgga gtgaaaaaac cggcgcgag cgtgaaagt 60
agctgcaaa gcagcggctt taacattaaa gattattata ttcattgggt gcgccaggcg 120
ccgggccagg gcttggaaat gatgggccc gatgatccg ataacggcga aagcacctat 180
gtgccgaaat ttcaggggcc cgtgaccatg accaccgata ccagcaccag caccgcgtat 240
atggaactgc gcagcctgcg cagcgtgatg accgcggtgt attattgcgc gcgcgaaggc 300
ctggattatg gcgattatta tgcggtggat tattggggcc agggcacctt ggtgaccgtc 360
tcgagc
366

```

<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 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 tgaccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc 60

```

```

ataacatgta gagcatctca agatatttcc aactatttga attggtacca acaaaaaacc 120
ggcaaaagcac ctaaaactcct cattactat acatcaagac tcctctccgg cgttccatca 180
cgattctcag gctccggctc cggcacagat ttcacactca ctatttctc cctccaacca 240
gaagattttg caacctatta ctgtcaacaa ggcgatacac tcccatacac attcggcggc 300
ggcacaaaag ttgaaattaa a
321

```

<210> 378

<211> 123

<212> PRT

<213> Mus musculus

<400> 378

```

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 gtataaaac caggagcaag cggttaaagt 60
tctgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg 120
ccaggacaag gattggaatg gatgggagaa attaacctta atagtggagg agcaggctac 180
aatcaaaaat tcaaaggag agttacaatg acaacagaca caagcacttc aacagcatat 240
atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg 300
tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc 360
gtctctagt
369

```

<210> 380

<217> 108

<212> PRT

<213> Mus musculus

<400> 380

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Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
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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

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<210> 381

<211> 324

<212> DNA

<213> Mus musculus

<400> 381

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atcacatgcc gcgcctcacc ttcagttaca tcttcttacc ttaattggta tcaacaaaaa 120
ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatc aggagttccc 180
tctcgatttt caggatctgg atcaggcaca gaatttacac ttactatata atcactccaa 240
ccagaagact tcgacctta ttactgccaa caatacgatt tttttccaag cacattcgga 300
ggaggtacaa aagtagaaat caag
324

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<210> 382

<211> 121

<212> PRT

<213> Mus musculus

<400> 382

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
 115 120

<210> 383

<221> 363

<212> DNA

<213> Mus musculus

<400> 383

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agttgcaaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc 120
cctggacaaa gacttgaatg gatgggagac attaacccctt ataacgacga cactacatac 180
aatcataaat ttaaaggaag agttacaatt acaagagata catccgcata aaccgcctat 240
atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact 300
gccgttatta ctactaacgc tatggattac tgggggtcaag gaaccactgt taccgtctct 360
agt
  
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<210> 384

<211> 108

<212> PRT

<213> Mus musculus

<400> 384

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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 Asp Arg Val Thr Ile Thr Cys 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 Gln Trp Ser Ser Tyr Pro
 85 90 95
 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100

105

<210> 385

<211> 324

<212> DNA

<213> Mus musculus

<400> 385

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cccggaagag cacctaaatc acttatatac ggcacatcaa atctcgcata aggcgttcct 180
tcaagatttt caggctctgg ctacggcacc gactttactc ttacaatatc ctccctccaa 240
cccgaagact tcgcaacctt ttactgtcaa caatggctct catatccact cacatttggc 300
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<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
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 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
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<210> 387

<211> 375

<212> DNA

<213> Mus musculus

<400> 387

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 cctgggacaag ggcttgagtg gattggaagg attgatcctg agaattggtg tactttatat 180
 gaccggaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac 240
 atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg 300
 gattatttcc acgatggtag ctctactggt tacttcgatg tctggggcgt tggcacctct 360
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<210> 388

<211> 106

<212> PRT

<213> Mus musculus

<400> 388

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 Ile Ser Tyr Ile
 20 25 30
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys 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
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<210> 389

<211> 318

<212> DNA

<213> Mus musculus

<400> 389

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 aaagccctta agctcctgat ctatgccaca tccaacctgg ctctgggggt cccatcaagg 180
 ttacagcgca gtggatctgg gacagaattc actctcaca tcagcagcct gcagcctgaa 240
 gattttgcaa ctattactg tcagcagtggt agtagtgacc cactcacggt cggcggaggg 300
 accaaggtag agatcaaa 318

<210> 390

<211> 121

<212> PRT

<213> Mus musculus

<400> 390

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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 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

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<210> 391

<211> 363

<212> DNA

<213> Mus musculus

<400> 391

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ccttgacaag ggcttgagt gatcggaagg gttgatcctg acaatgggtg gactgaattt 180
gccccgaagt tccccgggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac 300
tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct 360
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<210> 392

<211> 448

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 392

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

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<210> 393

<211> 446

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 393

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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 20 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
 35 Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
 50 Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
 65 Met Glu Leu Ser Ser 70 Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 Ala Arg Glu Thr Ala Val Ile Thr Thr 105 Asn Ala Met Asp Tyr Trp Gly
 115 Gln Gly Thr Thr Val Thr Val Ser 120 Ser Ala Ser Thr Lys Gly Pro Ser
 130 Val Phe Pro Leu Ala Pro Cys 135 Ser Arg Ser Thr Ser Glu Ser Thr Ala
 145 Ala Leu Gly Cys Leu Val 150 Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 165 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 180 Val Leu Gln Ser Ser Gly Leu Tyr Ser 185 Leu Ser Ser Val Val Thr Val
 195 Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
 210 Lys Pro Ser Asn Thr Lys Val 215 Asp Lys Thr Val Glu Arg Lys Cys Cys
 225 Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val 235 Ala Gly Pro Ser Val
 240 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr 250 Leu Met Ile Ser Arg Thr
 260 Pro Glu Val Thr Cys Val Val Val Asp 265 Val Ser His Glu Asp Pro Glu
 275 Val Gln Phe Asn Trp Tyr Val Asp 280 Gly Val Glu Val His Asn Ala Lys
 290 Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
 305 Val Leu Thr Val Val His 310 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 325 Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
 340 Ser Lys Thr Lys Gly Gln Pro Arg Glu 345 Pro Gln Val Tyr Thr Leu Pro
 355 Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 370 Val Lys Gly Phe Tyr Pro Ser 375 Asp Ile Ala Val Glu Trp Glu Ser Asn
 385 Gly Gln Pro Glu Asn Asn 390 Tyr Lys Thr Thr Pro Met Leu Asp Ser
 405 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 420 Trp Gln Gln Gly Asn Val Phe Ser Cys 425 Ser Val Met His Glu Ala Leu
 435 His Asn His Tyr Thr Gln Lys Ser 440 Leu Ser Leu Ser Pro Gly 445

<210> 394

<211> 450

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 394

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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 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 Ala Ser Thr
115      120      125
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
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
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      275
Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
280      285      290
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
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
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
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
Pro Gly
450

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<210> 395

<211> 446

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized antibody sequence

<400> 395

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20 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
50 Pro Gly Lys Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 Ala Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
100 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

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<210> 396

<211> 445

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 396

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Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
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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 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
340 345 350
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
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

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- [WO2005014650A \[0006\]](#)
- [US6395511B \[0047\]](#)
- [US6803453B \[0047\]](#)
- [US20040009535A \[0047\]](#)
- [US20050106683A \[0047\]](#)
- [US6703199B \[0049\]](#)
- [US20050238646A \[0049\]](#)
- [US4331647A \[0050\]](#)
- [US4840835A \[0057\]](#)
- [US4496689A \[0057\]](#)
- [US4301144A \[0057\]](#)
- [US4870417A \[0057\]](#)
- [US4791192A \[0057\]](#)

- [US4179337A \[0057\]](#)
- [US6133426A \[0057\]](#)
- [USRE32011E \[0078\]](#)
- [US4902614A \[0078\]](#)
- [US4543439A \[0078\]](#)
- [US4411993A \[0078\]](#)
- [US5877397A \[0080\]](#)
- [US4464456A \[0091\]](#)
- [WO9202551A \[0092\]](#)
- [US5627052A \[0092\]](#)
- [US5223409A \[0093\]](#)
- [US5698426A \[0093\]](#)
- [US2004014688A1 \[0388\]](#)
- [US10868497B \[0427\]](#)
- [US60478977B \[0427\]](#)
- [US5543158A \[0430\]](#)
- [US5641515A \[0430\]](#)
- [US5399363A \[0430\]](#)
- [US5466468A \[0431\]](#)
- [US5567434A \[0436\]](#)
- [US5552157A \[0436\]](#)
- [US5565213A \[0436\]](#)
- [US5738868A \[0436\]](#)
- [US5795587A \[0436\]](#)
- [US5145684A \[0437\]](#)
- [US60782244B \[0546\]](#)
- [US60776847B \[0546\]](#)
- [US60667583B \[0546\]](#)

Non-patent literature cited in the description

- RIGGS West J. Med., 1991, vol. 154, 63-77 [0002]
- KHOSLARIGGS Mayo Clin. Proc., 1995, vol. 70, 978982- [0004]
- BRUNKOW et al. Am. J. Hum. Genet., 2001, vol. 68, 577-589 [0006]
- BALEMANS et al. Hum. Mol. Genet., 2001, vol. 10, 537-543 [0006]
- HOLLINGERHUDSON Nature Biotechnology, 2005, vol. 23, 91126-1136 [0049]
- NISONOFF et al. Arch. Biochem. Biophys., 1960, vol. 89, 230- [0050]
- PORTER Biochem. J., 1959, vol. 73, 119- [0050]
- EDELMAN et al. Methods in Enzymology Academic Press 19670000 vol. 1, 422- [0050]
- ANDREWS, S.M. TITUS, J.A. et al. Current Protocols in Immunology John Wiley & Sons 200300002.8.1-2.8.102.10A.1-2.10A.5 [0050]
- LARRICK et al. Methods: A Companion to Methods in Enzymology, 1991, vol. 2, 106- [0052]
- Genetic Manipulation of Monoclonal Antibodies COURTENAY-LUCK et al. Monoclonal Antibodies: Production, Engineering and Clinical Application Cambridge University Press 19950000166- [0052]
- Genetic Manipulation and Expression of Antibodies WARD et al. Monoclonal Antibodies: Principles and Applications Wiley-Liss, Inc. 19950000137- [0052]
- MOULT J. Curr. Op. in Biotech., 1996, vol. 7, 4422-427 [0064]
- CHOU et al. Biochemistry, 1974, vol. 13, 2222-245 [0064]
- CHOU et al. Biochemistry, 1974, vol. 113, 2211-222 [0064]
- CHOU et al. Adv. Enzymol. Relat Areas Mol. Biol., 1978, vol. 47, 45-148 [0064]
- CHOU et al. Ann. Rev. Biochem., vol. 47, 251-276 [0064]
- CHOU et al. Biophys. J., 1979, vol. 26, 367-384 [0064]
- HOLM et al. Nucl. Acid. Res., 1999, vol. 27, 1244-247 [0064]
- BRENNER et al. Curr. Op. Struct. Biol., 1997, vol. 7, 3369-376 [0064]

- JONES, D. Curr. Opin. Struct. Biol., 1997, vol. 7, 3377-87 [0065]
- SIPPL et al. Structure, 1996, vol. 4, 115-19 [0065]
- BOWIE et al. Science, 1991, vol. 253, 164-170 [0065]
- GRIBSKOV et al. Meth. Enzym., 1990, vol. 183, 146-159 [0065]
- GRIBSKOV et al. Proc. Nat. Acad. Sci., 1987, vol. 84, 134355-4358 [0065]
- Proteins, Structures and Molecular Principles W. H. Freeman and Company 19840000 [0068]
- Introduction to Protein Structure Garland Publishing 19910000 [0068]
- THORNTON et al. Nature, 1991, vol. 354, 105- [0068]
- NYGRENUHLEN Current Opinion in Structural Biology, 1997, vol. 7, 463-469 [0071]
- ZHANG, W. et al. Molecular Immunology, 2005, vol. 42, 121445-1451 [0072]
- HWANG W. et al. Methods, 2005, vol. 36, 135-42 [0072]
- DALL'ACQUA WF et al. Methods, 2005, vol. 36, 143-60 [0072]
- CLARK, M. Immunology Today, 2000, vol. 21, 8397-402 [0072]
- KABAT et al. Sequences of Proteins of Immunological Interest U.S. Department of Health and Human Services, NIH 19870000 [0074] [0382]
- PLUCKTHUN et al. Methods Enzymol., 1989, vol. 178, 497-515 [0075]
- MANIATIS et al. Molecular Cloning, A Laboratory Manual Cold Spring Harbor Laboratory 19890000 [0076]
- SANGER et al. PNAS, 1977, vol. 74, 5463- [0076]
- KRAMER et al. Nucleic Acids Res., 1984, vol. 12, 9441- [0076]
- KUNKEL Proc. Natl. Acad. Sci. USA, 1985, vol. 82, 488-92 [0076]
- KUNKEL et al. Methods in Enzymol., 1987, vol. 154, 367-82 [0076]
- MOUNTAIN ADAIR, J R Biotechnology and Genetic Engineering Reviews Intercept 19920000 [0076]
- Current Protocols in Molecular Biology Wiley Interscience 19990000 [0076]
- YANG et al. J. Mol. Biol., 1995, vol. 254, 392-403 [0077]
- MARKS et al. Bio/Technology, 1992, vol. 10, 779-783 [0077]
- LOW et al. J. Mol. Biol., 1996, vol. 250, 350-368 [0077]
- PATTEN et al. Curr. Opin. Biotechnol., 1997, vol. 8, 724-733 [0077]
- THOMPSON et al. J. Mol. Biol., 1996, vol. 256, 7-88 [0077]
- CRAMERI et al. Nature, 1998, vol. 391, 288-291 [0077]
- VAUGHAN et al. Nature Biotechnology, 1998, vol. 16, 535-539 [0077]
- KOHLER et al. Nature, 1975, vol. 256, 495- [0078]
- Current Protocols in Immunology John Wiley & Sons 19910000 vol. 1, [0078]
- Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses Plenum Press 19800000 [0078]
- Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press 19880000 [0078]
- Production of monoclonal antibodies against proteins expressed in E. coli PICKSLEY et al. DNA Cloning 2: Expression Systems Oxford University Press 19950000 vol. 2, 93- [0078]
- Coligan, 2.7.1-2.7.1229.1-2.9.3 [0079]
- Purification of Immunoglobulin G (IgG) BAINES et al. Methods in Molecular Biology The Humana Press, Inc. 19920000 vol. 10, 79-104 [0079]
- GREEN et al. Nature Genet., 1994, vol. 7, 13- [0080]
- LONBERG et al. Nature, 1994, vol. 368, 856- [0080]
- TAYLOR et al. Int. Immun., 1994, vol. 6, 579- [0080]
- BRUGGEMANN et al. Curr. Opin. Biotechnol., 1997, vol. 8, 455-58 [0080] [0080]
- JAKOBOVITS et al. Ann. N. Y. Acad. Sci., 1995, vol. 764, 525-35 [0080]
- GLASKY et al. Hybridoma, 1989, vol. 8, 377-89 [0081]
- BOERNER et al. J. Immunol., 1991, vol. 147, 86-95 [0081]
- BABCOOK et al. Proc. Natl. Acad. Sci. USA, 1996, vol. 93, 7843-48 [0082]
- WINTER et al. Annu. Rev. Immunol., 1994, vol. 12, 433-55 [0083]
- BURTON et al. Adv. Immunol., 1994, vol. 57, 191-280 [0083]
- HUSE et al. Science, 1989, vol. 246, 1275-81 [0083]
- SASTRY et al. Proc. Natl. Acad. Sci. USA, 1989, vol. 86, 5728-32 [0083]
- ALTING-MEES et al. Strategies in Molecular Biology, 1990, vol. 3, 1-9 [0083]
- KANG et al. Proc. Natl. Acad. Sci. USA, 1991, vol. 88, 4363-66 [0083]
- HOOGENBOOM et al. J. Molec. Biol., 1992, vol. 227, 381-388 [0083]
- SCHLEBUSCH et al. Hybridoma, 1997, vol. 16, 47-52 [0083]
- BIRD et al. Science, 1988, vol. 242, 423-426 [0085]
- HARRIS, R.J. Journal of Chromatography, 1995, vol. 705, 129-134 [0091]
- ANGAL S et al. Mol Immunol, 1993, vol. 30, 1105-108 [0370]

- **SCATCHARD et al.**Ann. N. Y. Acad. Sci., 1949, vol. 51, 660-672 [0387]
- **WOLFF et al.**Cancer Res., 1993, vol. 53, 2560-65 [0387]
- **SUDO HKODAMA H-AAMAGAI YYAMAMOTO SKASAI S**In vitro Differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvariaJ. Cell Biol., 1983, vol. 96, 191-198 [0422]
- **SMITH EREDMAN RLOGG CCOETZEE GKASAHARA NFRENKEL B**Glucocorticoids inhibit developmental stage-specific osteoblast cell cycleJ. Biol. Chem., 2000, vol. 275, 19992-20001 [0422]
- Remington's Pharmaceutical Sciences1035-10381570-1580 [0432]
- **LASIC**Trends Biotechnol., 1998, vol. 16, 7307-21 [0436]
- **TAKAKURAN**Nippon Rinsho, 1998, vol. 56, 3691-95 [0436]
- **CHANDRAN et al.**Indian J. Exp. Biol., 1997, vol. 35, 8801-09 [0436]
- **MARGALIT**Crit. Rev. Ther. Drug Carrier Syst., 1995, vol. 12, 2-3233-61 [0436]
- **QUINTANAR-GUERRERO et al.**Drug Dev. Ind. Pharm., 1998, vol. 24, 121113-28 [0437]
- **COUVREUR et al.**Crit. Rev. Ther. Drug Carrier Syst., 1988, vol. 5, 11-20 [0437]
- **MUHLN et al.**Eur. J. Pharm. Biopharm., 1998, vol. 45, 2149-55 [0437]
- **ZAMBAUX et al.**J. Controlled Release, 1998, vol. 50, 1-331-40 [0437]
- **COMIER**Curr. Opin. in Rheu., 1995, vol. 7, 243- [0440]
- **GUINNESS-HEY**Metab. Bone Dis. Relat. Res., 1984, vol. 5, 177-181 [0440]
- **KALU, D.N.**The ovariectomized rat model of postmenopausal bone lossBone and Mineral, 1991, vol. 15, 175-192 [0440]
- **FROST, H.M.JEE, W.S.S.**On the rat model of human osteopenias and osteoporosisBone and Mineral, 1992, vol. 18, 227-236 [0440]
- **JEE, W.S.S.YAO, W.**Overview: animal models of osteopenia and osteoporosisJ. Musculoskel. Neuron. Interact., 2001, vol. 1, 193-207 [0440]
- **SUDO H et al.**In vitro Differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvariaJ. Cell Biol., vol. 96, 191-198 [0492]
- **SMITH EREDMAN RLOGG CCOETZEE GKASAHARA NFRENKEL B**Glucocorticoids inhibit developmental stage-specific osteoblast cell cycleJ Biol Chem, 2000, vol. 275, 19992-20001 [0492]
- **SUDO HKODAMA H-AAMAGAI YYAMAMOTO SKASAI S**In vitro differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvariaJ Cell Biol, 1983, vol. 96, 191-198 [0515]
- **BYRNE, F. R. et al.**Gut, 2005, vol. 54, 78-86 [0516]

Patentkrav

- 5 1. Monoklonalt antistof til anvendelse i en fremgangsmåde til at forøge
mindst en af knogledannelse, knoglemineraldensitet, knoglemineralindhold,
knoglemasse, knoglekvalitet og knoglestyrke hos et pattedyr og dermed be-
handle en tilstand, hvor en forøgelse af mindst en af knogledannelse, knog-
lemineraldensitet, knoglemineralindhold, knoglemasse, knoglekvalitet og
knoglestyrke ønskes, hvor det monoklonale antistof (a) binder til humant
10 sclerostin med en bindingsaffinitet på mindre end eller lig med 1×10^{-10} M og
(b) krydsblokerer bindingen af antistof Ab-13 eller Ab-14 til sclerostin og/eller
krydsblokeres fra at binde til sclerostin ved hjælp af Ab-13 eller Ab-14, hvor
antistoffet Ab-13 har lette kæder med SEQ ID NO: 205 og tunge kæder med
SEQ ID NO: 209, og antistof Ab-14 har lette kæder med SEQ ID NO: 213 og
15 tunge kæder med SEQ ID NO: 217 eller 393.
2. Monoklonalt antistof til anvendelse ifølge krav 1, der omfatter en konstant
letkæde- og/eller tungkæde-region.
3. Monoklonalt antistof til anvendelse ifølge krav 2, der omfatter en konstant
20 IgG-region.
4. Monoklonalt antistof til anvendelse ifølge krav 3, der omfatter en konstant
IgG4- eller IgG2-region.
- 25 5. Monoklonalt antistof anvendelse ifølge krav 1, der er et enkeltdomænean-
tistof, et enkeltkædeantistof eller et $F(ab')_2$ -, Fab-, Fab'- eller Fv-fragment.
6. Monoklonalt antistof til anvendelse ifølge et af kravene 1 til 5, der er et
humaniseret antistof eller et humant antistof.
- 30 7. Monoklonalt antistof til anvendelse ifølge et af kravene 1 til 6, der binder til
sclerostin med en bindingsaffinitet på mindre end eller lig med 1×10^{-11} M
eller mindre end eller lig med 1×10^{-12} M.
- 35 8. Monoklonalt antistof til anvendelse ifølge et af kravene 1 til 7, der binder til
humant sclerostin med en affinitet, der er mindst 50, 100, 250, 500, 1000 el-

ler 10.000 gange større end affiniteten for hønseæggehvide-lysozym.

9. Monoklonalt antistof til anvendelse ifølge et af kravene 1 til 8, hvor krydsblokeringen bestemmes ved overfladeplasmonresonans eller ELISA.

5

10. Monoklonalt antistof til anvendelse ifølge krav 9, hvor antistoffet er et krydsblokerende antistof, der binder til sclerostin i et krydsblokerende Biacore-assay, således at den registrerede binding under assayet og under nærværelse af et andet antistof er fra 75% til 4% af den maksimale teoretiske binding af de to antistoffer i kombination.

10

11. Monoklonalt antistof til anvendelse ifølge krav 9, der i opløsningsfasen i nævnte ELISA bevirker en reduktion på mellem 60% og 100% i den mængde af sclerostin, der er bundet ved hjælp af antistof, som er coatet på ELISA-pladen, sammenlignet med den mængde af sclerostin, der er bundet ved hjælp af det coatede antistof ved fravær af opløsningsfaseantistoffet.

15

12. Monoklonalt antistof ifølge et af kravene 1 til 11 til anvendelse ved behandling af osteoporose eller osteopeni.

20

13. Monoklonalt antistof ifølge et af kravene 1 til 11 til anvendelse ved behandling af osteopeni, osteoporose eller knogletab, der er forårsaget af akondroplasi, cleidocranial dysostose, enkondromatose, fibrøs dysplasi, Gauchers sygdom, hypofosfatæmisk rakitis, Marfans syndrom, multiple hereditære eksostoser, neurofibromatose, osteogenesis imperfecta, osteopoikilose, sklerotiske læsioner, pseudoartrose, pyogen osteomyelitis, periodontal sygdom, knogletab, der er induceret af anti-epileptiske lægemidler, primær og sekundær hyperparatyroidisme, familiære hyperparatyroidismesyndromer, knogletab, der er induceret af vægtløshed, osteoporose hos mænd, postmenopausalt knogletab, osteoarthritis, renal osteodystrofi, infiltrative knoglelidelser, oralt knogletab, osteonekrose i kæben, juvenil Pagets sygdom, meloreostose, metaboliske knoglesygdomme, mastocytose, seglcelleanæmi/sygdom, organtransplantationsrelateret knogletab, nyretransplantationsrelateret knogletab, systemisk lupus erythematosus, ankyloserende spondylitis, epilepsi, juvenil arthritis, thalassemia, mucopolysaccharidose, Fabrys sygdom, Turners syndrom, Downs syndrom, Klinefelters syndrom, spedalskhed,

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Perthes sygdom, adolescent idiopatisk scoliose, IOMID - infantile onset multi-system inflammatory disease, Winchesters syndrom, Menkes sygdom, Willems sygdom, iskæmisk knoglesygdom (såsom Legg-Calve-Perthes sygdom, regional migratorisk osteoporose), anæmiske tilstande, lidelser forårsaget af steroider, glukokortikoid-induceret knogletab, heparin-induceret knogletab, knoglemarvslidelser, skørbug, fejlnæring, kalciummangel, idiopatisk osteopeni eller osteoporose, arvelig osteopeni eller osteoporose, alkoholisme, kronisk leversygdom, postmenopausal tilstand, kroniske inflammatoriske tilstande, reumatoid arthritis, inflammatorisk tarmsygdom, colitis ulcerosa, inflammatorisk colitis, Crohns sygdom, oligomenoré, amenoré, graviditet, diabetes mellitus, hyperthyroidisme, skjoldbrusklidelser, biskjoldbrusklidelser, Cushings sygdom, akromegali, hypogonadisme, immobilisering eller inaktivitet, reflektorisk sympatisk dystrofi, regional osteoporose, osteomalaci, knogletab forbundet med ledudskiftning, knogletab forbundet med HIV, knogletab forbundet med tab af væksthormon, knogletab forbundet med cystisk fibrose, fibrøs dysplasi, knogletab forbundet med kemoterapi, tumorinduceret knogletab, cancer-relateret knogletab, hormonablativt knogletab, myelomatose, lægemiddelinduceret knogletab, anorexia nervosa, sygdomsrelateret ansigtsknogletab, sygdomsrelateret kranieknogletab, sygdomsrelateret knogletab i kæben, sygdomsrelateret knogletab i kraniet, og knogletab forbundet med rumrejser.

14. Monoklonalt antistof ifølge et af kravene 1 til 11 til anvendelse til forbedring af resultatet i ortopædiske indgreb, dentale indgreb, implantatkirurgi, ledudskiftning, knogletransplantation, kosmetisk knoglekirurgi eller knoglereparation, såsom frakturheling, pseudoarthroseheling, forsinket arthroseheling eller ansigtsrekonstruktion.

15. Farmaceutisk sammensætning, der omfatter et antistof og en farmaceutisk acceptabel bærer, excipients eller fortyndingsmiddel, hvor antistoffet er et monoklonalt antistof, der (a) binder til humant sclerostin med en bindingsaffinitet på mindre end eller lig med 1×10^{-10} M og (b) krydsblokerer bindingen af antistoffet Ab-13 eller Ab-14 til sclerostin og/eller krydsblokeres fra at binde til sclerostin ved hjælp af antistoffet Ab-13 eller Ab-14, hvor antistoffet Ab-13 har en let kæde med SEQ ID NO: 205 og tunge kæder med SEQ ID NO: 209, og antistof Ab-14 har lette kæder med SEQ ID NO: 213 og tunge kæder

med SEQ ID NO: 217 eller 393, og hvor den farmaceutiske sammensætning er til anvendelse i en fremgangsmåde til at forøge mindst en af knogledannelse, knoglemineraldensitet, knoglemineralindhold, knoglemasse, knoglekvalitet og knoglestyrke hos et pattedyr og dermed behandle en tilstand, hvor en forøgelse af mindst en af knogledannelse, knoglemineraldensitet, knoglemineralindhold, knoglemasse, knoglekvalitet og knoglestyrke ønskes.

DRAWINGS

A.

1 AQVLTQTPAS VSAAVGGTIVT INCSSQSVY DNNLANFQQ KPGQPKLLI
51 YDASDLASGV PSRFGSGSG TQFTLTISGV QCADAATYIC QGAYNDVIYA
101 FGGTEVVVK RUDAAPTVS1 FPPSEQLTS GGASVVCFLN NFYPKDINVK
151 WKIDGSEON GVLSNWDQD SKDSTYMS S TLATKDEYE RHNSYTCEAT
201 HKTSTSPIVK SFNRNEC

B.

1 QSLESGGRL VTPGTPLTIN CTASGFSLS YWNNVYQAP GEGLEWIGTI
51 DSGGRTDYAS WAKGRFTISR TSTMDIKMT SLITGDTARY FCARNNNLWG
101 QGTLVTVSSA STKGFSVYPL APGSAAGTNS MYTLGCLYKG YFEPVTVTW
151 NSGSLSSGVH TFPVVLQSDL YTLSSSVTVP SSTWSEYVT CNVAHPASST
201 KVDKKIVPRD CGKFCICTV PEVSSVFIFP PKPRDVLITIT LTRKVTCTVV
251 DISKDDPEVQ FSWFVDDVEV HTAQTPREE QFNSTFRSVS ELFMHQDWL
301 NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPP KEQWAKDKVS
351 LTCMITDFFP EDITVWQWN GQPAENYANT QPIMNTNGSY FVYSKLVQK
401 SNWEAGNTFT CSVLHEGLHN HHTKSLSHS FGR

Figure 1

A.

```

1 QIVLTQPTI VSASPGKVT LICSSSSVS FVDWFQQKPG TSPKRWIYRT
51 SNLGFVGPAP FSGGSGTSH SLTISRMEAE DAATYCCOOR STTPPTFGAG
101 TKLELKRADA APTVSIFPPS SEQLTSGGAS VVCFLNNFYP KDLNVKWKID
151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
201 TSPIVASFNK NEC

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B.

```

1 QVTLKESGP ILQPSQTLSL TCSFSGFSLS TSGMGVGWIR HPSGKNLEWL
51 AHIWDDVKR YNPVLKSLT ISKDTNSQV FLKIANVDTA DTATYYCARI
101 EDEFDYDEEY AMDYWGQGT VIVSSAKTTP PSVYPLAPGS AAQTNSMVTL
151 GCLVKGYPPE PVTVTNNGS LSSGVHTFEA VLQSDLYTLS SSVTPSSSTW
201 PSETVTCNVA HPASSTKVDK KIVERDCGCK PCICTVPEVS SVFIFPPKPK
251 DVLITITPK VTCVVVDISK DDEVEQFSWF VDDVEVHTAQ TQPREEQENS
301 TFRSVSELPV MHQDWLNGKE FKCRVNSAAF PAIEKTISK TKGRPKAPQV
351 YTIPPPREQM AKDKVSLTCM ITDFFPEDIT VEQWNGQPA ENYKNTQPIH
401 DTDGSYEVYS KLVQKSNWE AGNTFTCSVL HEGLNHHETE KSLSHSPCK

```

Figure 2

A.

```

1 DIVLQSPAS LTVSLGLRAT ISCKASQSYD YDGDYIMNWI QOKPGQPPKL
51 LIYAASNLES GIPARFSGNG SGTDFTLNTH PVEEDAVTY YCQSNEDFW
101 TFGGKLEI KRADAAPTYS IFFESSEOLT SGGASVVCFL NNFYPKDINV
151 KWKIDGERQ NGVLNSWTDQ DSKDSTYSMS SYLLTKDEY ERHNSYTCEA
201 THKTSTSPIV KSFNRNEC

```

B.

```

1 EVQLQQSGPE LVKPGTSVKM SCRASGYTFT DCYMNWVKQS HGKSLEWIGD
51 INPTNGGTTY NQKFKGKATL TVDKSSSTAY MQLNLSLSDS SAVIYCARSH
101 YIFDGRVPWD AMYWGQGS VTVSSAKTTP PSYPLAPGS AAQTNSMVTLL
151 GCLVKGYPPE FVTVTWNSGS LSSGVHTFPA VLQSDLYTLL SSVTVPSSTW
201 PSEIVTCNVA HPASTKVDK KIVPRDCGCK PCICTVPEVS SYVLEFPKPK
251 DVLITITLTPK VTCVVVDISK DDEVEQFSWF VDDVEVETAQ TQPREQFNS
301 TERSVSELPV MHQDWLNGKE FKCRVNSRAF PAPIEKTISK TGRPKAPQV
351 YTIPEPEQOM AKDKVSLTCM ITDEFPEDIT VEMQWNGQPA ENYKNTQDIM
401 DTDGSIYIYS KLVQKSNWE AGNTFTCSVL HEGILNHHTE KSLSHSPGK

```

Figure 3

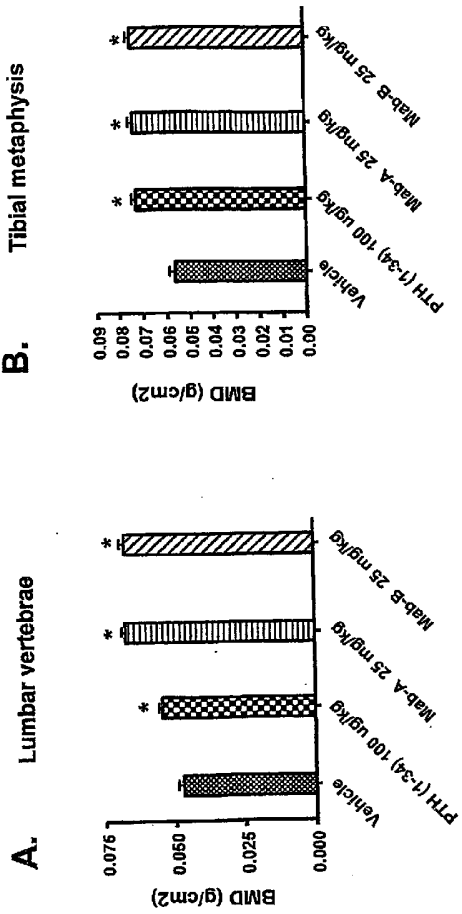
A.

1 DVQMIQSPSS LSASLGDIIVT MTCQASQGTG INLNWFQOKP GKAPKLLIYG
51 SSNLEDGVPS RFGSGRYGTD FTLTISSELED EDLATYFCIQ HSYLPYTFEG
101 GFKLEIKRAD AAPTYSIEPP SSEQLTSGGA SVVCFINNFI PKDINVKKKI
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC

B.

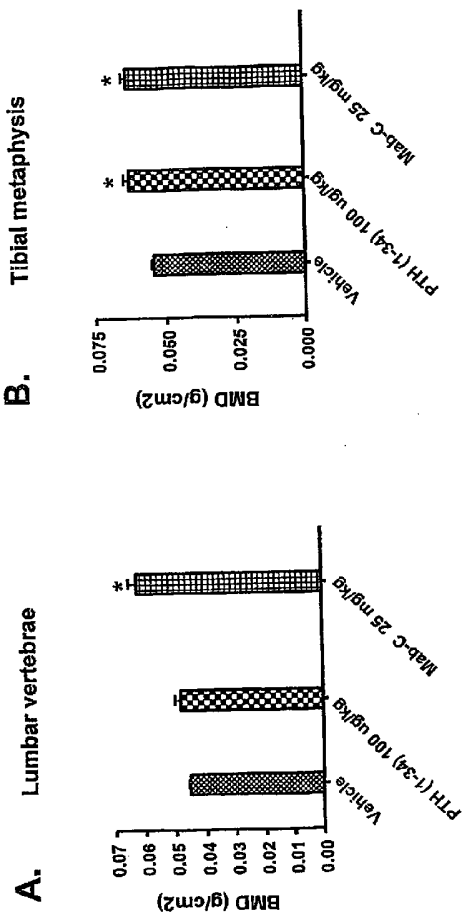
1 EVQLQDSGPE LVTPGASVKI SCKASGYTFT DHMSWVKQS HGKSLIEWIG
51 INPISGETTY NQKFKGTATL TVDKSSSIAY MEIRGLISED SAVIYCARD
101 YDASPEAYWG QGTLIVTVSAA KTTPEPSVYEL AFGSAAQTNK MYTLGCLVKG
151 YFPEPVTVTW NSGSLSSGVH TTPAVLQSDL YTLSSSVTVF SSTWPSSTVT
201 CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSSVFIEP PRPKDVLITIT
251 LTPKVTCTVV DISKDDPEVQ FSWFVDDVEV HTAQTPREE QFNSTFRSVS
301 ELPIMHQDWL NGKEFKCRVN SPAFPAPIEK TISKTKGREK APOVYITIPPP
351 KEQMAKDKVS LTCMITDFFP EDITVEWQVN GQPAENYKNT QPIMDTDGSY
401 FIYSKLVNQK SNWEAGNTFT CSVLHEGLHN HHTKSLSHS PGK

Figure 4



* = statistically significantly different from Vehicle
Error bars = Mean +/- 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 QGWQAFKND₁ TEIIP₂ELGEY₃ PEPPELENN₄ KTMNRAENG₅ RPPHFFETK₆

51 DVSEYSCREL₁ HFTRYVTDGP₂ CRS₃AKPVT₄EL₅ VCSGQC₆GP₇AR₈.LLPNAIGRGK₉

101 WWRPSG₁P₂DFR₃ CIP₄DRYRAQR₅ VQL₆LP₇GGEA₈ PRARKVRLVA₉ SCK₁₀KRLTRF₁₁

151 HNQSELKDFG₁ TEAR₂PQKGR₃ KPRPRARS₄AK₅ ANQAELENNAY₆

1 CAGGGGTGGC AGCGTTCAA GATGATGCC AC₂GGAATCA TCCCCGAGCT₃

51 CGGAGAGTAC CCGAGCCTC CACCGAGCT GGAGAACAA₂C AAGACCATGA₃

101 ACCGGGGGGA GAACGGAGGG CGGCTCC₂CC ACCACCCCT₃T TGAGACCAA₄

151 GACGTGTCCG AGTACAGCTG CCGGAGCTG CACTTCA₂CC GCTACGTGAC₃

201 CGATGGGCG TGCGCGAGCG CCAAGCCGT CACCGAGCTG GTGTGCTCCG₅

251 GCCAGTGGG CCGGCGCGC CTGTGCCCA AGCCATCG₂ CCGCGGCAAG₃

301 TGGTGGGAC CTAGTGGGC CGACTTCCG TGCATCC₂CG ACCGCTACCG₃

351 CGGCGACGCG GTGCAGCTGC TGTGTCCCG TGGTGA₂GGCG CCGCGCGCGC₃

401 GCAGGTCCG CCTGTGGCC TCGTGCAAGT GCAAGCGCT₂ CACCCGCTTC₃

451 CACAACCA₂GT CCGAGTCAA GGACTTCGG ACCGAGCGCG CTGGCGCGCA₃

501 GAGGGCGG AAGCGCGGC CCGCGCCCG GAGCGCAA₂ GCCAACCCAGG₃

551 CCGAGCTGGA GAACGCTAC

Figure 8

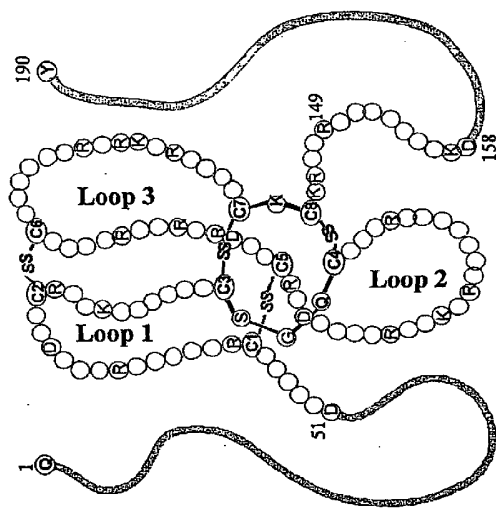


Figure 9

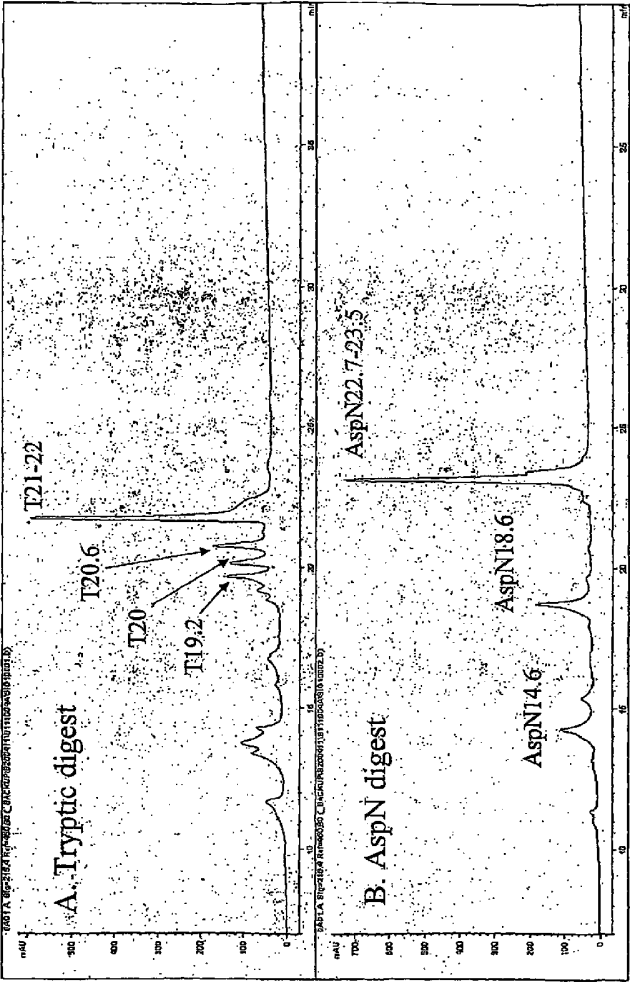


Figure 10

Peptides	Seq. pos.	Obs. Mass	Sequence
T19.2	65-72 121-132	2146.34 (2145.8)	1. YVTGDP CR (910) <u>C2</u> 2. VQLLCPGGEA PR (1239) <u>C6</u>
T20	51-90 104-149	9620.8 (MALDI); 9638.41 (ESI-MS) (4419.1)	1. DVSEYSCREL HFTRYVTDGP CRSAPVTEL VCSGQCGPAR
		(5226.2)	2. PSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SKCKRLT R
T20.6	51-64 101-117 73-90 138-149	7105.7 (MALDI); 7122.0 (ESI-MS) 3944.5	1. DVSEYSCREL HFTR (1740.9) <u>C1</u> 2. WWRPSGPPFR CIPDRYR (2206.6) <u>C5</u>
		3177.0	3. SAKPVTCLVC SGQCGPAR (1802.2) <u>C3, C4</u>
			4. LVASCKCKRL TR (1378.5) <u>C7, C8</u>
T21-22	51-90	10,147 (MALDI); 10170.3 (ESI-MS) (4419.1)	1. DVSEYSCREL HFTRYVTDGP CRSAPVTEL VCSGQCGPAR
	101-149	(5754.8)	2. WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SKCKRLTR

Figure 11

Peptides	Seq.pos.	Obs.Mass	Sequence
AspN14.6	34-47	1245.5	ENGGRPPHPF
	12-25	1585.4	EIIPELGFYP EPPP
	158-184	2964.5	DFGTEAARPQ KGRKPRPRAR SAKANQA
AspN18.6	9-50		DATEIIPELG EYPEPPPELE NNKTMNRAEN GGRPPHPFE TK (Glycopeptide)
AspN22.7-23.5	51-154	11,740	DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK WWRPSGPDFR CIPDRYRAQR VQLLCFGGEA PRARKVRLVA SCKCKRLTRF HNQS

Figure 12

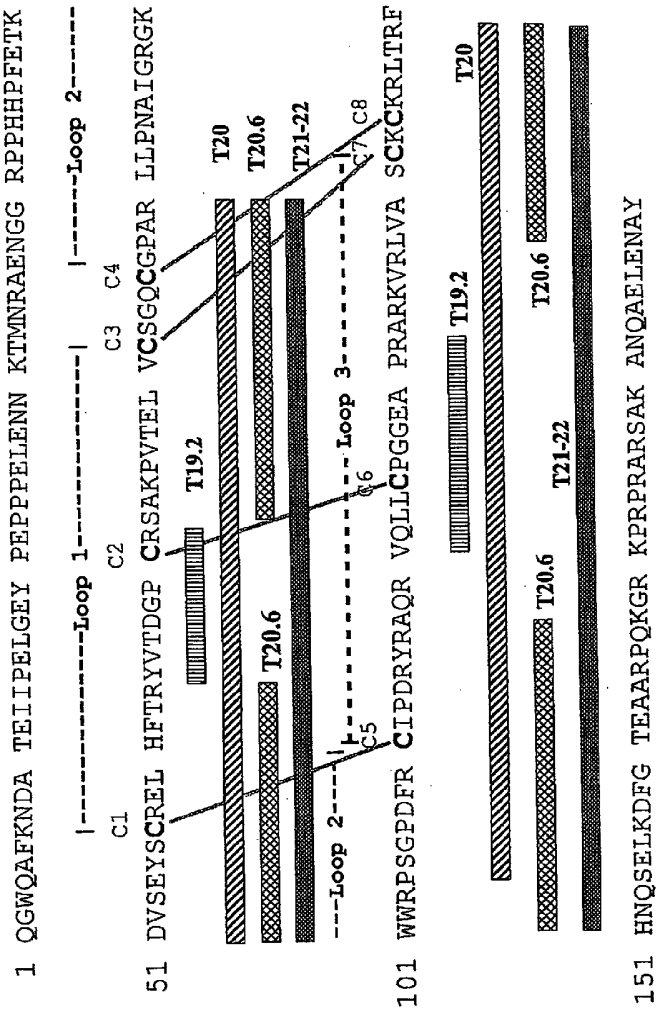


Figure 13

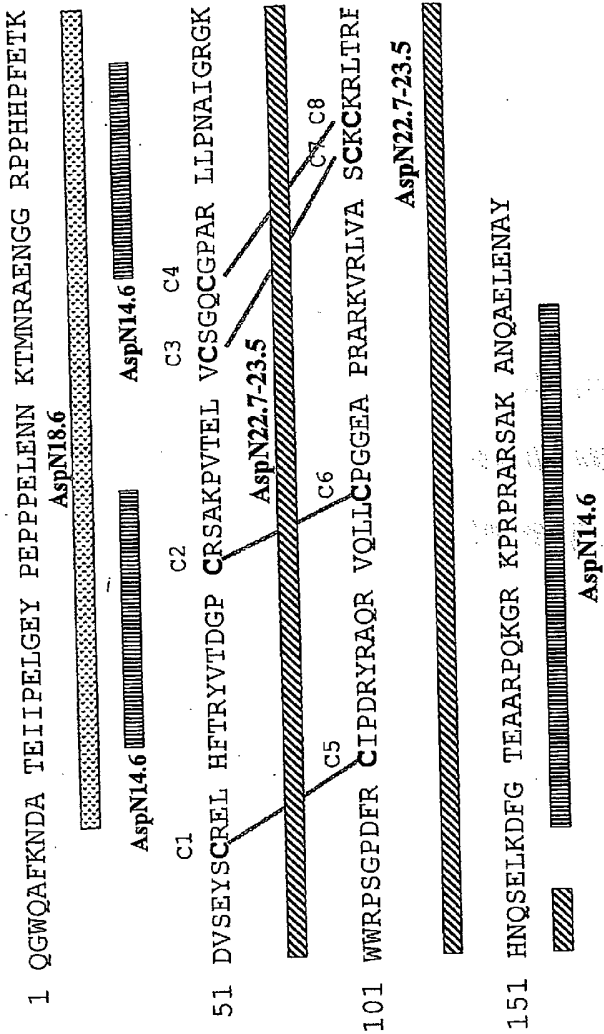


Figure 14

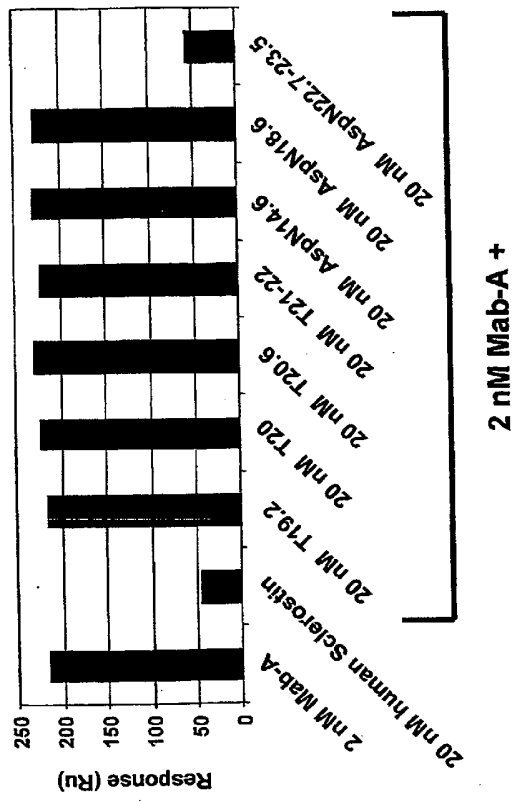


Figure 15

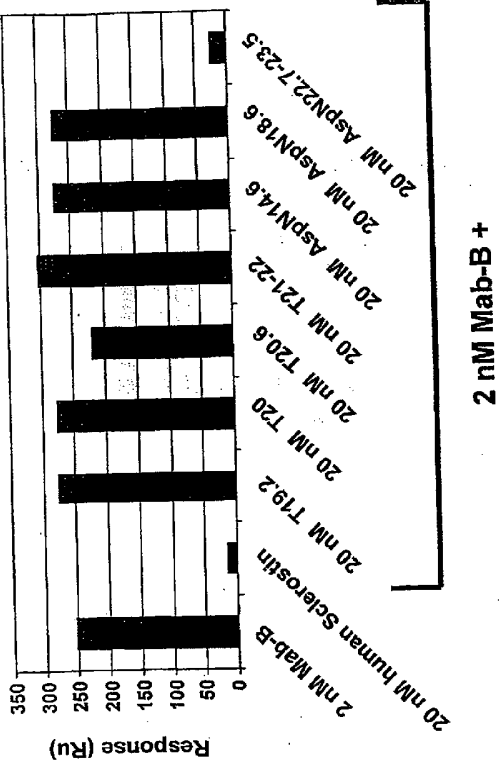


Figure 16

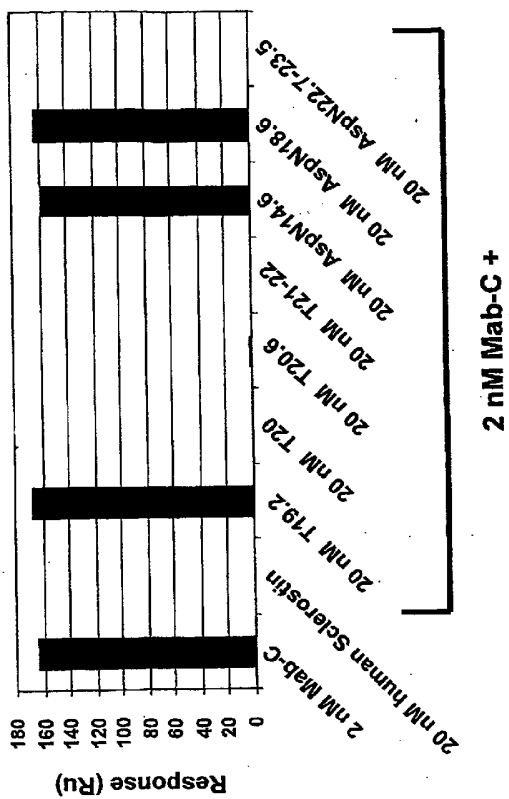


Figure 17

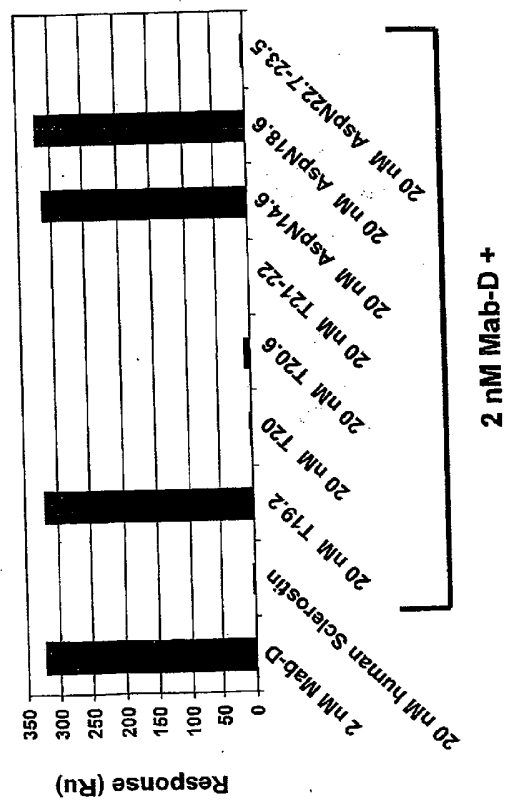


Figure 18

A. Loop 2 epitope for Mab-A and Mab-B

C4GPARLLPNAIGRGKWWRPSPGPDFRC5

B. T20.6 epitope for Mab-C and Mab-D

DVSEYSC1RELHFTR SAKPVTELVC3SGGQC4GPAR
WWRPSPGPDFRC5IPDRYR LVASC7K68KRLTR

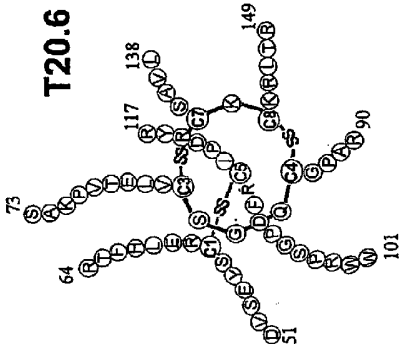


Figure 19

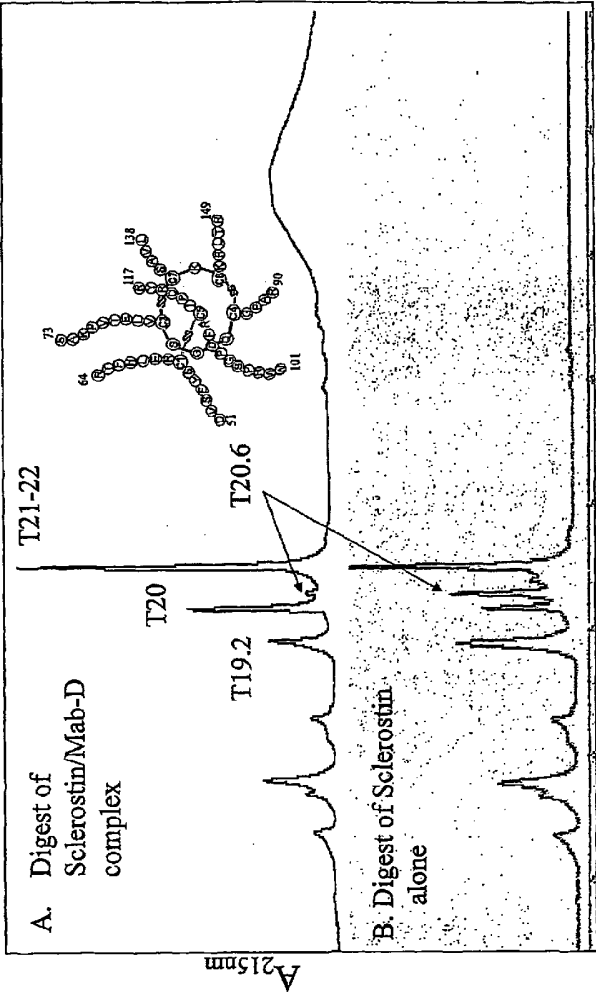
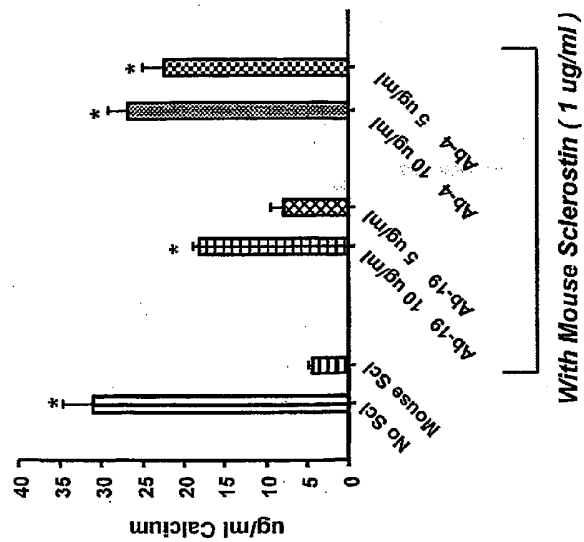


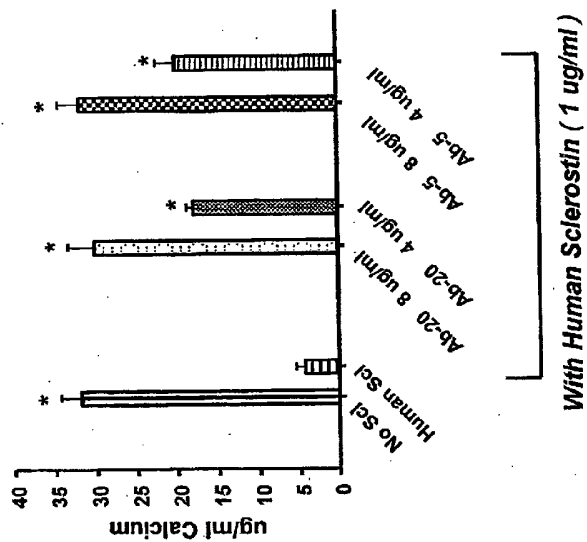
Figure 20



* = statistically significantly different from Mouse Scl group.

Error bars = Mean +/- SEM

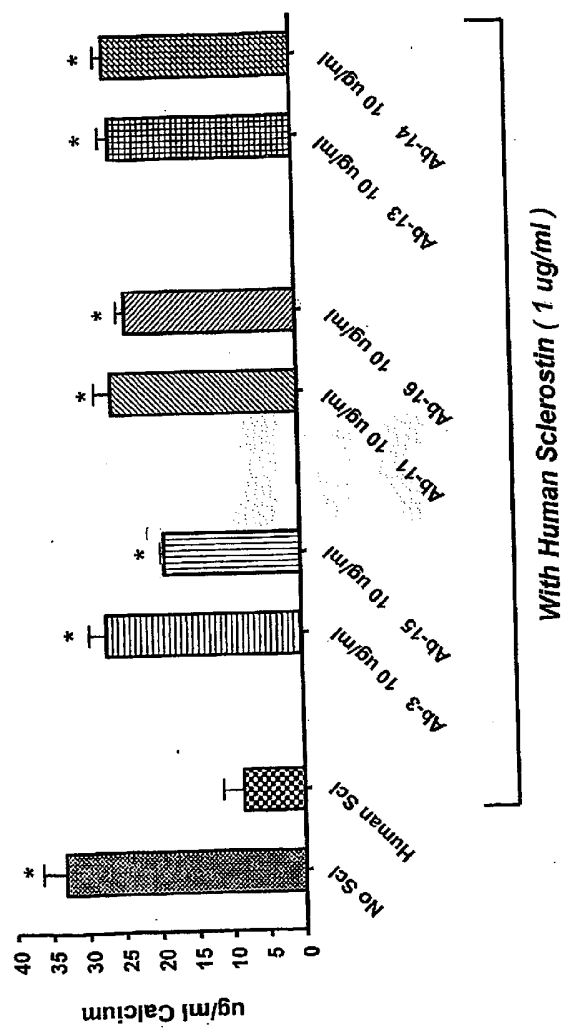
Figure 22



* = 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

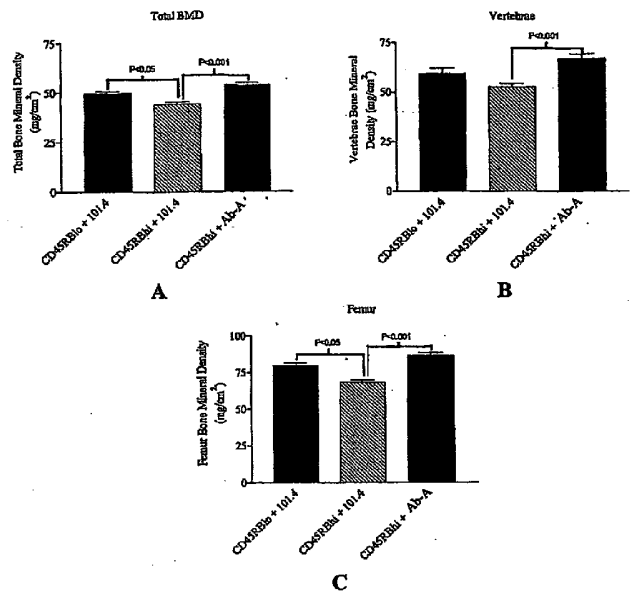


FIGURE 25