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DESCRIPTION

CROSS-REFERENCE TO RELATED APPLICATIONS

BACKGROUND

[0001] Highly concentrated liquid antibody formulations are useful for delivering doses in smaller volume. However, highly concentrated protein formulations pose several problems. One problem is instability due to the formation of particulates. Another problem is increased viscosity as a result of numerous intermolecular interactions from the macromolecular nature of antibodies. Highly viscous formulations are difficult to manufacture, draw into a syringe, and inject. The use of force in manipulating the viscous formulations leads to excessive frothing, which can lead to denaturation and inactivation of active biologics.

[0002] U.S. Patent No. 6,875,432 and U.S. Patent Application Publication Nos. 2006/0182740, 2007/0172479, 2008/0160014 disclose antibody formulations and methods of making them. None of these publications disclose the antibodies referenced herein.

[0003] WO2009/079471 discloses a method for treating bone fracture with anti-sclerostin antibodies. WO02/30463 discloses reduced-viscosity concentrated protein formulations. He F et al (Analytical Biochemistry (2010), 399: 141-143) discloses a high-throughput dynamic light scattering method for measuring the viscosity of concentrated protein solutions.

SUMMARY OF INVENTION

[0004] The present disclosure is based on the discovery that the addition of calcium acetate at low concentrations, e.g., 5-10 mM, reduced the effective viscosity in formulations comprising a high concentration of a selected anti-sclerostin antibody. In contrast, the same concentration of calcium acetate did not significantly reduce viscosity of other antibody formulations. The formulation is a sterile liquid formulation that comprises (a) an anti-sclerostin antibody at a concentration of at least 70 mg/mL, wherein the antibody comprises amino acid sequences of SEQ ID NO: 86 and SEQ ID NO: 84; and (b) calcium acetate at a concentration ranging from 1 mM to 20 mM, or from about 5 mM to about 10 mM, wherein the formulation has an absolute viscosity of 10 cP or less. Absolute viscosity as described herein is measured was measured using Brookfield LV-DVII cone and plate viscometer with a CPE-40 spindle with matching sample cup temperature regulated by a circulating water bath at constant 25°C.

[0005] The calcium salt is calcium acetate. Alternatively, in some embodiments, the calcium salt is present at a concentration that reduces viscosity of an antibody formulation by at least 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%,

26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60% or more compared to the same formulation of antibody lacking the calcium salt.

[0006] In a related aspect of the disclosure, the formulation is sterile and when in liquid or reconstituted liquid form comprises (a) an anti-sclerostin antibody at a concentration of from about 70 mg/mL to about 200 mg/mL, wherein the antibody comprises a set of six CDRs selected from the group consisting of SEQ ID NOs: 1-5 (Ab-A and Ab-1 CDRs), 15-20 (Ab-B CDRs), 25-30 (Ab-C CDRs), 35-40 (Ab-D CDRs), 45-50 (Ab-2 CDRs), 55-60 (Ab-3 and Ab-15 CDRs), 73-78 (Ab-4 and Ab-5 CDRs), 91-96 (Ab-6 CDRs), 101-106 (Ab-7 CDRs), 111-116 (Ab-8 CDRs), 121-126 (Ab-9 CDRs), 131-136 (Ab-10 CDRs), 141-146 (Ab-11 and Ab-16 CDRs), 159-164 (Ab-12 CDRs), 169-174 (Ab-13 and Ab-14 CDRs), 187-192 (Ab-17 and Ab-18 CDRs), 201-206 (Ab-19, Ab-20 and Ab-23 CDRs), 225-229 (Ab-21 and Ab-22 CDRs), or 239-244 (Ab-24 CDRs); and (b) calcium acetate at a concentration ranging from about 5 mM to about 15 mM, or from about 5 mM to about 10 mM, wherein the formulation has an absolute viscosity of about 10 cP or less. Alternatively, in some embodiments, the calcium acetate is present at a concentration that reduces viscosity of an antibody formulation by at least 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%. 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60% or more compared to the same formulation of antibody lacking the calcium acetate.

[0007] Also provided is a method for reducing the viscosity of a protein formulation, the method comprising; adding calcium acetate at a concentration of between 1 mM and 20 mM, to an anti-sclerostin immunoglobulin formulation, wherein the formulation comprises an immunoglobulin at a concentration of from 70 mg/mL to 200 mg/mL, wherein the anti-sclerostin immunoglobulin comprises amino acid sequences of SEQ ID NO: 86 and SEQ ID NO:84, and wherein the viscosity of the formulation with the calcium acetate is reduced compared to the viscosity of the antibody formulation without the calcium acetate.

[0008] In another aspect, the formulation is sterile and has an absolute viscosity of about 10 cP or less comprising: (a) Ab-5 at a concentration of at least 70 mg/mL to about 200 mg/mL; (b) calcium acetate at a concentration ranging from about 1 mM to about 20 mM; and (c) a polyol such as sucrose, for example, in an amount ranging from about 1% w/v to about 12% w/v. In certain embodiments, the polyol is in amount ranging from about 4% to 10%. The immunoglobulin comprises the amino acid sequences of SEQ ID NO: 86 (Ab-5 heavy chain variable region) and/or SEQ ID NO: 84 (Ab-5 light chain variable region).

[0009] In another aspect, the formulation is sterile and has an absolute viscosity of about 10 cP or less and comprises (a) Ab-5 at a concentration of at least 70 mg/mL to about 200 mg/mL; (b) calcium acetate at a concentration ranging from about 1 mM to about 20 mM; and (c) a polyol such as sucrose, for example, in an amount ranging from about 4% w/v to about 6% w/v.

[0010] In any of the preceding aspects, in some embodiments, the formulation further comprises (c) an acetate buffer, for example, sodium acetate, at a concentration of from about 5 mM to about 15 mM, or from about 5 mM to about 10 mM. In some embodiments, the total concentration of acetate is about 10 mM to about 50 mM, or about 20 mM to about 40 mM.

[0011] In a different aspect of the disclosure, the formulation is sterile and when in liquid or reconstituted liquid form comprises (a) an anti-sclerostin antibody at a concentration of from about 70 mg/mL to about 200 mg/mL, wherein the antibody comprises a set of six CDRs selected from the group consisting of SEQ ID NOs: 1-5 (Ab-A and Ab-1 CDRs), 15-20 (Ab-B CDRs), 25-30 (Ab-C CDRs), 35-40 (Ab-D CDRs), 45-50 (Ab-2 CDRs), 55-60 (Ab-3 and Ab-15 CDRs), 73-78 (Ab-4 and Ab-5 CDRs), 91-96 (Ab-6 CDRs), 101-106 (Ab-7 CDRs), 111-116 (Ab-8 CDRs), 121-126 (Ab-9 CDRs), 131-136 (Ab-10 CDRs), 141-146 (Ab-11 and Ab-16 CDRs), 159-164 (Ab-12 CDRs), 169-174 (Ab-13 and Ab-14 CDRs), 187-192 (Ab-17 and Ab-18 CDRs), 201-206 (Ab-19, Ab-20 and Ab-23 CDRs), 225-229 (Ab-21 and Ab-22 CDRs), or 239-244 (Ab-24 CDRs); and (b) an acetate salt and/or acetate buffer at a concentration ranging from about 10 mM to about 50 mM acetate, or from about 20 mM to about 40 mM acetate, wherein the formulation has an absolute viscosity of about 10 cP or less. In some embodiments, the acetate buffer comprises calcium acetate and/or sodium acetate. Alternatively, in some embodiments, the acetate salt and/or buffer is present at a concentration that reduces viscosity of an antibody formulation by at least 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%. 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60% or more compared to the same formulation of antibody lacking the acetate salt and/or buffer.

[0012] In any of the preceding aspects, in some embodiments, the total concentration of ions (cations and anions) in solution is about 20 mM to about 70 mM, or about 30 mM to about 60 mM. In any of these embodiments, the total osmolarity is less than about 400 mOsm/L or 350 mOsm/L, and is preferably close to isotonic, e.g. 250-350 mOsm/L. In some embodiments, the formulation is hypotonic. For example, in such embodiments, the osmolarity of the formulation is less than about 250 mOsm/L. In other embodiments, the formulation hypertonic. Thus, in such embodiments, the total osmolarity of the formulation is greater than about 350 mOsm/L.

[0013] In any of the formulations described herein, an anti-sclerostin antibody in the formulation can comprise mature heavy and/or light chain variable regions of any of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-17, Ab-19, Ab-21, Ab-23 or Ab-24. Thus, in specific embodiments of the disclosure, the antibody comprises the amino acid sequences of: SEQ ID NO: 14 (Ab-1 heavy chain variable region), and/or SEQ ID NO: 12 (Ab-1 light chain variable region); or SEQ ID NO: 68 (Ab-15 heavy chain variable region), and/or SEQ ID NO: 66 (Ab-15 light chain variable region); or SEQ ID NO: 86 (Ab-5 heavy chain variable region), and/or SEQ ID NO: 84 (Ab-5 light chain variable region); or SEQ ID NO: 154 (Ab-16 heavy chain variable region), and/or SEQ ID NO: 152 (Ab-16 light chain variable region); or SEQ ID NO: 182 (Ab-14 heavy chain

variable region) and/or SEQ ID NO: 180 (Ab-14 light chain variable region); or SEQ ID NO: 208 (Ab-19 heavy chain variable region) and/or SEQ ID NO: 207 (Ab-19 light chain variable region); or SEQ ID NO: 216 (Ab-20 heavy chain variable region) and/or SEQ ID NO: 214 (Ab-20 light chain variable region); or SEQ ID NO: 220 (Ab-23 heavy chain variable region) and/or SEQ ID NO: 218 (Ab-23 light chain variable region); or SEQ ID NO: 238 (Ab-22 heavy chain variable region) and/or SEQ ID NO: 236 (Ab-22 light chain variable region). In some embodiments of the disclosure, the antibody comprises the mature heavy and/or light chains of any of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 or Ab-24. In some embodiments of the disclosure, the antibody comprises amino acid sequences obtainable by expressing in mammalian host cells the cDNA encoding the heavy and/or light chain, or alternatively the heavy and/or light chain variable region, of any of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 or Ab-24, as described herein.

[0014] In any of the formulations described herein, the anti-sclerostin antibody may comprise the CDRs, or the mature heavy and light chain variable regions, or the mature heavy and light chains, of any of Ab-4 or Ab-5; Ab-13 or Ab-14; or Ab-19, Ab-20 or Ab-23. In any of the formulations described herein the antibody binds to sclerostin of SEQ ID NO: 1 with a K_D of 10^{-7} or less (lower numbers meaning higher binding affinity).

[0015] In any of the formulations described herein, in some embodiments, the antibody in the formulation is present at a concentration of at least 120 mg/mL, or at least 140 mg/mL. In any of the formulations described herein, in some embodiments, the absolute viscosity of the formulation is about 8 cP or less, or about 6 cP or less. In alternative embodiments, the antibody in the formulation is present at a concentration of about 70 mg/mL to about 130 mg/mL, wherein the formulation has an absolute viscosity of about 10 cP or less.

[0016] In some embodiments, any of the formulations described herein further comprises a polyol such as sucrose, for example, in an amount ranging from about 4% w/v to about 6%. In some embodiments, the formulation comprises about 9% sucrose. In some embodiments, any of the formulations described herein optionally comprises other pharmaceutically acceptable excipients, e.g. salt, buffer, amino acid, stabilizer, polyol, other tonicity agent, surfactant, bulking agent, cryoprotectant, lyoprotectant, antioxidant, metal ion, chelating agent, and/or preservative. In some embodiments, the formulation has less than 0.05% by weight surfactant.

[0017] In any of the formulations described herein, in some embodiments, the formulation has a pH ranging from about 4.5 to about 6, or about 5 to about 6, or about 5 to about 5.5. In some embodiments, the formulation has a pH of 5.2.

[0018] Also described herein are formulations for use in methods to treat any disorder associated with decreased bone density, including but not limited to, 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, pyogenic osteomyelitis, periodontal disease, anti-epileptic drug induced bone loss, primary or 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, Perthe's 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 or regional migratory osteoporosis), anemic states, conditions caused by steroids, glucocorticoid-induced bone loss, heparin-induced bone loss, bone marrow disorders, scurvy, malnutrition, calcium deficiency, osteoporosis, osteopenia, 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, 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, bone loss associated with aging, facial bone loss associated with aging, cranial bone loss associated with aging, jaw bone loss associated with aging, skull bone loss associated with aging, or bone loss associated with space travel.

[0019] The formulations described herein, in some embodiments, are 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 formulations may be administered before, during and/or after the procedure, replacement, graft, surgery or repair.

[0020] Such methods may comprise administering a formulation in a therapeutically effective amount, e.g. an amount effective to improve bone density, and may further comprise administering a second therapeutic agent.

[0021] Also disclosed herein is a vial, kit or container, e.g. a pre-filled syringe or injection device, comprising a formulation described herein and optionally a label comprising instructions to use the appropriate volume or amount of the formulation necessary to achieve a dose of from about 0.5-20 mg/kg, or 0.5-10 mg/kg of patient body weight.

[0022] It should be understood that while various embodiments in the specification are presented using "comprising" language, under various circumstances, a related embodiment may also be described using "consisting of" or "consisting essentially of" language. It is to be noted that the term "a" or "an", refers to one or more, for example, "an immunoglobulin molecule," is understood to represent one or more immunoglobulin molecules. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0023] It should also be understood that when describing a range of values, the characteristic being described could be an individual value found within the range. For example, "a pH from about pH 4 to about pH 6," could be, but is not limited to, pH 4, 4.2, 4.6, 5.1 5.5 etc. and any value in between such values. Additionally, "a pH from about pH 4 to about pH 6," should not be construed to mean that the pH of a formulation in question varies 2 pH units in the range from pH 4 to pH 6 during storage, but rather a value may be picked in that range for the pH of the solution, and the pH remains buffered at about that pH. In some embodiments, when the term "about" is used, it means the recited number plus or minus 5%, 10%, 15% or more of that recited number. The actual variation intended is determinable from the context.

[0024] In any of the ranges described herein, the endpoints of the range are included in the range. However, the description also contemplates the same ranges in which the lower and/or the higher endpoint is excluded. Additional features and variations of the invention will be apparent to those skilled in the art from the entirety of this application, including the drawing and detailed description, and all such features are intended as aspects of the invention. Likewise, features of the invention described herein can be re-combined into additional embodiments that also are intended as aspects of the invention, irrespective of whether the combination of features is specifically mentioned above as an aspect or embodiment of the invention. Also, only such limitations which are described herein as critical to the invention should be viewed as such; variations of the invention lacking limitations which have not been described herein as critical are intended as aspects of the invention.

DETAILED DESCRIPTION

[0025] Described herein are formulations comprising high concentrations of antibody that contain calcium salts and/or acetate salts or buffers to reduce viscosity, and containers or kits comprising these formulations.

I. Antibodies in the formulation

[0026] In some embodiments, the anti-sclerostin antibody in the formulation is present at a concentration of at least 70 mg/ml, about 71 mg/ml, about 72 mg/ml, about 73 mg/ml, about 74 mg/ml, about 75 mg/ml, about 76 mg/ml, about 77 mg/ml, about 78 mg/ml, about 79 mg/ml, about 80 mg/ml, about 81 mg/ml, about 82 mg/ml, about 83 mg/ml, about 84 mg/ml, about 85

mg/ml, about 86 mg/ml, about 87 mg/ml, about 88 mg/ml, about 89 mg/ml, about 90 mg/ml, about 91 mg/ml, about 92 mg/ml, about 93 mg/ml, about 94 mg/ml, about 95 mg/ml, about 96 mg/ml, about 97 mg/ml, about 98 mg/ml, about 99 mg/ml, about 100 mg/ml, about 101 mg/ml, about 102 mg/ml, about 103 mg/ml, about 104 mg/ml, about 105 mg/ml, about 106 mg/ml, about 107 mg/ml, about 108 mg/ml, about 109 mg/ml, about 110 mg/ml, about 111 mg/ml, about 112 mg/ml, about 113 mg/ml, about 114 mg/ml, about 115 mg/ml, about 116 mg/ml, about 117 mg/ml, about 118 mg/ml, about 119 mg/ml, about 120 mg/ml, about 121 mg/ml, about 122 mg/ml, about 123 mg/ml, about 124 mg/ml, about 125 mg/ml, about 126 mg/ml, about 127 mg/ml, about 128 mg/ml, about 129 mg/ml, about 130 mg/ml, about 131 mg/ml, about 132 mg/ml, about 132 mg/ml, about 133 mg/ml, about 134 mg/ml, about 135 mg/ml, about 136 mg/ml, about 137 mg/ml, about 138 mg/ml, about 139 mg/ml, about 140 mg/ml, about 141 mg/ml, about 142 mg/ml, about 143 mg/ml, about 144 mg/ml, about 145 mg/ml, about 146 mg/ml, about 147 mg/ml, about 148 mg/ml, about 149 mg/ml, about 150 mg/ml, about 151 mg/ml, about 152 mg/ml, about 153 mg/ml, about 154 mg/ml, about 155 mg/ml, about 156 mg/ml, about 157 mg/ml, about 158 mg/ml, about 159 mg/ml, or about 160 mg/ml, and may range up to , e.g., about 300 mg/ml, about 290 mg/ml, about 280 mg/ml, about 270 mg/ml, about 260 mg/ml, about 250 mg/ml, about 240 mg/ml, about 230 mg/ml, about 220 mg/ml, about 210 mg/ml, about 200 mg/ml, about 190 mg/ml, about 180 mg/ml, or about 170 mg/ml. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to: about 70 mg/ml to about 250 mg/ml, about 70 mg/ml to about 200 mg/ml, about 70 mg/ml to about 160 mg/ml, about 100 mg/ml to about 250 mg/ml, about 100 mg/l to about 200 mg/ml, or about 100 mg/ml to about 180 mg/ml.

[0027] 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 were previously described in U.S. Patent Application Publication No. 2007/0110747.

[0028] The anti-sclerostin antibodies described herein bind to sclerostin of SEQ ID NO: 1 with a K_D of 10^{-6} or less, or 10^{-7} or less, or 10^{-8} or less, or 10^{-9} or less (lower numbers meaning higher binding affinity). Affinity can be determined by any means known in the art, including via Biacore technology.

[0029] In the embodiments, the antibody comprises the heavy and/or light chain of antibody Ab-5. The amino acid sequences of the mature full length light chain of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-17, Ab-19, Ab-23 and Ab-24, including the constant region, are set forth in SEQ ID NOs: 8, 22, 32, 42, 52, 62, 80, 88, 98, 108, 118, 128, 138, 148, 166, 176, 184, 70, 210 222, and 246, respectively. The amino acid sequences of the mature full length heavy chain of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 and Ab-24, including the constant region, are set forth in SEQ ID NOs: 10, 24, 34, 44, 54, 64, 82, 90, 100, 110, 120, 130, 140, 150, 168, 178, 186, 72, 224, and 248.

[0030] Corresponding cDNA sequences encoding the full length light chain of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 and Ab-24, including the constant region, are set forth in SEQ ID NOs: 7, 21, 31, 41, 51, 61, 79, 87, 97, 107, 117, 127, 137, 147, 165, 175, 183, 69, 209, 221 and 245, respectively. Corresponding cDNA sequences encoding the full length heavy chain, including the constant region of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 and Ab-24, are set forth in SEQ ID NOs: 9, 23, 33, 43, 53, 63, 81, 89, 99, 109, 119, 129, 139, 149, 167, 177, 185, 71, 211, 223, and 247, respectively.

[0031] The antibody comprises the heavy and/or light chain variable region of antibody Ab-5. The antibody comprises SEQ ID NO: 86 (Ab-5 heavy chain variable region) and SEQ ID NO: 84 (Ab-5 light chain variable region.

[0032] In some embodiments of the disclosure, the antibody comprises the CDRs set forth in SEQ ID NOs: 1-5 (Ab-A and Ab-1 CDRs), or 15-20 (Ab-B CDRs), or 25-30 (Ab-C CDRs), or 35-40 (Ab-D CDRs), or 45-50 (Ab-2 CDRs), or 55-60 (Ab-3 and Ab-15 CDRs), or 73-78 (Ab-4 and Ab-5 CDRs), or 91-96 (Ab-6 CDRs), or 101-106 (Ab-7 CDRs), or 111-116 (Ab-8 CDRs), or 121-126 (Ab-9 CDRs), or 131-136 (Ab-10 CDRs), or 141-146 (Ab-11 and Ab-16 CDRs), or 159-164 (Ab-12 CDRs), or 169-174 (Ab-13 and Ab-14 CDRs), or 187-192 (Ab-17 and Ab-18 CDRs), or 201-206 (Ab-19, Ab-20 and Ab-23 CDRs), or 225-229 (Ab-21 and Ab-22 CDRs), or 239-244 (Ab-24 CDRs).

[0033] In some embodiments, the antibody comprises amino acid sequences obtainable by expressing in mammalian host cells the cDNA encoding the heavy and/or light chain, or alternatively the heavy and/or light chain variable region, of antibody Ab-5, as described herein. In any of the formulations described herein, in some embodiments, the antibody is a tetrameric immunoglobulin consisting of two heavy chains and two light chains.

[0034] In some embodiments of the disclosure, the antibody comprises the CDRs of any of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 or Ab-24, and comprises a heavy and/or light chain comprising an amino acid sequence at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the heavy and/or light chain of antibody Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 or Ab-24, respectively. In some embodiments of the disclosure, the antibody comprises the CDRs of any of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 or Ab-24, and comprises a heavy and/or light chain comprising an amino acid sequence at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the heavy and/or light chain variable region of antibody Ab-A, Ab-B, Ab-C, Ab-D, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-15, Ab-16, Ab-19, Ab-23 or Ab-24, respectively.

[0035] In some embodiments of the disclosure, the antibody:

1. 1) retains any one, two, three, four, five, or six of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and/or CDRL3 of any 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 or Ab-24, optionally including one or two mutations in such CDR(s),
2. 2) retains all of CDRH1, CDRH2, CDRH3, or the heavy chain variable region of, any of antibody 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 or Ab-24, optionally including one or two mutations in such CDR(s),
3. 3) retains all of CDRL1, CDRL2, CDRL3, or the light chain variable region of, any of antibody 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 or Ab-24, optionally including one or two mutations in such CDR(s),
4. 4) binds to the same epitope of sclerostin as antibody 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 or Ab-24, e.g. as determined through X-ray crystallography, or an amino acid within a loop formed by amino acids 86-111 of SEQ ID NO: 249; and/or
5. 5) competes with antibody 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 or Ab-24 for binding to sclerostin by more than about 75%, more than about 80%, or more than about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94% or 95%.

[0036] In some embodiments of the disclosure, the antibody comprises all three light chain CDRs, the mature light chain variable region, all three heavy chain CDRs, the mature heavy chain variable region, all six CDRs, or both the mature light chain and the mature heavy chain variable region. In some exemplary embodiments of the disclosure, two light chain CDRs from an antibody may be combined with a third light chain CDR from a different antibody. Alternatively, a CDRL1 from one antibody can be combined with a CDRL2 from a different antibody and a CDRL3 from yet another antibody, particularly where the CDRs are highly homologous. Similarly, two heavy chain CDRs from an antibody may be combined with a third heavy chain CDR from a different antibody; or a CDRH1 from one antibody can be combined with a CDRH2 from a different antibody and a CDRH3 from yet another antibody, particularly where the CDRs are highly homologous.

[0037] 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, Nature Biotechnology, 23(9):1 126-1136 (2005)).

[0038] An "isolated" antibody refers to an antibody, as that term is defined herein, that has been identified and separated from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In certain embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated naturally occurring antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

[0039] An "immunoglobulin" or "native antibody" is a tetrameric glycoprotein. In a naturally-occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a "variable" ("V") region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Immunoglobulins can be assigned to different classes depending on the amino acid sequence of the constant domain of their heavy chains. Heavy chains are classified as mu (μ), delta (Δ), gamma (γ), alpha (α), and epsilon (ε), and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Several of these may be further divided into subclasses or isotypes, e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. Different isotypes have different effector functions; for example, IgG1 and IgG3 isotypes have antibody-dependent cellular cytotoxicity (ADCC) activity. Human light chains are classified as kappa (κ) and lambda (λ) light chains. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology, Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)).

[0040] Allotypes are variations in antibody sequence, often in the constant region, that can be immunogenic and are encoded by specific alleles in humans. Allotypes have been identified for five of the human IGHC genes, the IGHG1, IGHG2, IGHG3, IGHA2 and IGHE genes, and are designated as G1m, G2m, G3m, A2m, and Em allotypes, respectively. At least 18 Gm allotypes are known: nG1m(1), nG1m(2), G1m (1, 2, 3, 17) or G1m (a, x, f, z), G2m (23) or G2m (n), G3m (5, 6, 10, 11, 13, 14, 15, 16, 21, 24, 26, 27, 28) or G3m (b1, c3, b5, b0, b3, b4, s, t, g1, c5, u, v, g5). There are two A2m allotypes A2m(1) and A2m(2).

[0041] The term "hypervariable" region refers to amino acid residues from a complementarity determining region or CDR (i.e., residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain and 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable

domain as described by Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). Even a single CDR may recognize and bind antigen, although with a lower affinity than the entire antigen binding site containing all of the CDRs.

[0042] An alternative definition of residues from a hypervariable "loop" is described by Chothia et al., J. Mol.Biol. 196: 901-917 (1987) as residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain.

[0043] "Framework" or FR residues are those variable region residues other than the hypervariable region residues.

[0044] "Antibody fragments" comprise a portion of an intact immunoglobulin, preferably an antigen binding or variable region of the intact antibody, and include multispecific (bispecific, trispecific, etc.) antibodies formed from antibody fragments. Fragments of immunoglobulins may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies.

[0045] Nonlimiting examples of antibody fragments include Fab, Fab', $F(ab')_2$, Fv (variable region), domain antibodies (dAb, containing a VH domain) (Ward et al., Nature 341:544-546, 1989), complementarity determining region (CDR) fragments, single-chain antibodies (scFv, containing VH and VL domains on a single polypeptide chain) (Bird et al., Science 242:423-426, 1988, and Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883, 1988, optionally including a polypeptide linker; and optionally multispecific, Gruber et al., J. Immunol. 152: 5368 (1994)), single chain antibody fragments, diabodies (VH and VL domains on a single polypeptide chain that pair with complementary VL and VH domains of another chain) (EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993)), triabodies, tetrabodies, minibodies (scFv fused to CH3 via a peptide linker (hingeless) or via an IgG hinge) (Olafsen, et al., Protein Eng Des Sel. 2004 Apr;17(4):315-23), linear antibodies (tandem Fd segments (VH -CH1-VH -CH1) (Zapata et al., Protein Eng.,8(10):1057-1062 (1995)); chelating recombinant antibodies (crAb, which can bind to two adjacent epitopes on the sane antigen) (Neri et al., J Mol Biol. 246:367-73, 1995), bibodies (bispecific Fab-scFv) or tribodies (trispecific Fab-(scFv)(2)) (Schoonjans et al., J Immunol. 165:7050-57, 2000; Willems et al., J Chromatogr B Analyt Technol Biomed Life Sci. 786:161-76, 2003), intrabodies (Biocca, et al., EMBO J. 9:101-108, 1990; Colby et al., Proc Natl Acad Sci U S A. 101:17616-21, 2004) which may also comprise cell signal sequences which retain or direct the antibody intracellularly (Mhashilkar et al, EMBO J 14:1542-51, 1995; Wheeler et al., FASEB J. 17:1733-5, 2003), transbodies (cell-permeable antibodies containing a protein transduction domain (PTD) fused to scFv (Heng et al., Med Hypotheses. 64:1105-8, 2005), nanobodies (approximately 15kDa variable domain of the heavy chain) (Cortez-Retamozo et al., Cancer Research 64:2853-57, 2004), small modular immunopharmaceuticals (SMIPs) (WO03/041600, U.S. Patent publication 20030133939 and US Patent Publication 20030118592), an antigen-binding-domain immunoglobulin fusion protein, a camelized antibody (in which VH recombines

with a constant region that contains hinge, CH1, CH2 and CH3 domains) (Desmyter et al., J. Biol. Chem. 276:26285-90, 2001; Ewert et al., Biochemistry 41:3628-36, 2002; U.S. Patent Publication Nos. 20050136049 and 20050037421), a VHH containing antibody, heavy chain antibodies (HCAbs, homodimers of two heavy chains having the structure H2L2), or variants or derivatives thereof, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide, such as a CDR sequence, as long as the antibody retains the desired biological activity.

[0046] The term "variant" when used in connection with antibodies refers to a polypeptide sequence of an antibody that contains at least one amino acid substitution, deletion, or insertion in the variable region or the portion equivalent to the variable region, provided that the variant retains the desired binding affinity or biological activity. In addition, the antibodies as described herein may have amino acid modifications in the constant region to modify effector function of the antibody, including half-life or clearance, ADCC and/or CDC activity. Such modifications can enhance pharmacokinetics or enhance the effectiveness of the antibody in treating cancer, for example. See Shields et al., J. Biol. Chem., 276(9):6591-6604 (2001). In the case of IgG1, modifications to the constant region, particularly the hinge or CH2 region, may increase or decrease effector function, including ADCC and/or CDC activity. An IgG2 constant region may be modified to decrease antibody-antigen aggregate formation. In the case of IgG4, modifications to the constant region, particularly the hinge region, may reduce the formation of half-antibodies.

[0047] The term "modification" when used in connection with antibodies or polypeptides described herein, includes but is not limited to, one or more amino acid change (including substitutions, insertions or deletions); chemical modifications that do not interfere with hepcidin-binding activity; covalent modification by conjugation to therapeutic or diagnostic agents; labeling (e.g., with radionuclides or various enzymes); covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or substitution by chemical synthesis of non-natural amino acids. In Modified polypeptides (including antibodies) may retain the binding properties of unmodified molecules of the invention.

[0048] The term "derivative" when used in connection with antibodies or polypeptides of the invention refers to antibodies or polypeptides that are covalently modified by conjugation to therapeutic or diagnostic agents, labeling (e.g., with radionuclides or various enzymes), covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or substitution by chemical synthesis of non-natural amino acids. Derivatives may retain the binding properties of underivatized molecules.

[0049] Methods for making bispecific or other multispecific antibodies are known in the art and include chemical cross-linking, use of leucine zippers [Kostelny et al., J. Immunol. 148:1547-1553, 1992]; diabody technology [Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-48, 1993]; scFv dimers [Gruber et al., J. Immunol. 152: 5368, 1994], linear antibodies [Zapata et al., Protein Eng. 8:1057-62, 1995]; and chelating recombinant antibodies [Neri et al., J Mol Biol. 246:367-73, 1995].

[0050] Proteins and non-protein agents may be conjugated to the antibodies by methods that are known in the art. Conjugation methods include direct linkage, linkage via covalently attached linkers, and specific binding pair members (e.g., avidin-biotin). Such methods include, for example, that described by Greenfield et al., Cancer Research 50, 6600-6607 (1990) for the conjugation of doxorubicin and those described by Arnon et al., Adv. Exp. Med. Biol. 303, 79-90 (1991) and by Kiseleva et al., Mol. Biol. (USSR) 25, 508-514 (1991) for the conjugation of platinum compounds.

[0051] In some embodiments, antibodies and antibody fragments described herein are obtained, for example, from naturally-occurring antibodies, or Fab or scFv phage display libraries. The phrase "humanized antibody" refers to an antibody derived from a sequence of a non-human antibody, typically a rodent monoclonal antibody, which comprises modifications that render the sequence more human-like. Alternatively, a humanized antibody may be derived from a chimeric antibody.

[0052] Antibody fragments include domain antibody (dAb) fragment (Ward et al., Nature 341:544-546, 1989) which consists of a V_H domain, "linear antibodies" comprise a pair of tandem Fd segments (V_H-C_H1-V_H-C_H1) which form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific (Zapata et al. Protein Eng. 8:1057-62 (1995)); "minibody" consisting of scFv fused to CH3 via a peptide linker (hingeless) or via an IgG hinge has been described in Olafsen, et al., Protein Eng Des Sel. 2004 Apr;17(4):315-23; "maxibody" refers to bivalent scFvs covalently attached to the Fc region of an immunoglobulin, see, for example, Fredericks et al, Protein Engineering, Design & Selection, 17:95-106 (2004) and Powers et al., Journal of Immunological Methods, 251:123-135 (2001); heavy-chain antibodies, e.g. the VH_H domain, or H_2L_2 (referred to as "heavy-chain antibodies" or "HCAbs"); or camelized V_{HH} (See, e.g., Reichman, etal., J Immunol Methods 1999, 231:25-38, Desmyter et al., J. Biol. Chem. 276:26285-90, 2001, Ewert et al., Biochemistry 41:3628-36, 2002; nanobody (Cortez-Retamozo et al., Cancer Research 64:2853-57, 2004);intrabodies are single chain antibodies which demonstrate intracellular expression and can manipulate intracellular protein function (Biocca, et al., EMBO J. 9:101-108, 1990; Colby et al., Proc Natl Acad Sci U S A. 101:17616-21, 2004, Mhashilkar et al, EMBO J 14:1542-51, 1995, Wheeler et al. (FASEB J. 17:1733-5. 2003); transbodies are cell-permeable antibodies in which a protein transduction domains (PTD) is fused with single chain variable fragment (scFv) antibodies Heng et al., (Med Hypotheses. 64:1105-8, 2005); SMIPs or binding domain immunoglobulin fusion proteins specific for target protein are single-chain polypeptides comprising antigen binding domains fused to immunoglobulin domains necessary to carry out antibody effector functions. See e.g., WO03/041600, U.S. Patent publication 20030133939 and US Patent Publication 20030118592.

II. Calcium and acetate salts or buffers

[0053] It has been found that adding relatively low concentrations of calcium acetate to

formulations of a selected antibody reduces the viscosity of the formulation. The term "viscosity" as used herein refers to "absolute viscosity." Absolute viscosity, sometimes called dynamic or simple viscosity, is the product of kinematic viscosity and fluid density: Absolute Viscosity=Kinematic Viscosity x Density. The dimension of kinematic viscosity is L^2/T where L is a length and T is a time. Commonly, kinematic viscosity is expressed in centistokes (cSt). The SI unit of kinematic viscosity is mm^2/s, which is 1 cSt. Absolute viscosity is expressed in units of centipoise (cP). The SI unit of absolute viscosity is the millipascal-second (mPa-s), where 1 cP=1 mPa-s.

[0054] Such viscosity measurements may be made hours (e.g., 1-23 hours), days (e.g., 1-10 days), weeks (e.g., 1-5 weeks), or months (e.g., 1-12 months), or years (e.g., 1-2 years, 1-3 years) after the addition of a viscosity reducing agent to an antibody formulation. Viscosity measurements may be made at a storage or administration temperature, e.g. 2-8°C or 25°C (room temperature). In some embodiments, absolute viscosity of the liquid or reconstituted liquid formulation at the storage and/or administration temperature is 10, 9, 8, 7, 6, 5, or 4 cP or less.

[0055] In some embodiments, the viscosity of the protein formulation is measured prior to and after the addition of the calcium acetate (and/or buffer). Methods of measuring viscosity are well known in the art and include, for example, using a capillary viscometer, or a cone-plate rheometer. Any methods may be used provided the same method is used to compare the test and reference formulations.

[0056] The viscosity of an antibody formulation can be reduced by the addition of a calcium salt, and/or an acetate salt (and/or buffer) to the formulation. Viscosity of an antibody formulation can be reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, and about 90% compared to the viscosity of a comparable antibody formulation lacking the calcium salt, and/or acetate salt (and/or buffer).

[0057] Exemplary calcium salts include, but are not limited to, calcium acetate, calcium carbonate and calcium chloride. In some embodiments, the calcium acetate is at a concentration of at least 0.5 mM, 1 mM, 2 mM, 3 mM, 4 mM, 5 mM, 6 mM, 7 mM, 8 mM, 9 mM or 10 mM. In certain embodiments, the concentration of calcium acetate is not greater than 11 mM, 12 mM, 13 mM, 14 mM, 15 mM, 16 mM, 17 mM, 18 mM, 19 mM, or 20 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to from about 0.5 mM to about 10 mM, about 5 mM to about 10 mM, or about 5 mM to about 15 mM. In some embodiments, the calcium acetate is present at a concentration that reduces viscosity of an antibody formulation by at least 30%, 40%, 50%, 60% or more compared to the same formulation of antibody lacking the acetate salt and/or buffer, or that achieves a viscosity of 10 cP or less, or 9, 8, 7, 6, or 5 cP or less. In certain embodiments, the calcium acetate is added at low concentrations so as not to negatively impact the protein formulation. For example, at calcium chloride or magnesium chloride concentrations of 20 mM or greater,

proteins may form a gel at low storage temperatures (e.g., 2-8°C). Accordingly, a concentration of a calcium salt is generally selected for which the viscosity is reduced at the intended storage temperature of the reduced viscosity formulation.

[0058] In all of the ranges described herein, the concentration of cation, anion or salt described is the final concentration in the liquid or reconstituted liquid formulation that is to be administered. In any of the ranges described herein, the endpoints of the range are included in the range. However, the description also contemplates the same ranges in which the lower and/or the higher endpoint is excluded.

[0059] In some embodiments, a formulation described herein further comprises, in addition to the calcium salt, an acetate buffer at a concentration of at least 5 mM, 6 mM, 7 mM, 8 mM, 9 mM, 10 mM, or 15 mM. In some embodiments, the concentration is no greater than 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM or 50 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to from about 5 mM to about 15 mM, or from about 5 mM to about 10 mM. The buffer is preferably added to a concentration that maintains pH around 5-6 or 5-5.5 or 4.5-5.5. In some embodiments, the total concentration of acetate is about 10 mM to about 50 mM, or about 20 mM to about 40 mM.

[0060] In some aspects, the formulation comprises a total concentration of acetate that is at least about 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, or 50 mM. In some embodiments, the concentration of acetate is no greater than about 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, 85 mM, or 90 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to: about 10 mM to about 50 mM, about 20 mM to about 50 mM, about 20 mM to about 40 mM, about 30 mM to about 50 mM, or about 30 mM to about 75 mM. In some embodiments, the acetate buffer comprises calcium acetate and/or sodium acetate. Alternatively, in some embodiments, the acetate salt and/or buffer is present at a concentration that reduces viscosity of an antibody formulation by at least 30%, 40%, 50%, 60% or more compared to the same formulation of antibody lacking the acetate salt and/or buffer, or that achieves a viscosity of 10 cP or less, or 9, 8, 7, 6, or 5 cP or less. By way of non limiting example, a solution containing 10 mM calcium acetate will have 20 mM acetate anion and 10 mM of calcium cation, because of the divalent nature of the calcium cation, while a solution containing 10 mM sodium acetate will have 10 mM sodium cation and 10 mM acetate anion.

[0061] In some embodiments, the total concentration of ions (cations and anions) in solution is at least 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, or 85 mM. In some embodiments, the total concentration of ions is no greater than about 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, 85 mM, 90 mM, 95 mM, 100 mM, 110 mM, 120 mM, 130 mM, 140 mM, 150 mM, 160 mM, 170 mM, 180 mM, 190 mM or 200 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to: about 30 mM to about 60 mM, or about 30 mM to about 70 mM, or about 30 mM to about 80 mM, or

about 40 mM to about 150 mM, or about 50 mM to about 150 mM. By way of nonlimiting example, a solution of 10 mM calcium acetate will have a 30 mM total concentration of ions (10 mM cations and 20 mM anions).

[0062] In any of the formulations described herein, in some embodiments, the total osmolarity is no greater than 500 mOsm/L, 450 mOsm/L, 400 mOsm/L, or 350 mOsm/L, and is preferably close to isotonic, e.g. 250-350 mOsm/L.

[0063] Other excipients known in the art or described herein can be further included in the formulation.

III. Excipients in the formulation

[0064] Protein formulations are generally administered parenterally. When given parenterally, they must be sterile. Sterile diluents include liquids that are pharmaceutically acceptable (safe and non-toxic for administration to a human) and useful for the preparation of a liquid formulation, such as a formulation reconstituted after lyophilization. Exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (e.g. phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution. Diluents can include aqueous solutions of salts and/or buffers.

[0065] Excipients are additives that are included in a formulation because they either impart or enhance the stability, delivery and manufacturability of a drug product. Regardless of the reason for their inclusion, excipients are an integral component of a drug product and therefore need to be safe and well tolerated by patients. For protein drugs, the choice of excipients is particularly important because they can affect both efficacy and immunogenicity of the drug. Hence, protein formulations need to be developed with appropriate selection of excipients that afford suitable stability, safety, and marketability.

[0066] The excipients described herein are organized either by their chemical type or their functional role in formulations. Brief descriptions of the modes of stabilization are provided when discussing each excipient type. Given the teachings and guidance provided herein, those skilled in the art will readily be able to vary the amount or range of excipient without increasing viscosity to an undesirable level. Excipients may be chosen to achieve a desired osmolality (i.e., isotonic, hypotonic or hypertonic) of the final solution, pH, desired stability, resistance to aggregation or degradation or precipitation, protection under conditions of freezing, lyophilization or high temperatures, or other properties. A variety of types of excipients are known in the art. Exemplary excipients include salts, amino acids, other tonicity agents, surfactants, stabilizers, bulking agents, cryoprotectants, lyoprotectants, antioxidants, metal ions, chelating agents and/or preservatives.

[0067] Further, where a particular excipient is reported in a formulation by, e.g., percent (%) w/v, those skilled in the art will recognize that the equivalent molar concentration of that

excipient is also contemplated.

A. Buffers

[0068] The pH range of optimal stability needs to be identified early during pre-formulation studies. Several approaches such as accelerated stability studies and calorimetric screening studies have been demonstrated to be useful in this endeavor (Remmele R.L. Jr., et al., Biochemistry, 38(16): 5241-7 (1999)). Once a formulation is finalized, the drug product must be manufactured and maintained within a predefined specification throughout its shelf-life. Hence, buffering agents are almost always employed to control pH in the formulation.

[0069] Organic acids, phosphates and Tris have been employed routinely as buffers in protein formulations (Table 1). The buffer capacity of the buffering species is maximal at a pH equal to the pKa and decreases as pH increases or decreases away from this value. Ninety percent of the buffering capacity exists within one pH unit of its pKa. Buffer capacity also increases proportionally with increasing buffer concentration.

[0070] Several factors need to be considered when choosing a buffer. First and foremost, the buffer species and its concentration need to be defined based on its pKa and the desired formulation pH. Equally important is to ensure that the buffer is compatible with the protein drug, other formulation excipients, and does not catalyze any degradation reactions. Recently, polyanionic carboxylate buffers such as citrate and succinate have been shown to form covalent adducts with the side chain residues of proteins. A third important aspect to be considered is the sensation of stinging and irritation the buffer may induce. For example, citrate is known to cause stinging upon injection (Laursen T, et al., Basic Clin Pharmacol Toxicol., 98(2): 218-21 (2006)). The potential for stinging and irritation is greater for drugs that are administered via the SC or IM routes, where the drug solution remains at the site for a relatively longer period of time than when administered by the IV route where the formulation gets diluted rapidly into the blood upon administration. For formulations that are administered by direct IV infusion, the total amount of buffer (and any other formulation component) needs to be monitored. For example, it has been reported that potassium ions administered in the form of the potassium phosphate buffer, can induce cardiovascular effects in a patient (Hollander-Rodriguez JC, et al., Am. Fam. Physician., 73(2): 283-90 (2006)).

Table 1: Commonly used buffering agents and their pK_a values

Buffer	pK_a	Example drug product
Acetate	4.8	Neupogen, Neulasta
Succinate	pK_{a1} = 4.8, pK_{a2} = 5.5	Actimmune
Citrate	pK_{a1} = 3.1, pK_{a2} = 4.8, pK_{a3} = 6.4	Humira
Histidine (imidazole)	6.0	Xolair

Buffer	pK_a	Example drug product
Phosphate	pK_{a1} = 2.15, pK_{a2} = 7.2, pK_{a3} = 12.3	Enbrel (liquid formulation)
Tris	8.1	Leukine

[0071] The buffer system present in the formulation is selected to be physiologically compatible and to maintain a desired pH.

[0072] The pH buffering compound may be present in any amount suitable to maintain the pH of the formulation at a predetermined level. The pH buffering agent, e.g. acetate, may be present at a concentration between 0.1 mM and 1000 mM (1 M). In one embodiment, the pH buffering agent is at least 0.1, 0.5, 0.7, 0.8 0.9, 1.0, 1.2, 1.5, 1.7, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, 700, or 900 mM. In another embodiment, the concentration of the pH buffering agent is between 1, 1.2, 1.5, 1.7, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, or 90 mM and 100 mM. In still another embodiment, the concentration of the pH buffering agent is between 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, or 40 mM and 50 mM. In yet another embodiment, the concentration of the pH buffering agent is 10 mM.

[0073] Other exemplary pH buffering agents used to buffer the formulation as set out herein include, but are not limited to glycine, glutamate, succinate, phosphate, acetate, and aspartate. Amino acids such as histidine and glutamic acid can also be used as buffering agents.

B. Stabilizers and bulking agents

[0074] Stabilizers include a class of compounds that can serve as cryoprotectants, lyoprotectants, and glass forming agents. Cryoprotectants act to stabilize proteins during freezing or in the frozen state at low temperatures. Lyoprotectants stabilize proteins in the freeze-dried solid dosage form by preserving the native-like conformational properties of the protein during dehydration stages of freeze-drying. Glassy state properties have been classified as "strong" or "fragile" depending on their relaxation properties as a function of temperature. It is important that cryoprotectants, lyoprotectants, and glass forming agents remain in the same phase with the protein in order to impart stability. Sugars, polymers, and polyols fall into this category and can sometimes serve all three roles.

[0075] Polyols encompass a class of excipients that includes sugars, (e.g. mannitol, sucrose, sorbitol), and other polyhydric alcohols (e.g., glycerol and propylene glycol). The polymer polyethylene glycol (PEG) is included in this category. Polyols are commonly used as stabilizing excipients and/or isotonicity agents in both liquid and lyophilized parenteral protein formulations. Polyols can protect proteins from both physical and chemical degradation pathways.

[0076] Exemplary C3-C6 polyols include propylene glycol, glycerin (glycerol), threose, threitol, erythrose, erythritol, ribose, arabinose, arabitol, lyxose, maltitol, sorbitol, sorbose, glucose, mannose, mannitol, levulose, dextrose, maltose, trehalose, fructose, xylitol, inositol, galactose, xylose, fructose, sucrose, 1,2,6-hexanetriol and the like. Higher order sugars include dextran, propylene glycol, or polyethylene glycol. Reducing sugars such as fructose, maltose or galactose oxidize more readily than do non-reducing sugars. Additional examples of sugar alcohols are glucitol, maltitol, lactitol or iso-maltulose. Additional exemplary lyoprotectants include glycerin and gelatin, and the sugars mellibiose, melezitose, raffinose, mannotriose and stachyose. Examples of reducing sugars include glucose, maltose, lactose, maltulose, iso-maltulose and lactulose. Examples of non-reducing sugars include non-reducing glycosides of polyhydroxy compounds selected from sugar alcohols and other straight chain polyalcohols. Monoglycosides include compounds obtained by reduction of disaccharides such as lactose, maltose, lactulose and maltulose.

[0077] In some embodiments, the formulations described herein also comprise a stabilizer (or a combination of stabilizers) is added to the formulation. The term "stabilizer" means an excipient capable of preventing aggregation or other physical degradation, as well as chemical degradation (for example, autolysis, deamidation, oxidation, etc.) in an aqueous and solid state. Stabilizers that are conventionally employed in pharmaceutical compositions include, but are not limited to, sucrose, trehalose, mannose, maltose, lactose, glucose, raffinose, cellobiose, gentiobiose, isomaltose, arabinose, glucosamine, fructose, mannitol, sorbitol, glycine, arginine HCL, poly-hydroxy compounds, including polysaccharides such as dextran, starch, hydroxyethyl starch, cyclodextrins, N-methyl pyrollidene, cellulose and hyaluronic acid, sodium chloride, [Carpenter et al., Develop. Biol. Standard 74:225, (1991)]. In one embodiment, the stabilizer is incorporated in a concentration of about 0% to about 40% w/v. In another embodiment, the stabilizer is incorporated in a concentration of at least 0.5, 1,2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, or 40% w/v. In another embodiment, the stabilizer is incorporated in a concentration of about 1, 2, 3, 4, 5, 6, 7, 8, 9% to about 10% w/v. In still another embodiment, the stabilizer is incorporated in a concentration of about 2% to about 6% w/v. In yet another embodiment, the stabilizer is incorporated in a concentration of about 4% w/v. In yet another embodiment, the stabilizer is incorporated in a concentration of about 6% w/v.

[0078] If desired, the formulations also include appropriate amounts of bulking and osmolarity regulating agents suitable for forming a lyophilized "cake". Bulking agents may be either crystalline (for example, mannitol, glycine) or amorphous (for example, sucrose, polymers such as dextran, polyvinylpyrolidone, carboxymethylcellulose). Other exemplary bulking agents include lactose, sorbitol, trehalose, or xylitol. In a further embodiment, the bulking agent is incorporated in a concentration of about 0% to about 10% w/v. In another embodiment, the bulking agent is incorporated in a concentration of at least 0.2, 0.5, 0.7, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, or 9.5% w/v. In a yet further embodiment the bulking agent is in a concentration of about 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5% to 5.0% w/v, to produce a mechanically and pharmaceutically stable cake.

C. Surfactants

[0079] Protein molecules have a high propensity to interact with surfaces making them susceptible to adsorption and denaturation at air-liquid, vial-liquid, and liquid-liquid (silicone oil) interfaces. This degradation pathway has been observed to be inversely dependent on protein concentration and result in either the formation of soluble and insoluble protein aggregates or the loss of protein from solution via adsorption to surfaces. In addition to container surface adsorption, surface-induced degradation is exacerbated with physical agitation, as would be experienced during shipping and handling of the product.

[0080] Surfactants are commonly used in protein formulations to prevent surface-induced degradation. Surfactants are amphipathic molecules with the capability of out-competing proteins for interfacial positions. Hydrophobic portions of the surfactant molecules occupy interfacial positions (e.g., air/liquid), while hydrophilic portions of the molecules remain oriented towards the bulk solvent. At sufficient concentrations (typically around the detergent's critical micellar concentration), a surface layer of surfactant molecules serve to prevent protein molecules from adsorbing at the interface. Thereby, surface-induced degradation is minimized. The most commonly used surfactants are fatty acid esters of sorbitan polyethoxylates, i.e. polysorbate 20 and polysorbate 80 (e.g., Avonex®, Neupogen®, Neulasta®). The two differ only in the length of the aliphatic chain that imparts hydrophobic character to the molecules, C-12 and C-18, respectively. Accordingly, polysorbate-80 is more surface-active and has a lower critical micellar concentration than polysorbate-20. The surfactant poloxamer 188 has also been used in several marketed liquid products such Gonal-F ®, Norditropin ®, and Ovidrel ®.

[0081] Detergents can also affect the thermodynamic conformational stability of proteins. Here again, the effects of a given excipient will be protein specific. For example, polysorbates have been shown to reduce the stability of some proteins and increase the stability of others. Detergent destabilization of proteins can be rationalized in terms of the hydrophobic tails of the detergent molecules that can engage in specific binding with partially or wholly unfolded protein states. These types of interactions could cause a shift in the conformational equilibrium towards the more expanded protein states (i.e. increasing the exposure of hydrophobic portions of the protein molecule in complement to binding polysorbate). Alternatively, if the protein native state exhibits some hydrophobic surfaces, detergent binding to the native state may stabilize that conformation.

[0082] Another aspect of polysorbates is that they are inherently susceptible to oxidative degradation. Often, as raw materials, they contain sufficient quantities of peroxides to cause oxidation of protein residue side-chains, especially methionine. The potential for oxidative damage arising from the addition of stabilizer emphasizes the point that the lowest effective concentrations of excipients should be used in formulations. For surfactants, the effective concentration for a given protein will depend on the mechanism of stabilization. It has been postulated that if the mechanism of surfactant stabilization is related to preventing surface-

denaturation the effective concentration will be around the detergent's critical micellar concentration. Conversely, if the mechanism of stabilization is associated with specific protein-detergent interactions, the effective surfactant concentration will be related to the protein concentration and the stoichiometry of the interaction (Randolph T.W., et al., Pharm Biotechnol., 13:159-75 (2002)).

[0083] Surfactants may also be added in appropriate amounts to prevent surface related aggregation phenomenon during freezing and drying [Chang, B, J. Pharm. Sci. 85:1325, (1996)]. Exemplary surfactants include anionic, cationic, nonionic, zwitterionic, and amphoteric surfactants including surfactants derived from naturally-occurring amino acids. Anionic surfactants include, but are not limited to, sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, and glycodeoxycholic acid sodium salt. Cationic surfactants include, but are not limited to, benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, and hexadecyltrimethylammonium bromide. Zwitterionic surfactants include, but are not limited to, CHAPS, CHAPSO, SB3-10, and SB3-12. Non-ionic surfactants include, but are not limited to, digitonin, Triton X-100, Triton X-114, TWEEN-20, and TWEEN-80. In another embodiment, surfactants include lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 40, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, soy lecithin and other phospholipids such as DOPC, DMPG, DMPC, and DOPG; sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose.

[0084] Formulations described herein may further comprise these surfactants, either individually or as a mixture in different ratios. In one embodiment, the surfactant is incorporated in a concentration of about 0% to about 5% w/v. In another embodiment, the surfactant is incorporated in a concentration of at least 0.001, 0.002, 0.005, 0.007, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, or 4.5% w/v. In another embodiment, the surfactant is incorporated in a concentration of about 0.001 % to about 0.5% w/v. In still another embodiment, the surfactant is incorporated in a concentration of about 0.004, 0.005, 0.007, 0.01, 0.05, or 0.1% w/v to about 0.2% w/v. In yet another embodiment, the surfactant is incorporated in a concentration of about 0.01% to about 0.1% w/v.

[0085] In some embodiments, viscosity reduction is achieved with relatively little or no surfactant, e.g. 0.1% or less total surfactant, or 0.05% or less, or 0.01% or less.

D. Amino acids

[0086] Amino acids have found versatile use in protein formulations as buffers, bulking agents, stabilizers and antioxidants. Histidine and glutamic acid are employed to buffer protein formulations in the pH range of 5.5 - 6.5 and 4.0 - 5.5 respectively. The imidazole group of histidine has a pKa = 6.0 and the carboxyl group of glutamic acid side chain has a pKa of 4.3

which makes them suitable for buffering in their respective pH ranges. Glutamic acid is found in some formulations (e.g., Stemgen®). Histidine is commonly found in marketed protein formulations (e.g., Xolair®, Herceptin®, Recombinate®). It provides a good alternative to citrate, a buffer known to sting upon injection. Interestingly, histidine has also been reported to have a stabilizing effect when used at high concentrations in both liquid and lyophilized presentations (Chen B, et al., Pharm Res., 20(12): 1952-60 (2003)). Histidine (up to 60 mM) was also observed to reduce the viscosity of a high concentration formulation of this antibody. However, in the same study, the authors observed increased aggregation and discoloration in histidine containing formulations during freeze-thaw studies of the antibody in stainless steel containers. The authors attributed this to an effect of iron ions leached from corrosion of steel containers. Another note of caution with histidine is that it undergoes photo-oxidation in the presence of metal ions (Tomita M, et al., Biochemistry, 8(12): 5149-60 (1969)). The use of methionine as an antioxidant in formulations appears promising; it has been observed to be effective against a number of oxidative stresses (Lam XM, et al., J Pharm Sci., 86(11): 1250-5 (1997)).

[0087] The amino acids glycine, proline, serine and alanine stabilize proteins. Glycine is also a commonly used bulking agent in lyophilized formulations (e.g., Neumega ®, Genotropin®, Humatrope®). Arginine has been shown to be an effective agent in inhibiting aggregation and has been used in both liquid and lyophilized formulations (e.g., Activase®, Avonex®, Enbrel® liquid).

E. Antioxidants

[0088] Oxidation of protein residues arises from a number of different sources. Beyond the addition of specific antioxidants, the prevention of oxidative protein damage involves the careful control of a number of factors throughout the manufacturing process and storage of the product such as atmospheric oxygen, temperature, light exposure, and chemical contamination. The most commonly used pharmaceutical antioxidants are reducing agents, oxygen/free-radical scavengers, or chelating agents. Antioxidants in therapeutic protein formulations must be water-soluble and remain active throughout the product shelf-life. Reducing agents and oxygen/free-radical scavengers work by ablating active oxygen species in solution. Chelating agents such as EDTA can be effective by binding trace metal contaminants that promote free-radical formation. For example, EDTA was utilized in the liquid formulation of acidic fibroblast growth factor to inhibit the metal ion catalyzed oxidation of cysteine residues. EDTA has been used in marketed products like Kineret® and Ontak®.

[0089] However, antioxidants themselves can induce other covalent or physical changes to the protein. A number of such cases have been reported in the literature. Reducing agents (like glutathione) can cause disruption of intramolecular disulfide linkages, which can lead to disulfide shuffling. In the presence of transition metal ions, ascorbic acid and EDTA have been shown to promote methionine oxidation in a number of proteins and peptides (Akers MJ, and Defelippis MR. Peptides and Proteins as Parenteral Solutions. In: Pharmaceutical Formulation

Development of Peptides and Proteins. Sven Frokjaer, Lars Hovgaard, editors. Pharmaceutical Science. Taylor and Francis, UK (1999)); Fransson J.R., J. Pharm. Sci. 86(9): 4046-1050 (1997); Yin J, et al., Pharm Res., 21(12): 2377-83 (2004)). Sodium thiosulfate has been reported to reduce the levels of light and temperature induced methionine-oxidation in rhuMab HER2; however, the formation of a thiosulfate-protein adduct was also reported in this study (Lam XM, Yang JY, et al., J Pharm Sci. 86(11): 1250-5 (1997)). Selection of an appropriate antioxidant is made according to the specific stresses and sensitivities of the protein.

F. Metal Ions

[0090] In general, transition metal ions are undesired in protein formulations because they can catalyze physical and chemical degradation reactions in proteins. However, specific metal ions are included in formulations when they are co-factors to proteins and in suspension formulations of proteins where they form coordination complexes (e.g., zinc suspension of insulin). Recently, the use of magnesium ions (10 -120 mM) has been proposed to inhibit the isomerization of aspartic acid to isoaspartic acid (WO 2004/039337).

[0091] Two examples where metal ions confer stability or increased activity in proteins are human deoxyribonuclease (rhDNase, Pulmozyme®), and Factor VIII. In the case of rhDNase, Ca^{+2} ions (up to 100 mM) increased the stability of the enzyme through a specific binding site (Chen B, et al., J Pharm Sci., 88(4): 477-82 (1999)). In fact, removal of calcium ions from the solution with EGTA caused an increase in deamidation and aggregation. However, this effect was observed only with Ca^{+2} ions; other divalent cations - Mg^{+2}, Mn^{+2} and Zn^{+2} were observed to destabilize rhDNase. Similar effects were observed in Factor VIII. Ca^{+2} and Sr^{+2} ions stabilized the protein while others like Mg^{+2}, Mn^{+2} and Zn^{+2}, Cu^{+2} and Fe^{+2} destabilized the enzyme (Fatouros, A., et al., Int. J. Pharm., 155, 121-131 (1997). In a separate study with Factor VIII, a significant increase in aggregation rate was observed in the presence of Al^{+3} ions (Derrick TS, et al., J. Pharm. Sci., 93(10): 2549-57 (2004)). The authors note that other excipients like buffer salts are often contaminated with Al^{+3} ions and illustrate the need to use excipients of appropriate quality in formulated products.

G. Preservatives

[0092] Preservatives are necessary when developing multi-use parenteral formulations that involve more than one extraction from the same container. Their primary function is to inhibit microbial growth and ensure product sterility throughout the shelf-life or term of use of the drug product. Commonly used preservatives include phenol, benzyl alcohol, meta-cresol, alkyl parabens such as methyl paraben or propyl paraben, benzalkonium chloride, and benzethonium chloride. Other examples of compounds with amtimicrobial preservative activity include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride. Other types of

preservatives include aromatic alcohols such as butyl alcohol, phenol, benzyl alcohol; atechol, resorcinol, cyclohexanol, 3-pentanol. Although preservatives have a long history of use, the development of protein formulations that includes preservatives can be challenging. Preservatives almost always have a destabilizing effect (aggregation) on proteins, and this has become a major factor in limiting their use in multi-dose protein formulations (Roy S, et al., J Pharm Sci., 94(2): 382-96 (2005)).

[0093] Multi-use injection pen presentations include preserved formulations. For example, preserved formulations of hGH are currently available on the market. Norditropin® (liquid, Novo Nordisk), Nutropin AQ® (liquid, Genentech) & Genotropin (lyophilized - dual chamber cartridge, Pharmacia & Upjohn) contain phenol while Somatrope® (Eli Lilly) is formulated with m-cresol.

[0094] Several aspects need to be considered during the formulation development of preserved dosage forms. The effective preservative concentration in the drug product must be optimized. This requires testing a given preservative in the dosage form with concentration ranges that confer anti-microbial effectiveness without compromising protein stability. For example, three preservatives were successfully screened in the development of a liquid formulation for interleukin-1 receptor (Type I), using differential scanning calorimetry (DSC). The preservatives were rank ordered based on their impact on stability at concentrations commonly used in marketed products (Remmele RL Jr., et al., Pharm Res., 15(2): 200-8 (1998)).

[0095] Some preservatives can cause injection site reactions, which is another factor that needs consideration when choosing a preservative. In clinical trials that focused on the evaluation of preservatives and buffers in Norditropin, pain perception was observed to be lower in formulations containing phenol and benzyl alcohol as compared to a formulation containing m-cresol (Kappelgaard A.M., Horm Res. 62 Suppl 3:98-103 (2004)). Interestingly, among the commonly used preservative, benzyl alcohol possesses anesthetic properties (Minogue SC, and Sun DA., Anesth Analg., 100(3): 683-6 (2005)).

IV. Kits

[0096] As an additional aspect of the disclosure, the described herein are kits which comprise one or more formulations described herein packaged in a manner which facilitates their use for administration to subjects. Such a kit may include a formulation described herein (e.g., a composition comprising any of the antibodies described therein), packaged in a container such as a sealed bottle, vessel, single-use or multi-use vial, prefilled syringe, or prefilled injection device, optionally with a label affixed to the container or included in the package that describes use of the compound or composition in practicing the method. In one aspect of the disclosure, the compound or composition is packaged in a unit dosage form. The kit may further include a device suitable for administering the composition according to a specific route of administration. Preferably, the kit contains a label that describes use of an antibody described

herein or formulation described herein.

V. Dosages

[0097] The dosage regimen involved in a method for treating a condition described herein will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. In various aspects, the daily regimen is in the range of 0.1-50 mg of a preparation of antibody per kilogram of body weight (calculating the mass of the protein alone, without chemical modification). In some embodiments, the dosage is about 0.5 mg/kg to 20 mg/kg, or about 0.5-10 mg/kg.

[0098] The formulations are generally administered parenterally, e.g. intravenously, subcutaneously, intramuscularly, via aerosol (intrapulmonary or inhalational administration), or via depot for long-term release. In some embodiments, the formulation is administered intravenously by an initial bolus followed by a continuous infusion to maintain therapeutic circulating levels of drug product. In other embodiments, the formulation is administered as a one-time dose. Those of ordinary skill in the art will readily optimize effective dosages and administration regimens as determined by good medical practice and the clinical condition of the individual patient. The frequency of dosing will depend on the pharmacokinetic parameters of the agents and the route of administration. The optimal pharmaceutical formulation will be determined by one skilled in the art depending upon the route of administration and desired dosage. See for example, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712. Such formulations may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the administered agents. Depending on the route of administration, a suitable dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art without undue experimentation, especially in light of the dosage information and assays disclosed herein, as well as the pharmacokinetic data observed in the human clinical trials discussed above. Appropriate dosages may be ascertained through use of established assays for determining blood level dosages in conjunction with appropriate dose-response data. The final dosage regimen will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the drug's specific activity, the severity of the damage and the responsiveness of the patient, the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. As studies are conducted, further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

VI. Therapeutic Uses of the Formulation

[0099] The formulations described herein are useful for treating or preventing bone-related disorders, such as bone-related disorders associated with abnormal osteoblast or osteoclast activity. In some embodiments, the formulation is administered to a subject suffering from a bone related disorder selected from the group consisting of 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, 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, Perthe's 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 and regional migratory osteoporosis), anemic states, conditions caused by steroids, glucocorticoid-induced bone loss, heparin-induced bone loss, bone marrow disorders, scurvy, malnutrition, calcium deficiency, osteoporosis, osteopenia, 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, 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, bone loss associated with aging, facial bone loss associated with aging, cranial bone loss associated with aging, jaw bone loss associated with aging, skull bone loss associated with aging, and bone loss associated with space travel.

[0100] In some embodiments, the formulations described herein are 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.

[0101] The formulation need not cure the subject of the disorder or completely protect against the onset of a bone-related disorder to achieve a beneficial biological response. The formulation may be used prophylactically, meaning to protect, in whole or in part, against a

bone-related disorder or symptom thereof. The formulation also may be used therapeutically to ameliorate, in whole or in part, a bone-related disorder or symptom thereof, or to protect, in whole or in part, against further progression of a bone-related disorder or symptom thereof. Indeed, the materials and methods of the invention are particularly useful for increasing bone mineral density and maintaining the increased bone mineral density over a period of time.

[0102] One or more administrations of a formulation described herein may be carried out over a therapeutic period of, for example, about 1 month to about 12 months (e.g., about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, or about 11 months). In some embodiments, a subject is administered one or more doses of the formulation to maintain bone mineral density. The term "maintain bone mineral density" as used herein means that the increased bone mineral density resulting the initial dose of the formulation does not fall more than about 1% to about 5% over the course of about 6 months, about 9 months about 1 year, about 18 months, about 2 years, or over the course of the patient's life). It will be appreciated that a patient can require alternate treatment phases for increasing bone density and maintaining bone density.

[0103] In addition, it may be advantageous to administer multiple doses of the formulation or space out the administration of doses, depending on the therapeutic regimen selected for a particular subject. The formulation can be administered periodically over a time period of one year or less (e.g., 9 months or less, 6 months or less, or 3 months or less). In this regard, the formulation can be administered to the human once every about 7 days, or 2 weeks, or 3 weeks, or 1 month, or 5 weeks, or 6 weeks, or 7 weeks, or 2 months, or 9 weeks, or 10 weeks, or 11 weeks, or 3 months, or 13 weeks, or 14 weeks, or 15 weeks, or 4 months, or 17 weeks, or 18 weeks, or 19 weeks, or 5 months, or 21 weeks, or 22 weeks, or 23 weeks, or 6 months, or 12 months.

VII. Combination therapy

[0104] Treatment of a pathology by combining two or more agents that target the same pathogen or biochemical pathway sometimes results in greater efficacy and diminished side effects relative to the use of the therapeutically relevant dose of each agent alone. In some cases, the efficacy of the drug combination is additive (the efficacy of the combination is approximately equal to the sum of the effects of each drug alone), but in other cases the effect can be synergistic (the efficacy of the combination is greater than the sum of the effects of each drug given alone). As used herein, the term "combination therapy" means the two compounds can be delivered in a simultaneous manner, e.g. concurrently, or wherein one of the compounds is administered first, followed by the second agent, e.g., sequentially. The desired result can be either a subjective relief of one or more symptoms or an objectively identifiable improvement in the recipient of the dosage.

[0105] In some embodiments, the formulation is administered along with a standard of care therapeutic for the treatment of decreased bone mineral density. As used herein, the term

"standard of care" refers to a treatment that is generally accepted by clinicians for a certain type of patient diagnosed with a type of illness. In some embodiments, the standard of care therapeutic is selected from the group consisting of an anti-resorptive drug, a bone-forming agent, an estrogen receptor antagonist (including, but not limited to, raloxifene, bazedoxifene and lasofoxifene) and a drug that has a stimulatory effect on osteoclasts. In some embodiments, the anti-resorptive drug includes, but is not limited to, a bisphosphonate (including, but not limited to, alendronate, risedronate, ibandronate and zoledronate), an estrogen or estrogen analogue, a selective estrogen receptor modulator (SERM) and a calcium source, Tibolone, calcitonin, a calcitriol and hormone replacement therapy. In some embodiments, the bone-forming agent includes, but is not limited to parathyroid hormone (PTH) or a peptide fragment thereof, PTH-related protein (PTHrp), bone morphogenetic protein, osteogenin, NaF, a PGE_2 agonist, a statin, and a RANK ligand (RANKL). In some embodiments, the drug having a stimulatory effect on osteoclasts includes, but it not limited to, vitamin D, or a vitamin D derivative or mimic thereof.

[0106] In some embodiments, the formulation is administered to a subject when treatment of a standard of care therapeutic described herein is contraindicated.

EXAMPLES

Example 1 - Calcium acetate reduced the effective viscosity of sclerostin antibody formulations

[0107] 10 ml of a selected anti-sclerostin antibody (75.7 mg/ml) was dialyzed against 2 liters of 10 mM Na(OAc) and 9% sucrose at 4°C for 2 hours. A selected anti-sclerostin antibody (75.7 mg/ml) was concentrated to approximately 160 mg/ml and diluted with water to approximately 140 mg/ml and 120 mg/ml. Absorbance of the diluted samples were determined to be 120, 142 and 157 mg/ml, respectively

[0108] 10 µl 1.0M $Ca(OAc)_2$ was added to 1 ml of the 120 mg/ml, 140 mg/ml and 160 mg/ml samples. Absolute viscosity, pH and osmolarity of the samples were determined (See Table 2). Absolute viscosity of the samples (500µl) was measured using Brookfield LV-DVII cone and plate viscometer with a CPE-40 spindle with matching sample cup temperature regulated by a circulating water bath at constant 25°C. .

Table 2

Sample	Viscosity (cP)	pH	Osmolarity
120 mg/ml (Control)	18	5.3	375
120 mg/ml + 10 mM $Ca(OAc)_2$	8.4	5.4	398
142 mg/ml + 10 mM $Ca(OAc)_2$	17	5.4	450

Sample	Viscosity (cP)	pH	Osmolarity
157 mg/ml + 10 mM $Ca(OAc)_2$	36	5.4	610

[0109] Results indicated that 10 mM $Ca(OAc)_2$ spiked into a liquid composition of the selected antibody reduced viscosity by about half. This experiment is performed for each of antibodies Ab-4, Ab-5, Ab-13, Ab-14, Ab-19, Ab-20 and Ab-23.

Example 2 - Formulations adjustment

[0110] 10 ml of a selected anti-sclerostin antibody (75.7 mg/ml) was dialyzed against 2 liters of 10 mM Na(OAc), 6% sucrose or 4% sucrose at 4°C for 2 hours. Each sucrose formulation was then concentrated using Amicons to approximately 140 mg/ml then diluted with water back down to the targeted concentrations (i.e., 120 mg/ml, 140 mg/ml and 160 mg/ml). Absorbance values of the diluted samples were determined to be 124 mg/ml (4% sucrose), 119.5 mg/ml (6% sucrose), 137.5 mg/ml (4% sucrose) and 142 mg/ml (6% sucrose), respectively.

[0111] 10 µl 1.0M $Ca(OAc)_2$ was added to 1 ml of the samples. Viscosity, osmolarity and pH of the samples were determined (See Table 3)

Table 3

Sample	mM	Mg/mL	pH	Osmolarity	Viscosity (cP)
120 mg/mL + 10 mM CaOAC + 4% sucrose	10	124	5.285	214	6.2
120 mg/mL + 10 mM CaOAC + 6% sucrose	10	119.5	5.25	282	5.7
140 mg/mL + 10 mM CaOAC + 4% sucrose	10	137.5	5.303	231	9.5
140 mg/mL + 10 mM CaOAC + 6% sucrose	10	142	5.307	294	11

[0112] The assay was repeated as follows: 10 ml of a selected anti-sclerostin antibody (75.7 mg/ml) was dialyzed against 2 liters of 10 mM Na(OAc), 6% sucrose or 4% sucrose at 4°C for 2 hours. Each sucrose formulation was then concentrated using Amicon filter to approximately 140 mg/ml then diluted with water back down to the targeted concentrations (i.e., 70 mg/ml, 100 mg/ml and 120 mg/ml). Absorbance values of the diluted samples were determined to be 71 mg/ml (4% sucrose), 68.2 mg/ml (6% sucrose), 99.4 mg/ml (4% sucrose), 100.5 (6% sucrose), 122 mg/ml (4% sucrose) and 113 mg/ml (6% sucrose), respectively.

[0113] pH, osmolarity and viscosity of the samples were determined. See Table 4.

Table 4

Sample	mM	Mg/mL	pH	Osmolarity	Viscosity (cP)
70 mg/mL + 4% sucrose	10	71	5.205	154	3.5
70 mg/mL + 10 mM CaOAC + 4% sucrose	10	71	5.233	183	2.2
70 mg/mL 6% sucrose	10	68.2	5.201	231	3.4
70 mg/mL + 10 mM CaOAC + 6% sucrose	10	68.2	5.279	256	2.4
100 mg/mL + 4% sucrose	10	99.4	5.265	165	8.1
100 mg/mL + 10 mM CaOAC + 4% sucrose	10	99.4	5.288	191	4.1
100 mg/mL + 6% sucrose	10	100.5	5.273	241	8.4
100 mg/mL + 10 mM CaOAC + 6% sucrose	10	100.5	5.303	270	4.3
120 mg/mL + 4% sucrose	10	122	5.295	177	15.6
120 mg/mL + 10 mM CaOAC + 4% sucrose	10	122	5.306	202	6.9
120 mg/mL + 6% sucrose	10	113	5.3	249	15.4
120 mg/mL + 10 mM CaOAC + 6% sucrose	10	113	5.311	274	6.6

[0114] Lowering pH of $Ca(OAc)_2$ buffer to 5.2 kept all final formulation pHs between 5.25 and 5.307. The 4% sucrose formulations were below the isotonic range (250-350 mOsm/kg), but the 6% sucrose formulations were near the middle of the isotonic range.

[0115] To further assess the effect of 6% sucrose with 10 mM $Ca(OAc)_2$ in reducing viscosity, the assay above was repeated with further concentrations of anti-sclerostin antibody up to 160 mg/ml.

[0116] Samples were prepared as described above with the following concentrations: 120 mg/ml, 140 mg/ml and 160 mg/ml. 10 µl of 1.0M $Ca(OAc)_2$, pH 5.2, was added to each of the samples. pH, osmolarity and viscosity of the samples were determined. See Table 5.

Table 5

Sample	mM	Mg/mL	pH	Osmolarity	Viscosity (cP)
100 mg/mL + 10 mM CaOAC + 6% sucrose	10	107	5.285	271	4.3
100 mg/mL + 10 mM CaOAC + 6% sucrose	10	107	5.285	277	4.3

Sample	mM	Mg/mL	pH	Osmolarity	Viscosity (cP)
120 mg/mL + 10 mM CaOAC + 6% sucrose	10	120	5.311	279	6.1
120 mg/mL + 10 mM CaOAC + 6% sucrose	10	120	5.311	278	6
140 mg/mL + 10 mM CaOAC + 6% sucrose	10	145	5.329	X	12
140 mg/mL + 10 mM CaOAC + 6% sucrose	10	145	5.329	309	11.7
160 mg/mL + 10 mM CaOAC + 6% sucrose	10	168.7	5.343	X	18.8
160 mg/mL + 10 mM CaOAC + 6% sucrose	10	168.7	5.343	X	18.8

[0117] The above-described experiments are performed for each of antibodies Ab-4, Ab-5, Ab-13, Ab-14, Ab-19, Ab-20 and Ab-23.

Example 3 - Effect of calcium acetate in other high protein concentration formulations.

[0118] The following Example determined whether calcium acetate reduces the viscosity of formulations containing high concentration of protein other than a sclerostin antibody.

[0119] Non-sclerostin antibodies #1-#5 were determined to have a concentration of 131.6 mg/ml, 94 mg/ml, 113.2 mg/ml, 50 mg/ml and 106.3, respectively. The term "non-sclerostin antibody" as used herein means an antibody other than a sclerostin antibody described herein.

[0120] 10 µl 1.0M $Ca(OAc)_2$ was added to 1 ml of the 5 samples discussed above. Viscosity, pH and osmolarity of the samples were determined (See Table 6).

Table 6

Sample	Mg/mL	Viscosity (cP)
Non-sclerostin antibody #1	94	6.8
Non-sclerostin antibody #1+ 10 mM $Ca(OAc)_2$	94	5.10
Non-sclerostin antibody #2	135	9.8
Non-sclerostin antibody #2 + 10 mM $Ca(OAc)_2$	135	8.3
Protein # 1	50	3.3
Protein #1 + 10 mM $Ca(OAc)_2$	50	3.2
Protein #1	106.3	16.6

Sample	Mg/mL	Viscosity (cP)
Protein #1 + 10 mM $Ca(OAc)_2$	106.3	15.6

[0121] Calcium acetate did not significantly reduce the viscosity of any of the samples.

Example 4 - Effect of non-calcium salts on the viscosity of high concentration anti-sclerostin antibody formulation.

[0122] The following experiment was performed to determine whether non-calcium salts would be capable of reducing the viscosity of an anti-sclerostin antibody formulation.

[0123] A selected anti-sclerostin antibody (the same as in Examples 1-2 above) was concentrated to ~130 mg/mL. 10 µl of either 1.0M $(NH_4)_2SO_4$ or 1.0M $MgSO_4$ was added to 1 ml of antibody sample. Viscosity of the control was determined to be 30 cP. $MgSO_4$ was determined to significantly reduce viscosity of the sample ($MgSO_4$ + sample = 16 cP). $(NH_4)_2SO_4$ did not significantly reduce viscosity of the sample.

Example 5 - Effect of other calcium salts on the viscosity of high concentration anti-sclerostin antibody formulation.

[0124] The following experiment was performed to determine whether calcium salts other than calcium acetate would be capable of reducing the viscosity of an anti-sclerostin antibody formulation.

[0125] A selected anti-sclerostin antibody (the same as in Examples 1-2 above) was concentrated to ~125 mg/mL. 10 µl of either 25 mM $CaCl_2$ or 25 mM $MgCl_2$ was added to 1 ml of antibody sample. Viscosity of the control was determined to be 18.5 cP. $CaCl_2$ and $MgCl_2$ were determined to significantly reduce viscosity of the sample ($CaCl_2$ + sample = 9 cP and $MgCl_2$ + sample = 8).

Example 6 - Effect of calcium acetate on another anti-sclerostin antibody.

[0126] The following experiment was performed to determine whether calcium acetate would be capable of reducing the viscosity of an anti-sclerostin antibody formulation comprising a different anti-sclerostin antibody than in Examples 1-2 above.

[0127] A selected anti-sclerostin antibody was concentrated to ~131 mg/mL. 10 µl 1.0M

$Ca(OAc)_2$ was added to 1 ml of antibody sample. Viscosity of the control was determined to be 17.3 cP. $Ca(OAc)_2$ was determined to slightly reduce viscosity of the sample (15.3 cP)

[0128] Numerous modifications and variations in the practice of the invention are expected to occur to those of skill in the art upon consideration of the presently preferred embodiments thereof. Consequently, the only limitations which should be placed upon the scope of the invention are those which appear in the appended claims.

SEQUENCE LISTING

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ccatcgcggt tcagtggcag tggatctggg acacagttca ctctcaccat cagcggcgtg 240

cagtgtgccg atgctgccac ttactactgt caaggcgctt ataatgatgt tatttatgct 300

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    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
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                165                 170                 175

Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His
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tgggcaaaag gccgattcac catctccaga acctcgacta cgatggatct gaaaatgacc 240

agtctgacga ccggggacac ggcccgttat ttctgtgcca gaaattggaa cttgtggggc 300

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Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
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Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
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Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
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Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
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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
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            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
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35 40 45

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Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
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    50                  55                  60

Gly Ser Gly Thr Ser His Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Thr Tyr Pro Pro Thr
                85                  90                  95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
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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
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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
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acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cacccatcag ggaagaatct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataacccag tcctgaagag ccgactgact atctccaagg atacctccaa cagccaggta 240

ttcctcaaga tcgccaatgt ggacactgca gatactgcca catactactg tgctcgaata 300

gaggactttg attacgacga ggagtattat gctatggact actggggtca aggaacctca 360

gtcatcgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct 420

gctgcccaaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag 480

ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct 540

gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg 600

cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag 660

aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca 720

tctgtcttca tcttcccccc aaagcccaag gatgtgctca ccattactct gactcctaag 780

gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt 840

gtagatgatg tggaggtgca cacagctcag acgcaacccc gggaggagca gttcaacagc 900

actttccgct cagtcagtga acttcccatc atgcaccagg actggctcaa tggcaaggag 960

ttcaaatgca gggtcaacag tgcagctttc cctgcccccа tcgagaaaac catctccaaa 1020

accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg 1080

gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact 1140

gtggagtggc agtggaatgg gcagccagcg gagaactaca agaacactca gcccatcatg 1200

gacacagatg gctcttactt cgtctacagc aagctcaatg tgcagaagag caactgggag 1260

gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag 1320

aagagcctct cccactctcc tggtaaatga 1350

<210> 24
<211> 449
<212> PRT
<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-B heavy chain (no signal)

<400> 24

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

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg His Pro Ser Gly Lys Asn Leu Glu
        35                  40                  45

Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Val
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Asn Ser Gln Val
65                  70                  75                  80

Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Ile Glu Asp Phe Asp Tyr Asp Glu Glu Tyr Tyr Ala Met
            100                 105                 110

Asp Tyr Trp Gly Gln Gly Thr Ser Val Ile 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 Val 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> 25

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-C LCDR1

<400> 25

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

<210> 26
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-C LCDR2

<400> 26
Ala Ala Ser Asn Leu Glu Ser
1 5

<210> 27
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-C LCDR3

<400> 27
Gln Gln Ser Asn Glu Asp Pro Trp Thr
1 5

<210> 28
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-C HCDR1

<400> 28
Asp Cys Tyr Met Asn
1 5

<210> 29
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-C HCDR2

<400> 29
Asp Ile Asn Pro Phe Asn Gly Gly Thr Thr Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 30

<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-C HCDR3

<400> 30
Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp Asp Ala Met Asp Tyr
1 5 10 15

<210> 31
<211> 657
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-C light chain (no signal)

<400> 31
gacattgtgc tgacccaatc tccagcttct ttgactgtgt ctctaggcct gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtac 120

cagcagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 180

gggatcccag ccaggtttag tggcaatggg tctgggacag acttcaccct caacatccat 240

cctgtggagg aggaggatgc tgtaacctat tactgtcaac aaagtaatga ggatccgtgg 300

acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc 360

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 480

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 540

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600

actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag 657

<210> 32
<211> 218
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-C light chain (no signal)

<400> 32
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Thr Val Ser Leu Gly
1 5 10 15

```
Leu Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20                  25                  30

Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
    50                  55                  60

Arg Phe Ser Gly Asn Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Glu Glu Asp Ala Val Thr Tyr Tyr Cys Gln Gln Ser Asn
                85                  90                  95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
        115                 120                 125

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

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln

145                 150                 155                 160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
            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> 33

<211> 1350

<212> DNA

<213> Mus musculus

<220>

<221> misc_feature

<223> Ab-C heavy chain (no signal)

<400> 33

```
gaggtccagc tgcaacaatc tggacctgag ctggtgaagc ctgggacttc agtgaagatg      60

tcctgtaagg cttctggata cacattcact gactgctaca tgaactgggt gaagcagagc     120

catgggaaga gccttgaatg gattggagat attaatcctt tcaacggtgg tactacctac     180

aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac     240

atgcagctca acagcctgac atctgacgac tctgcagtct attactgtgc aagatcccat     300

tattacttcg atggtagagt cccttgggat gctatggact actggggtca aggaacctca     360

gtcaccgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct     420

gctgcccaaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag     480

ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct     540

gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg     600

cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag     660

aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca     720

tctgtcttca tcttcccccc aaagcccaag gatgtgctca ccattactct gactcctaag     780

gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt     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 aagtcagtct gacctgcatg ataacagact tcttccctga agacattact    1140

gtggagtggc agtggaatgg gcagccagcg gagaactaca agaacactca gcccatcatg    1200

gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag    1260

gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag    1320

aagagcctct cccactctcc tggtaaatga                                     1350
```

<210> 34

<211> 449

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-C heavy chain (no signal)

<400> 34

```
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
```

```
            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> 35

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-D LCDR1

<400> 35

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

<210> 36

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-D LCDR2

<400> 36

Gly Ser Ser Asn Leu Glu Asp
1 5

<210> 37
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-D LCDR3

<400> 37
Leu Gln His Ser Tyr Leu Pro Tyr Thr
1 5

<210> 38
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-D HCDR1

<400> 38
Asp His Tyr Met Ser
1 5

<210> 39
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-D HCDR2

<400> 39
Asp Ile Asn Pro Tyr Ser Gly Glu Thr Thr Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 40
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-D HCDR3

<400> 40
Asp Asp Tyr Asp Ala Ser Pro Phe Ala Tyr
1 5 10

<210> 41
<211> 645
<212> DNA
<213> Mus musculus

<400> 41
gatgtccaga tgattcagtc tccatcctcc ctgtctgcat ctttgggaga catagtcacc 60

atgacttgcc aggcaagtca gggcactagc attaatttaa actggtttca gcaaaaacca 120

gggaaggctc ctaagctcct gatctatgct tcaagcaact tggaagatgg ggtcccatca 180

aggttcagtg gcagtagata tgggacagat ttcactctca ccatcagcag cctggaggat 240

gaagatctgg caacttattt ctgtctacaa catagttatc tccccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 42
<211> 214
<212> PRT
<213> Mus musculus

<400> 42
Asp Val Gln Met Ile Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Ile Val Thr Met Thr Cys Gln Ala Ser Gln Gly Thr Ser Ile Asn
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ser Ser Asn Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Asp
65 70 75 80

Glu Asp Leu Ala Thr Tyr Phe Cys Leu Gln His Ser Tyr Leu Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
100 105 110

```
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile

    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            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> 43

<211> 1332

<212> DNA

<213> Mus musculus

<400> 43

```
gaggtccagc tgcaacagtc tggacctgaa ctggtgacgc ctggggcttc agtgaagata       60

tcttgtaagg cttctggata cacattcact gaccactaca tgagctgggt gaagcagagt      120

catggaaaaa gccttgagtg gattggagat attaatccct attctggtga aactacctac      180

aaccagaagt tcaagggcac ggccacattg actgtagaca agtcttccag tatagcctac      240

atggagatcc gcggcctgac atctgaggac tctgcagtct attactgtgc aagagatgat      300

tacgacgcct ttccgtttgc ttactggggc caagggactc tggtcactgt ctctgcagcc      360

aaaacgacac ccccatctgt ctatccactg gcccctggat ctgctgccca aactaactcc      420

atggtgaccc tgggatgcct ggtcaagggc tatttccctg agccagtgac agtgacctgg      480

aactctggat ccctgtccag cggtgtgcac accttcccag ctgtcctgca gtctgacctc      540

tacactctga gcagctcagt gactgtcccc tccagcacct ggcccagcga gaccgtcacc      600

tgcaacgttg cccacccggc cagcagcacc aaggtggaca agaaaattgt gcccagggat      660

tgtggttgta agccttgcat atgtacagtc ccagaagtat catctgtctt catcttcccc      720

ccaaagccca aggatgtgct caccattact ctgactccta aggtcacgtg tgttgtggta      780

gacatcagca aggatgatcc cgaggtccag ttcagctggt ttgtagatga tgtggaggtg      840

cacacagctc agacgcaacc ccgggaggag cagttcaaca gcactttccg ctcagtcagt      900
```

gaacttccca tcatgcacca ggactggctc aatggcaagg agttcaaatg cagggtcaac 960

agtccagctt tccctgcccc catcgagaaa accatctcca aaaccaaagg cagaccgaag 1020

gctccacagg tgtacaccat tccacctccc aaggagcaga tggccaagga taaagtcagt 1080

ctgacctgca tgataacaga cttcttccct gaagacatta ctgtggagtg gcagtggaat 1140

gggcagccag cggagaacta caagaacact cagcccatca tggacacaga tggctcttac 1200

ttcatctaca gcaagctcaa tgtgcagaag agcaactggg aggcaggaaa tactttcacc 1260

tgctctgtgt tacatgaggg cctgcacaac caccatactg agaagagcct ctcccactct 1320

cctggtaaat ga 1332

<210> 44

<211> 443

<212> PRT

<213> Mus musculus

<400> 44

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

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp His
20 25 30

Tyr Met Ser Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Ser Gly Glu Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Thr Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Ile Ala Tyr
65 70 75 80

Met Glu Ile Arg Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Asp Tyr Asp Ala Ser Pro Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr
115 120 125

Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu
130 135 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp

145 150 155 160

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu

```
                165                 170                 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser
            180                 185                 190

Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys
    210                 215                 220

Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro
225                 230                 235                 240

Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr
                245                 250                 255

Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser
            260                 265                 270

Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg
        275                 280                 285

Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile
    290                 295                 300

Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn
305                 310                 315                 320

Ser Pro Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
                325                 330                 335

Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu
            340                 345                 350

Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe
        355                 360                 365

Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala
    370                 375                 380

Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr

385                 390                 395                 400

Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly
                405                 410                 415

Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His
            420                 425                 430

Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440
```

<210> 45
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-2 LCDR1

<400> 45
Arg Ala Ser Ser Ser Val Tyr Tyr Tyr Met His
1 5 10

<210> 46
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-2 LCDR2

<400> 46
Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 47
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-3 LCDR3

<400> 47
Gln Gln Trp Ser Ser Asp Pro Leu Thr
1 5

<210> 48
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-2 HCDR1

<400> 48
Asp Tyr Phe Ile His
1 5

<210> 49
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> Ab-2 HCDR2

<400> 49
Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala Pro Lys Phe Gln
1 5 10 15

Asp

<210> 50
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-2 HCDR3

<400> 50
Glu Asp Tyr Asp Gly Thr Tyr Thr Phe Phe Pro Tyr
1 5 10

<210> 51
<211> 642
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-2 light chain (no signal)

<400> 51
caaattgttc tctcccagtc tccagcaatc ctgtctacat ctccagggga gaaggtcaca 60

atgacttgca gggccagctc aagtgtatat tacatgcact ggtaccagca gaagccagga 120

tcctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgttcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcaccagagt ggaggctgaa 240

gatgctgcca cttattactg ccagcagtgg agtagtgacc cactcacgtt cggtgctggg 300

accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 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 aggccactca caagacatca 600

acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag 642

<210> 52
<211> 213
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-2 light chain (no signal)

<400> 52

```
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 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> 53
<211> 1338
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-2 heavy chain (no signal)

<400> 53

gaggttcagg tgcagcagtc tgggccagaa cttgtgaagc caggggcctc agtcaagttg 60

tcctgcacag cttctggctt caacattaaa gactacttta tacactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggaagg cttgatcctg aggatggtga aagtgatcat 180

gccccgaagt tccaggacaa ggccattatg acagcagaca catcatccaa cacagcctat 240

cttcagctca gaagcctgac atctgaggac actgccatct attattgtga gagagaggac 300

tacgatggta cctacacctt ttttccttac tggggccaag ggactctggt cactgtctct 360

gcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact 420

aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg 480

acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct 540

gacctctaca ctctgagcag ctcagtgact gtccctcca gcacctggcc cagcgagacc 600

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660

agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc 720

ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt 780

gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg 840

gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca 900

gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960

gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga 1020

ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080

gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1140

tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1200

tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1260

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320

cactctcctg gtaaatga 1338

<210> 54
<211> 445

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-2 heavy chain (no signal)

<400> 54

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

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                 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

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> 55

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-3 and Ab-15 LCDR1

<400> 55

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

<210> 56
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-3 and Ab-15 LCDR2

<400> 56
Gly Thr Ser Asn Leu Ala Ser
1 5

<210> 57
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-3 and Ab-15 LCDR3

<400> 57
Gln Gln Trp Ser Ser Tyr Pro Leu Thr
1 5

<210> 58
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-3 and Ab-15 HCDR1

<400> 58
Asp Phe Tyr Leu His
1 5

<210> 59
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-3 and Ab-15 HCDR2

<400> 59
Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe Gln
1 5 10 15

Asp

<210> 60

<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-3 and Ab-15 HCDR3

<400> 60

Glu	Ala	Asp	Tyr	Phe	His	Asp	Gly	Thr	Ser	Tyr	Trp	Tyr	Phe	Asp	Val
1				5				10					15		

<210> 61
<211> 648
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-3 light chain

<400> 61

gaaattgtgc tcacccagtc tccagcactc atggctgcat ctccggggga gaaggtcacc 60

atcacctgca gtgtcagttc aactataagt tccaaccact tgcactggtt ccagcagaag 120

tcagacacct cccccaaacc ctggatttat ggcacatcca acctggcttc tggagtccct 180

gttcgcttca gtggcagtgg atctgggacc tcttattctc tcacaatcag cagcatggag 240

gctgaggatg ctgccactta ttactgtcaa cagtggagta gttacccact cacgttcggc 300

gctgggacca agctggagct gagacgggct gatgctgcac caactgtatc catcttccca 360

ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 420

taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 480

ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 540

acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 600

acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 648

<210> 62
<211> 215
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-3 light chain (no signal)

<400> 62

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 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> 63

<211> 1350

<212> DNA

<213> Mus musculus

<220>

<221> misc_feature

<223> Ab-3 heavy chain

<400> 63

```
gaggttcagc tgcagcagtc tggggctgaa cttgtgaggc caggggcctt agtcaagttg       60

tcctgcacag cttctgactt caacattaaa gacttctatc tacactggat gaggcagcgg      120

cctgaacagg gcctggactg gattggaagg attgatcctg agaatggtga tactttatat      180

gacccgaagt tccaggacaa ggccactctt acaacagaca catcctccaa cacagcctac      240

ctgcagctca gcggcctgac atctgagacc actgccgtct attactgttc tagagaggcg      300

gattatttcc acgatggtac ctcctactgg tacttcgatg tctggggcgc agggaccaca      360

atcaccgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct      420

gctgcccaaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag      480

ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct      540

gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtccctc cagcacctgg       600

cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag      660

aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca      720

tctgtcttca tcttcccccc aaagcccaag gatgtgctca ccattactct gactcctaag      780

gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt      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 aagtcagtct gacctgcatg ataacagact tcttccctga agacattact     1140

gtggagtggc agtggaatgg gcagccagcg gagaactaca agaacactca gcccatcatg     1200

gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag     1260

gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag     1320

aagagcctct cccactctcc tggtaaatga                                      1350
```

<210> 64
<211> 449
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-3 heavy chain (no signal)

<400> 64

```
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
```

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> 65
<211> 324
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-15 light variable

<400> 65
gacatccaga tgacccagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca 60

ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcattggtt ccaacagaaa 120

cccggcaaag cacctaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct 180

tcaagatttt caggctctgg ctcaggcacc gactttactc ttacaatatc ctccctccaa 240

cccgaagact tcgcaaccta ttactgtcaa caatggtcct catatccact cacatttggc 300

ggcggcacaa aagtagaaat taaa 324

<210> 66
<211> 108

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-15 light variable

<400> 66

```
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 Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 67

<211> 375

<212> DNA

<213> Mus musculus

<220>

<221> misc_feature

<223> Ab-15 heavy variable

<400> 67

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc       60

tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc      120

cctggacaag ggcttgagtg gattggaagg attgatcctg agaatggtga tactttatat      180

gacccgaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac      240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg      300

gattatttcc acgatggtac ctcctactgg tacttcgatg tctggggccg tggcaccctg      360

gtcaccgtct ctagt                                                       375
```

<210> 68
<211> 125
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-15 heavy variable

<400> 68

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

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Phe
            20                  25                  30

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe
    50                  55                  60

Gln Asp Lys Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe
            100                 105                 110

Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
```

<210> 69
<211> 645
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized antibody

<220>
<221> misc_feature
<223> Ab-15 light chain

<400> 69

```
gacatccaga tgacccagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca       60
```

```
ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcattggtt ccaacagaaa      120

cccggcaaag cacctaaatc acttatatac ggcacatcaa atcacgcatc aggcgttcct      180

tcaagatttt caggctctgg ctcaggcacc gactttactc ttacaatatc ctccctccaa      240

cccgaagact tcgcaaccta ttactgtcaa caatggtcct catatccact cacatttggc      300

ggcggcacaa aagtagaaat taaacgtacg gtggctgcac catctgtctt catcttcccg      360

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc      420

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc      480

caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg      540

acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag      600

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt                      645
```

<210> 70
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody sequence

<220>
<221> MISC_FEATURE
<223> Ab-15 light chain

<400> 70

```
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 Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110
```

```
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 71

<211> 1353

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody

<220>

<221> misc_feature

<223> Ab-15 heavy chain

<400> 71

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc      60

tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc     120

cctggacaag ggcttgagtg gattggaagg attgatcctg agaatggtga tactttatat     180

gacccgaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac     240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg     300

gattatttcc acgatggtac ctcctactgg tacttcgatg tctggggccg tggcaccctg     360

gtcaccgtct ctagtgcctc caccaagggc ccatcggtct tccccctggc gccctgctcc     420

aggagcacct ccgagagcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa     480

ccggtgacgg tgtcgtggaa ctcaggcgct ctgaccagcg gcgtgcacac cttcccagct     540

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcaac     600

ttcggcaccc agacctacac ctgcaacgta gatcacaagc ccagcaacac caaggtggac     660
```

```
aagacagttg agcgcaaatg ttgtgtcgag tgcccaccgt gcccagcacc acctgtggca      720

ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc      780

cctgaggtca cgtgcgtggt ggtggacgtg agccacgaag accccgaggt ccagttcaac      840

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccacggga ggagcagttc      900

aacagcacgt tccgtgtggt cagcgtcctc accgttgtgc accaggactg gctgaacggc      960

aaggagtaca agtgcaaggt ctccaacaaa ggcctcccag ccccatcga gaaaaccatc     1020

tccaaaacca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag     1080

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta ccccagcgac     1140

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacacctccc     1200

atgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg     1260

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac     1320

acgcagaaga gcctctccct gtctccgggt aaa                                  1353
```

<210> 72
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody sequence

<220>
<221> MISC_FEATURE
<223> Ab-15 heavy chain

<400> 72

```
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 Glu Thr Ser Tyr Trp Tyr Phe
```

```
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

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val

        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

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

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Lys
    450
```

<210> 73

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-4 and Ab-5 LCDR1

<400> 73

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

<210> 74

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-4 and Ab-5 LCDR2

<400> 74

```
Tyr Thr Ser Arg Leu Leu Ser
1               5
```

<210> 75

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-4 and Ab-5 LCDR3

<400> 75

```
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1               5
```

<210> 76
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-4 and Ab-5 HCDR1

<400> 76
Asp Tyr Asn Met His
1 5

<210> 77
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-4 and Ab-5 HCDR2

<400> 77
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 78
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> HCDR3

<400> 78
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1 5 10

<210> 79
<211> 645
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-4 light chain

<400> 79
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60

atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240

gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300

gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 80
<211> 214
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-4 light chain

<400> 80

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 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> 81

<211> 1344

<212> DNA

<213> Mus musculus

<220>

<221> misc_feature

<223> Ab-4 heavy chain

<400> 81

```
gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg       60

tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac      120

caaggaaaga ccctagagtg gataggagaa attaatccta acagtggtgg tgctggctac      180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac      240

atgqagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc      300

tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc      360

gtctcctcag ccaaaacgac accccatct gtctatccac tggccctgg atctgctgcc       420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg      480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg      540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc      600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt      660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc      720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg      780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat      840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc      900
```

```
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa      960

tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa     1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag     1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag     1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca     1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga     1260

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc     1320

ctctcccact ctcctggtaa atga                                            1344
```

<210> 82
<211> 447
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-4 heavy chain

<400> 82

```
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                  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

His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
```

<210> 83
<211> 321
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-5 light variable

<400> 83

```
gacatccaga tgacccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc       60

ataacatgta gagcatctca agatatttcc aactatttga attggtacca acaaaaaccc      120

ggcaaagcac ctaaactcct catttactat acatcaagac tcctctccgg cgttccatca      180

cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca      240

gaagattttg caacctatta ctgtcaacaa ggcgatacac tcccatacac attcggcggc      300

ggcacaaaag ttgaaattaa a                                                321
```

<210> 84
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-5 light variable

<400> 84

```
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> 85
<211> 369
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-5 heavy variable

<400> 85

```
gaggtgcagc tggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgttaaagtt       60

tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg      120

ccaggacaag gattggaatg gatgggcgaa attaacccta atagtggagg agcaggctac      180

aatcaaaaat tcaaagggag agttacaatg acaacagaca caagcacttc aacagcatat      240

atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg      300

tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc      360

gtctctagt                                                              369
```

<210> 86
<211> 123
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-5 heavy variable

<400> 86

```
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

100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 87
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized antibody

<220>
<221> misc_feature
<223> Ab-5 light chain

<400> 87
gacatccaga tgacccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc 60

ataacatgta gagcatctca agatatttcc aactatttga attggtacca acaaaaaccc 120

ggcaaagcac ctaaactcct catttactat acatcaagac tcctctccgg cgttccatca 180

cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca 240

gaagattttg caacctatta ctgtcaacaa ggcgatacac tcccatacac attcggcggc 300

ggcacaaaag ttgaaattaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 88
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<220>

<221> MISC_FEATURE

<223> Ab-5 light chain

<400> 88

```
 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 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

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 89

<211> 1347

<212> DNA

<213> Artificial Sequence

<220>
<223> Humanized antibody

<220>
<221> misc_feature
<223> Ab-5 heavy chain

<400> 89
gaggtgcagc tggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgttaaagtt 60

tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg 120

ccaggacaag gattggaatg gatgggcgaa attaacccta atagtggagg agcaggctac 180

aatcaaaaat tcaaagggag agttacaatg acaacagaca caagcacttc aacagcatat 240

atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg 300

tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc 360

gtctctagtg cctccaccaa gggcccatcg gtcttccccc tggcgccctg ctccaggagc 420

acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 480

acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 540

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag caacttcggc 600

acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 660

gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 720

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 780

gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 840

gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 900

acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 960

tacaagtgca aggtctccaa caaaggcctc ccagccccca tcgagaaaac catctccaaa 1020

accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1080

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1140

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1200

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1260

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1320

aagagcctct ccctgtctcc gggtaaa 1347

<210> 90
<211> 449
<212> PRT
<213> Artificial Sequence

<220>

<223> Humanized antibody

<220>

<221> MISC_FEATURE

<223> Ab-5 heavy chain

<400> 90

```
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 Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
        195                 200                 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys

    210                 215                 220
```

```
Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
```

<210> 91
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-6 LCDR1

<400> 91
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn

1 5 10

<210> 92
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-6 LCDR2

<400> 92
Tyr Thr Ser Arg Leu His Ser
1 5

<210> 93
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-6 LCDR3

<400> 93
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 94
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-6 HCDR1

<400> 94
Asp Tyr Asn Met His
1 5

<210> 95
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-6 HCDR2

<400> 95
Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 96
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-6 HCDR3

<400> 96
Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr Phe Asp Val
1 5 10

<210> 97
<211> 645
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-6 light chain

<400> 97
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtttca gcagaaacca 120

gatggaactc ttaaactcct gatcttctac acatcaagat tacactcagg agttccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 240

gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcgggggg 300

gggaccaagc tggaaataag acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 98
<211> 214
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-6 light chain

<400> 98

```
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 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 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> 99

<211> 1344

<212> DNA

<213> Mus musculus

<220>

<221> misc_feature

<223> Ab-6 heavy chain

<400> 99

```
gaggtccagc tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg       60

tcctgcaagg cttctggata cacattcact gactacaaca tgcactgggt gaaacagaac      120

caaggaaaga gcctagagtg gataggagaa attaatccta acagtggtgg tagtggctac      180

aaccaaaagt tcaaaggcaa ggccacattg actgtagaca agtcttccag cacagcctac      240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattggtc      300

tacgatggca gctacgagga ctggtacttc gatgtctggg gcgcagggac cacggtcacc      360

gtctcctcag ccaaaacgac accccccatct gtctatccac tggccctgg atctgctgcc      420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg      480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg      540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc      600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt      660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc      720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg      780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat      840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc      900

cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa      960

tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa     1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag     1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag     1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca     1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga     1260

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc     1320

ctctcccact ctcctggtaa atga                                            1344
```

<210> 100
<211> 447
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-6 heavy chain

<400> 100

```
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 Ser Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr Phe Asp Val
            100                 105                 110

Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Pro
        115                 120                 125

Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser
    130                 135                 140

Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe

                165                 170                 175

Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
            180                 185                 190

Val Pro Ser 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> 101

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-7 LCDR1

<400> 101

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

<210> 102

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-7 LCDR2

<400> 102

```
Tyr Thr Ser Arg Leu His Ser
```

Tyr Thr Ser Arg Leu His Ser
1 5

<210> 103
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-7 LCDR3

<400> 103
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 104
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-7 HCDR1

<400> 104
Asp Tyr Asn Met His
1 5

<210> 105
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-7 HCDR2

<400> 105
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Gln Phe Lys
1 5 10 15

Gly

<210> 106
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-7 HCDR3

<400> 106
Leu Gly Tyr Val Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
1 5 10

<210> 107
<211> 642
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-7 light chain

<400> 107
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60

atctgttgca gggcaagtca ggtcattacc aattatttat actggtatca gcagaaacca 120

gatggaactt ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggaacag 240

gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 108
<211> 214
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-7 light chain

<400> 108
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
            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> 109

<211> 1341

<212> DNA

<213> Mus musculus

<220>

<221> misc_feature

<223> Ab-7 heavy chain

<400> 109

```
gaggtccagc tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg       60

tcctgcaagg cttctggata cacattcact gactacaaca tgcactggat gaagcagaac      120

caaggaaaga gcctagaatg gataggagaa attaatccta acagtggtgg tgctggctac      180

aaccagcagt tcaaaggcaa ggccacattg actgtagaca agtcctccag gacagcctac      240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc      300

tacgttggta attacgagga ctggtacttc gatgtctggg gcgcagggac cacggtcacc      360

gtctcctcag ccaaaacgac accccatct gtctatccac tggcccctgg atctgctgcc      420
```

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900

cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960

tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320

ctctcccact ctcctggtaa a 1341

<210> 110
<211> 447
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-7 heavy chain

<400> 110

```
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                  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 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                 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> 111

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-8 LCDR1

<400> 111

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

<210> 112

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-8 LCDR2

<400> 112

```
Tyr Thr Ser Arg Leu Leu Ser
1               5
```

<210> 113

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-8 LCDR3

<400> 113

```
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1               5
```

<210> 114
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-8 HCDR1

<400> 114
Asp Tyr Asn Met His
1 5

<210> 115
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-8 HCDR2

<400> 115
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 116
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-8 HCDR3

<400> 116
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1 5 10

<210> 117
<211> 645
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> Ab-8 light chain

<400> 117
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60

atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120

```
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca      180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa      240

gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg      300

gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca      360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac      420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg      480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg      540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca      600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                      645
```

<210> 118

<211> 214

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-8 light chain

<400> 118

```
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 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> 119

<211> 1344

<212> DNA

<213> Mus musculus

<220>

<221> misc_feature

<223> Ab-8 heavy chain

<400> 119

```
gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg       60

tcctgcaagg cttctggata cattcact gactacaaca tgcactgggt gaagcagaac       120

caaggaaaga ccctagactg gataggagaa attaatccta acagtggtgg tgctggctac       180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac       240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc       300

tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc       360

gtctcctcag ccaaaacgac accccccatct gtctatccac tggccctgg atctgctgcc       420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg       480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg       540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc       600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt       660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc       720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg       780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat       840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc       900

cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa       960
```

```
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa     1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag     1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag     1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca     1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga     1260

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc     1320

ctctcccact ctcctggtaa atga                                           1344
```

<210> 120
<211> 447
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> Ab-8 heavy chain

<400> 120

```
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

His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
```

435 440 445

<210> 121
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-9 LCDR1

<400> 121
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 122
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-9 LCDR2

<400> 122
Tyr Thr Ser Arg Leu Phe Ser
1 5

<210> 123
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-9 LCDR3

<400> 123
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 124
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-9 HCDR1

<400> 124
Asp Tyr Asn Met His
1 5

<210> 125
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-9 HCDR2

<400> 125
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 126
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-9 HCDR3

<400> 126
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1 5 10

<210> 127
<211> 642
<212> DNA
<213> Mus musculus

<400> 127
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtcacc 60

atcagttgca gggcaagtca agacattagc aattatttaa attggtatca gcagaaacca 120

gatggaactt ttaaactcct tatcttctac acatcaagat tattttcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240

gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300

gggaccaagg tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 128
<211> 214
<212> PRT

<213> Mus musculus

<400> 128

```
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 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 Gly Thr Lys Val Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            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> 129

<211> 1350

<212> DNA

<213> Mus musculus

<400> 129

```
gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctgggacttc agtgaagatg        60
```

tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagacc 120

caaggaaaga ccctagagtg gataggagaa attaatccta acagtggtgg tgctggctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aaaattgggc 300

tacgatgata tctacgacga ctggtatttc gatgtctggg gcgcagggac cacggtcacc 360

gtctcctcag ccaaaacaac agccccatcg gtctatccac tggccctgt gtgtggagat 420

acaactggct cctcggtgac tctaggatgc ctggtcaagg gttatttccc tgagccagtg 480

accttgacct ggaactctgg atccctgtcc agtgatgtgc acaccttccc agctctcctg 540

cagtctggcc tctacaccct cagcagctca gtgactgtaa ccacctggcc cagccagacc 600

atcacctgca atgtggccca cccggcaagc agcaccaaag tggacaagaa aattgagccc 660

agagggtccc caacacataa accctgtcct ccatgcccag ctcctaacct cttgggtgga 720

ccatccgtct tcatcttccc tccaaagatc aaggatgtac tcatgatctc cctgagcccc 780

atggtcacgt gtgtggtggt ggatgtgagc gaggatgacc cagatgtcca tgtcagctgg 840

ttcgtgaaca acgtggaagt acacacagct cagacacaaa cccatagaga ggattacaac 900

agtactatcc gggtggtcag tgccctcccc atccagcacc aggactggat gaggcaaag 960

gagttcaaat gcaaggtcaa caacaaagcc ctcccagcgc ccatcgagag aaccatctca 1020

aaacccaaag ggccagtaag agctccacag gtatatgtct tgcctccacc agaagaagag 1080

atgactaaga aacaggtcac tctgacctgc atgatcacag acttcatgcc tgaagacatt 1140

tacgtggagt ggaccaacaa cgggcaaaca gagctaaact acaagaacac tgaaccagtc 1200

ctggactctg atggttctta cttcatgtac agcaagctga gagtggaaaa gaagaactgg 1260

gtggaaagaa atagctactc ctgttcagtg gtccacgagg gtctgcacaa tcaccacacg 1320

actaagagct tctcccggac tccgggtaaa 1350

<210> 130
<211> 450
<212> PRT
<213> Mus musculus

<400> 130

```
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> 131

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-10 LCDR1

<400> 131

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

<210> 132

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-10 LCDR2

<400> 132

```
Tyr Thr Ser Arg Leu Leu Ser
1               5
```

<210> 133

<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-10 LCDR3

<400> 133
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 134
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-10 HCDR1

<400> 134
Asp Tyr Asn Met His
1 5

<210> 135
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-10 HCDR2

<400> 135
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 136
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-10 HCDR3

<400> 136
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1 5 10

<210> 137
<211> 645
<212> DNA

<213> Mus musculus

<400> 137

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtcacc 60

atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240

gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300

gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacta 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 138

<211> 214

<212> PRT

<213> Mus musculus

<400> 138

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> 139

<211> 1344

<212> DNA

<213> Mus musculus

<400> 139

```
gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg      60

tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac     120

caaggaaaga ccctagaatg gataggagaa attaatccta acagtggtgg tgctggctac     180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac     240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc     300

tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc     360

gtctcctcag ccaaaacgac accccccatct gtctatccac tggccctgg atctgctgcc     420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg     480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg     540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc     600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt     660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc     720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg     780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat     840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc     900

cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa     960

tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa    1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag    1080
```

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320

ctctcccact ctcctggtaa atga 1344

<210> 140

<211> 447

<212> PRT

<213> Mus musculus

<400> 140

```
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                  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

His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
```

<210> 141

<211> 10

<212> PRT

<213> Artificial Sequence

<220>
<223> Ab-11 and Ab-16 LCDR1

<400> 141
Arg Ala Ser Ser Ser Ile Ser Tyr Ile His
1 5 10

<210> 142
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-11 and Ab-16 LCDR2

<400> 142
Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 143
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-11 and Ab-16 LCDR3

<400> 143
Gln Gln Trp Ser Ser Asp Pro Leu Thr
1 5

<210> 144
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-11 and Ab-16 HCDR1

<400> 144
Asp Tyr Tyr Ile His

1 5

<210> 145
<211> 17
<212> PRT
<213> Artificial Sequence

<220>

<223> Ab-11 and Ab-16 HCDR2

<400> 145

```
Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe Pro
1               5                  10                  15

Gly
```

<210> 146

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-11 and Ab-16 HCDR3

<400> 146

```
Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr
1               5                  10
```

<210> 147

<211> 642

<212> DNA

<213> Mus musculus

<400> 147

```
caaattgttc tctcccagtc tccagcattc ctgtctgtat ctccagggga taaggtcaca      60

atgacttgca gggccagctc aagtataagt tacatacact ggtttcagca gaagccagga     120

tcctccccca gatcctggat ttatgccaca tccaacctgg cttctggagt ccctggtcgc     180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgag     240

gatgctgcca cttattactg ccagcagtgg agtagtgacc cactcacgtt cggtgctggg     300

accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc     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 aggccactca caagacatca     600

acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag                        642
```

<210> 148

<211> 213

<212> PRT

<213> Mus musculus

<400> 148

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 Ser Ile Ser Tyr Ile
20 25 30

His Trp Phe Gln 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 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> 149
<211> 1338
<212> DNA
<213> Mus musculus

<400> 149
gaagttcagc tgcaacagtc tggggcagac cttgtgcagc caggggcctc agtcaaggtg 60

```
tcctgcacag cttctggctt cgacattaag gactactata tacactggat gaaacagagg      120
cctgaccagg gcctggagtg gattggaagg gttgatcctg acaatggtga gactgaattt      180
gccccgaagt tcccgggcaa ggccactttt acaacagaca catcctccaa cacagcctac      240
ctacaactca gaggcctgac atctgaggac actgccatct attactgtgg gagagaagac      300
tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt cactgtctct      360
gcagccaaaa cgacacccCC atctgtctat ccactggccc ctggatctgc tgcccaaact      420
aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg      480
acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct      540
gacctctaca ctctgagcag ctcagtgact gtccCctcca gcacctggcc cagcgagacc      600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc      660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc      720
ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt      780
gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg      840
gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca      900
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg      960
gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga     1020
ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa     1080
gtcagtctga cctgcatgat aacagacttc ttcCctgaag acattactgt ggagtggcag     1140
tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc     1200
tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact     1260
ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc     1320
cactctcctg gtaaatga                                                   1338
```

<210> 150

<211> 445

<212> PRT

<213> Mus musculus

<400> 150

```
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

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> 151

<211> 318

<212> DNA

<213> Mus musculus

<400> 151

```
gacatccagt tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc       60

atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg      120

aaagccccta agctcctgat ctatgccaca tccaacctgg cttctggggt cccatcaagg      180

ttcagcggca gtggatctgg gacagaattc actctcacaa tcagcagcct gcagcctgaa      240

gattttgcaa cttattactg tcagcagtgg agtagtgacc cactcacgtt cggcggaggg      300

accaaggtgg agatcaaa                                                    318
```

<210> 152

<211> 106

<212> PRT

<213> Mus musculus

<400> 152

```
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Ile Ser Tyr Ile
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        35                  40                  45
```

```
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 153

<211> 363

<212> DNA

<213> Mus musculus

<400> 153

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc      60

tcctgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc     120

cctggacaag ggcttgagtg gatcggaagg gttgatcctg acaatggtga gactgaaatt     180

gccccgaagt tcccgggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac     240

atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac     300

tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct     360

agt                                                                  363
```

<210> 154

<211> 121

<212> PRT

<213> Mus musculus

<400> 154

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asp Ile Lys Asp Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
    50                  55                  60

Pro Gly Lys Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 155
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized antibody sequence

<400> 155

```
gacatccagt tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc       60

atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg      120

aaagccccta agctcctgat ctatgccaca tccaacctgg cttctggggt cccatcaagg      180

ttcagcggca gtggatctgg gacagaattc actctcacaa tcagcagcct gcagcctgaa      240

gattttgcaa cttattactg tcagcagtgg agtagtgacc cactcacgtt cggcggaggg      300

accaaggtgg agatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct      360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc      420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag      480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg      540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg      600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt                              639
```

<210> 156
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody sequence

<400> 156

```
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Ile Ser Tyr Ile
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
```

```
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        35                  40                  45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

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> 157

<211> 1341

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 157

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc      60

tcctgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc     120

cctggacaag ggcttgagtg gatcggaagg gttgatcctg acaatggtga gactgaattt     180

gccccgaagt tcccgggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac     240
```

atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac 300

tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct 360

agtgcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420

gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480

tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600

acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660

cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780

tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840

ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900

cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960

tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020

gggcagcccc gagaaccaca ggtgtacacc ctgccccccat cccgggagga gatgaccaag 1080

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140

tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc 1200

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320

ctctccctgt ctccgggtaa a 1341

<210> 158

<211> 447

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 158

```
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

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350
```

```
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> 159
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-12 LCDR1

<400> 159
```
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1               5                   10
```

<210> 160
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-12 LCDR2

<400> 160
```
Tyr Thr Ser Thr Leu Gln Ser
1               5
```

<210> 161
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-12 LCDR3

<400> 161
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 162
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-12 HCDR1

<400> 162
Asp Tyr Asn Met His
1 5

<210> 163
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-12 HCDR2

<400> 163
Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 164
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-12 HCDR3

<400> 164
Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
1 5 10

<210> 165
<211> 645
<212> DNA
<213> Mus musculus

<400> 165
gatctccaga tgacacagac tacttcctcc ctgtctgcct ctctgggaga cagagtcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120

```
gatggaactg ttaagctcct gatcttctac acatcaacat tacagtcagg agtcccatcg      180

aggttcagtg gcagtgggtc tggaacaaat tattctctca ccattaccaa cctggagcaa      240

gatgatgctg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg      300

gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca      360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac      420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg      480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg      540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca      600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                      645
```

<210> 166

<211> 214

<212> PRT

<213> Mus musculus

<400> 166

```
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                  80

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                 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> 167

<211> 1344

<212> DNA

<213> Mus musculus

<400> 167

```
gaggtccagt tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg       60

tcctgcaagg cttctggata cacattcact gactacaaca tgcactggat gaagcagaac      120

caaggaaaga gcctagagtg gataggagag attaatccta acagtggtgg ttctggtiac      180

aaccagaagt tcaaaggcaa ggccacattg actgtagaca agtcctccag cacagcctac      240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc      300

tactatggta actacgagga ctggtatttc gatgtctggg gcgcagggac cacggtcacc      360

gtctcctctg ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc      420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg      480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg      540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc      600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt      660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc      720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg      780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat      840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc      900

cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa      960

tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa     1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag     1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag     1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca     1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga     1260
```

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320

ctctcccact ctcctggtaa atga 1344

<210> 168

<211> 447

<212> PRT

<213> Mus musculus

<400> 168

```
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 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> 169

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-13 and Ab-14 LCDR1

<400> 169

```
Arg Ala Ser Ser Ser Val Thr Ser Ser Tyr Leu Asn
```

1 5 10

<210> 170
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-13 and Ab-14 LCDR2

<400> 170
Ser Thr Ser Asn Leu Ala Ser
1 5

<210> 171
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-13 and Ab-14 LCDR3

<400> 171
Gln Gln Tyr Asp Phe Phe Pro Ser Thr
1 5

<210> 172
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-13 and Ab-14 HCDR1

<400> 172
Asp Tyr Tyr Met Asn
1 5

<210> 173
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-13 and Ab-14 HCDR2

<400> 173
Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe Lys
1 5 10 15

Gly

<210> 174
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-13 and Ab-14 HCDR3

<400> 174

```
Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp
1               5                  10
```

<210> 175
<211> 645
<212> DNA
<213> Mus musculus

<400> 175

```
cagattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc       60

atgacctgca gggccagctc aagtgtaact tccagttact tgaactggta ccagcagaag      120

ccaggatctt cccccaaact ctggatttat agcacatcca acctggcttc aggagtccca      180

gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagtgtggag      240

gctgaggatg ctgccactta ttactgccag cagtatgatt ttttcccatc gacgttcggt      300

ggaggcacca agctggaaat caagcgggct gatgctgcac caactgtatc catcttccca      360

ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc      420

taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc      480

ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc      540

acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag      600

acatcaactt cacccatcgt caagagcttc aacaggaatg agtgt                      645
```

<210> 176
<211> 215
<212> PRT
<213> Mus musculus

<400> 176

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Thr Ser Ser
            20                  25                  30

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
        35                  40                  45
```

```
Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

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 Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala
            100                 105                 110

Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser
        115                 120                 125

Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp
    130                 135                 140

Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val
145                 150                 155                 160

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> 177

<211> 1335

<212> DNA

<213> Mus musculus

<400> 177

```
gaggtccagc tgcaacaatc tggacctgag ctggtgaagc ctggggcttc agtgaagatg       60

tcctgtaagg cttctggata cacattcact gactactaca tgaactgggt gaagcagagc      120

catggagaga gccttgagtg 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 cgacacccca tctgtctat ccactggccc ctggatctgc tgcccaaact      420
```

```
aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg      480

acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct      540

gacctctaca ctctgagcag ctcagtgact gtccctcca gcacctggcc cagcgagacc      600

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc      660

agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc      720

ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt      780

gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg      840

gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca      900

gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg      960

gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga     1020

ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa     1080

gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag     1140

tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc     1200

tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact     1260

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc     1320

cactctcctg gtaaa                                                      1335
```

<210> 178

<211> 445

<212> PRT

<213> Mus musculus

<400> 178

```
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 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

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> 179
<211> 324
<212> DNA
<213> Mus musculus

<400> 179
gacatccagc tgacccagag ccccagcttc ctttccgcat ccgttggtga ccgagtaaca 60

atcacatgcc gcgcctcatc ttcagttaca tcttcttatc ttaattggta tcaacaaaaa 120

ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatc aggagttccc 180

tctcgatttt caggatctgg atcaggcaca gaatttacac ttactatatc atcactccaa 240

ccagaagact tcgccactta ttactgccaa caatacgatt tttttccaag cacattcgga 300

ggaggtacaa aagtagaaat caag 324

<210> 180
<211> 108
<212> PRT
<213> Mus musculus

<400> 180
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Thr Ser Ser
20 25 30

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Phe Phe Pro
85 90 95

```
Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 181
<211> 363
<212> DNA
<213> Mus musculus

<400> 181

```
gaggtgcagc tggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaaggtt      60

agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc     120

cctggacaaa gacttgaatg gatgggagac attaaccctt ataacgacga cactacatac     180

aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat     240

atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact     300

gccgttatta ctactaacgc tatggattac tggggtcaag gaaccactgt taccgtctct     360

agt                                                                  363
```

<210> 182
<211> 121
<212> PRT
<213> Mus musculus

<400> 182

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 183

<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized antibody sequence

<400> 183
gaggtgcagc tggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaaggtt 60

agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc 120

cctggacaaa gacttgaatg gatgggagac attaaccctt ataacgacga cactacatac 180

aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat 240

atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact 300

gccgttatta ctactaacgc tatggattac tggggtcaag gaaccactgt taccgtctct 360

agt 363

<210> 184
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody sequence

<400> 184
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Thr Ser Ser
20 25 30

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Phe Phe Pro
85 90 95

Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser

```
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 185

<211> 1341

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 185

```
gaggtgcagc tggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaaggtt       60

agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc      120

cctggacaaa gacttgaatg gatgggagac attaaccctt ataacgacga cactacatac      180

aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat      240

atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact      300

gccgttatta ctactaacgc tatggattac tggggtcaag gaaccactgt taccgtctct      360

agtgcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc      420

gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg      480

tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc      540

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag      600

acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag      660

cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc      720

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg      780

tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac      840
```

```
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc      900

cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag      960

tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa     1020

gggcagcccc gagaaccaca ggtgtacacc ctgccccccat cccgggagga gatgaccaag     1080

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag     1140

tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc     1200

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg     1260

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc     1320

ctctccctgt ctccgggtaa a                                               1341
```

<210> 186

<211> 447

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 186

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser 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

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430
```

```
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> 187
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-17 and Ab-18 LCDR1

<400> 187
```
Ser Val Ser Ser Ser Ile Ser Ser Ser Asn Leu His
1               5                   10
```

<210> 188
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-17 and Ab-18 LCDR2

<400> 188
```
Gly Thr Ser Asn Leu Ala Ser
1               5
```

<210> 189
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> LCDR3

<400> 189
```
Gln Gln Trp Thr Thr Thr Tyr Thr
1               5
```

<210> 190
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-17 and Ab-18 HCDR1

<400> 190
```
Asp Tyr Tyr Ile His
1               5
```

<210> 191
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-17 and Ab-18 HCDR2

<400> 191
Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val Pro Lys Phe Gln
1 5 10 15

Gly

<210> 192
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 192
Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val Asp Tyr
1 5 10

<210> 193
<211> 390
<212> DNA
<213> Mus musculus

<400> 193
atggattttc aggtgcagat tttcagcttc atgctaatca gtgtcacagt catattgtcc 60

agtggagaaa ttgtgctcac ccagtctcca gcactcatgg ctgcatctcc aggggagaag 120

gtcaccatca cctgcagtgt cagctcgagt ataagttcca gcaacttaca ctggtcccag 180

cagaagtcag gaacctcccc caaactctgg atttatggca catccaacct tgcttctgga 240

gtccctgttc gcttcagtgg cagtggatct gggacctctt attctctcac aatcagcagc 300

atggaggctg aagatgctgc cacttattac tgtcaacagt ggactactac gtatacgttc 360

ggatcgggga ccaagctgga gctgaaacgt 390

<210> 194
<211> 130
<212> PRT
<213> Mus musculus

<400> 194
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Met Leu Ile Ser Val Thr
1 5 10 15

```
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> 195

<211> 423

<212> DNA

<213> Mus musculus

<400> 195

```
atgggatgga actggatcat cttcttcctg atggcagtgg ttacaggggt caattcagag       60

gtgcagttgc ggcagtctgg ggcagacctt gtgaagccag gggcctcagt caagttgtcc      120

tgcacagctt ctggcttcaa cattaaagac tactatatac actgggtgaa gcagaggcct      180

gaacagggcc tggagtggat tggaaggatt gatcctgata atggtgaaag tacatatgtc      240

ccgaagttcc agggcaaggc cactataaca gcagacacat catccaacac agcctaccta      300

caactcagaa gcctgacatc tgaggacact gccatctatt attgtgggag agaggggctc      360

gactatggtg actactatgc tgtggactac tggggtcaag gaacctcggt cacagtctcg      420

agc                                                                    423
```

<210> 196

<211> 141

<212> PRT

<213> Mus musculus

<400> 196

```
Met Gly Trp Asn Trp Ile Ile Phe Phe Leu Met Ala Val Val Thr Gly
```

```
1               5                   10                  15

Val Asn Ser Glu Val Gln Leu Arg Gln Ser Gly Ala Asp Leu Val Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
        35                  40                  45

Lys Asp Tyr Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val
65                  70                  75                  80

Pro Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn
                85                  90                  95

Thr Ala Tyr Leu Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Ile
            100                 105                 110

Tyr Tyr Cys Gly Arg Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
    130                 135                 140
```

<210> 197

<211> 390

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 197

```
atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gccgggcgcg       60

cgctgcgata ttcagctgac ccagagcccg agctttctga gcgcgagcgt gggcgatcgc      120

gtgaccatta cctgcagcgt gagcagcagc attagcagca gcaacctgca ttggtatcag      180

cagaaaccgg gcaaagcgcc gaaactgctg atttatggca ccagcaacct ggcgagcggc      240

gtgccgagcc gctttagcgg cagcggcagc ggcaccgaat ttaccctgac cattagcagc      300

ctgcagccgg aagattttgc gacctattat tgccagcagt ggaccaccac ctatacctt       360

ggccagggca ccaaactgga aattaaacgt                                       390
```

<210> 198

<211> 130

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 198

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Pro Gly Ala Arg Cys Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Val Ser
        35                  40                  45

Ser Ser Ile Ser Ser Ser Asn Leu His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

Lys Ala Pro Lys Leu Leu Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly
65                  70                  75                  80

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
                85                  90                  95

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
            100                 105                 110

Gln Trp Thr Thr Thr Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile

        115                 120                 125

Lys Arg
    130
```

<210> 199

<211> 423

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 199

```
atggattgga cctggagcat tctgtttctg gtggcggcgc cgaccggcgc gcatagcgaa       60

gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc      120

tgcaaagcga gcggctttaa cattaaagat tattatattc attgggtgcg ccaggcgccg      180

ggccagggcc tggaatggat gggccgcatt gatccggata acggcgaaag cacctatgtg      240

ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg      300

gaactgcgca gcctgcgcag cgatgatacc gcggtgtatt attgcgcgcg cgaaggcctg      360

------ -------- -------- --------- --------- ------ --      420
```

gattatggcg attattatgc ggtggattat tggggccagg gcaccctggt gaccgtctcg 420

agc 423

<210> 200

<211> 141

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 200

```
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 Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val

65                  70                  75                  80

Pro Lys Phe Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140
```

<210> 201

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Ab-19, Ab-20 and Ab-23 LCDR1

<400> 201

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

<210> 202
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-19, Ab-20 and Ab-23 LCDR2

<400> 202
Ser Thr Ser Arg Leu Asn Ser
1 5

<210> 203
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-19, Ab-20 and Ab-23 LCDR3

<400> 203
Gln Gln Asp Ile Lys His Pro Thr
1 5

<210> 204
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-19, Ab-20 and Ab-23 HCDR1

<400> 204
Asp Tyr Ile Met His
1 5

<210> 205
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-19, Ab-20 and Ab-23 HCDR2

<400> 205
Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe Lys
1 5 10 15

Gly

<210> 206

<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-19, Ab-20 and Ab-23 HCDR3

<400> 206
Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
1 5 10

<210> 207
<211> 107
<212> PRT
<213> Mus musculus

<400> 207
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Asn Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Ala Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile Lys His Pro Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg
100 105

<210> 208
<211> 120
<212> PRT
<213> Mus musculus

<400> 208
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
        115                 120
```

<210> 209

<211> 381

<212> DNA

<213> Mus musculus

<400> 209

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt       60

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcaac      120

atcagctgca gggcaagtca ggacattagc agttatttaa actggtatca gcagaaacca      180

gatggaactg ttaaactcct gatctactcc acatcaagat taaactcagg agtcccatca      240

aggttcagtg gcagtgggtc tgggacagat tattctctca ctattagcaa cctggcacaa      300

gaagatattg ccacttactt ttgccaacag gatattaagc atccgacgtt cggtggaggc      360

accaagttgg agctgaaacg t                                                381
```

<210> 210

<211> 127

<212> PRT

<213> Mus musculus

<400> 210

```
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
1               5                   10                  15

Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
            20                  25                  30

Ala Ser Leu Gly Asp Arg Val Asn Ile Ser Cys Arg Ala Ser Gln Asp
        35                  40                  45

Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
```

```
    50                  55                  60

Lys Leu Leu Ile Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser
                85                  90                  95

Asn Leu Ala Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile
            100                 105                 110

Lys His Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg
        115                 120                 125
```

<210> 211

<211> 417

<212> DNA

<213> Mus musculus

<400> 211

```
atggaatgga tctggatatt tctcttcctc ctgtcaggaa ctgcaggtgt ccactctgag       60

gtccagctgc agcagtctgg acctgagctg gtaaagcctg 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 tgagggctct gcggtctatt actgtgcaag atcgatttat      360

tactacgatg ccccgtttgc ttactgggcc caagggactc tggtcacagt ctcgagc         417
```

<210> 212

<211> 139

<212> PRT

<213> Mus musculus

<400> 212

```
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> 213

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 213

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt      60

gatatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc     120

atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca     180

gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca     240

cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct     300

gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc     360

accaaggtgg agatcaaacg t                                               381
```

<210> 214

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 214

```
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 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> 215

<211> 417

<212> DNA

<213> Mus musculus

<400> 215

```
atggaatgga tctggatatt tctcttcctc ctgtcaggaa ctgcaggtgt ccactctgag       60

gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc      120

tgcaaggctt ctggttttac cttcaccgac tatattatgc actgggtgcg tcaggccccc      180

ggtcaagggc ttgagtggat gggctatatc aacccttata atgatgacac cgaatacaac      240

gagaagttca agggccgtgt cacgattacc gcggacaaat ccacgagcac agcctacatg      300

gagctgagca gcctgcgctc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat      360

tactacgatg ccccgtttgc ttactgggcc caagggactc tggtcacagt ctcgagc         417
```

<210> 216

<211> 139

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 216

```
Met Glu Trp Ile Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1               5                   10                  15

Val His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
        35                  40                  45
```

```
Thr Asp Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135
```

<210> 217

<211> 318

<212> DNA

<213> Mus musculus

<400> 217

```
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc       60

atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca      120

gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca      180

cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct      240

gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc      300

accaaggtgg agatcaaa                                                    318
```

<210> 218

<211> 106

<212> PRT

<213> Mus musculus

<400> 218

```
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 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> 219

<211> 360

<212> DNA

<213> Mus musculus

<400> 219

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc       60

tcctgcaagg cttctggttt taccttcacc gactatatta tgcactgggt gcgtcaggcc      120

cctggtcaag ggcttgagtg gatgggctat atcaaccctt ataatgatga caccgaatac      180

aacgagaagt tcaagggccg tgtcacgatt accgcggaca aatccacgag cacagcctac      240

atggagctga gcagcctgcg ctctgaggac acggccgtgt attactgtgc gcgttcgatt      300

tattactacg atgccccgtt tgcttactgg ggccaaggga ctctggtcac cgtctctagt      360
```

<210> 220

<211> 120

<212> PRT

<213> Mus musculus

<400> 220

```
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> 221
<211> 639
<212> DNA
<213> Mus musculus

<400> 221

```
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc      60

atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca     120

gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca     180

cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct     240

gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc     300

accaaggtgg agatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct     360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc     420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag     480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg     540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg     600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt                             639
```

<210> 222
<211> 213
<212> PRT
<213> Mus musculus

<400> 222

```
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 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
```

```
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> 223

<211> 1338

<212> DNA

<213> Mus musculus

<400> 223

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc      60

tcctgcaagg cttctggttt taccttcacc gactatatta tgcactgggt gcgtcaggcc     120

cctggtcaag ggcttgagtg gatgggctat atcaaccctt ataatgatga caccgaatac     180

aacgagaagt tcaagggccg tgtcacgatt accgcggaca aatccacgag cacagcctac     240

atggagctga gcagcctgcg ctctgaggac acggccgtgt attactgtgc gcgttcgatt     300

tattactacg atgccccgtt tgcttactgg ggccaaggga ctctggtcac cgtctctagt     360

gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag     420

agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg     480

tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca     540

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc     600

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc     660

aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc     720
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aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 780

gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 840

gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 900

gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 960

aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1020

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggtaaa 1338

<210> 224

<211> 446

<212> PRT

<213> Mus musculus

<400> 224

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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 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
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            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
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<210> 225
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-21 and Ab-22 LCDR1

<400> 225
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1               5                   10
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<210> 226
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-21 and Ab-22 LCDR2

<400> 226
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Trp Ala Ser Thr Arg His Thr
1               5
```

<210> 227
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-21 and Ab-22 LCDR3

<400> 227
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Gln Gln Tyr Ser Ser Tyr Pro Leu Thr
1               5
```

<210> 228
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-21 and Ab-22 HCDR1

<400> 228
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Asp Tyr Tyr Met His
1               5
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<210> 229
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-21 and Ab-22 HCDR2

<400> 229
Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe Gln
1 5 10 15

Gly

<210> 230
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Ab-21 and Ab-22 HCDR3

<400> 230
Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr
1 5 10

<210> 231
<211> 381
<212> DNA
<213> Mus musculus

<400> 231
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gacattgtga tgacccagtc tcacaaattc atgtccacgt cagtaggaga cagggtcacc 120

atcacctgca aggccagtca ggatgtcttt actgctgtag cctggtatca acagaaacca 180

ggacaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccctgat 240

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct 300

gaagacttgg cagattattt ctgtcaacaa tatagcagct atcctctcac gttcggtgct 360

gggaccaagt tggagctgaa a 381

<210> 232
<211> 128
<212> PRT
<213> Mus musculus

<400> 232
Met Lys Ser Gln Thr Gln Val Phe Val Tyr Met Leu Leu Trp Leu Ser

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1               5                   10                  15

Gly Val Glu Gly Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser
            20                  25                  30

Thr Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp
        35                  40                  45

Val Phe Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro
    50                  55                  60

Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp
65                  70                  75                  80

Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95

Asn Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Ser
            100                 105                 110

Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
        115                 120                 125
```

<210> 233

<211> 411

<212> DNA

<213> Mus musculus

<400> 233

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tgcaaagctt ctggcttcaa tattaaagac tactatatgc actgggtgaa gcagaggcct      180

gaacagggcc tggagtggat tggaaggatt gatcctgaga atggtgatat tatatatgac      240

ccgaagttcc agggcaaggc cagtataaca acagacacat cctccaacac agcctacctg      300

cagctcagca gcctgacgtc tgaggacact gccgtctatt actgtgctta cgatgctggt      360

gaccccgcct ggtttactta ctggggccaa gggactctgg tcaccgtctc g               411
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<210> 234

<211> 138

<212> PRT

<213> Mus musculus

<400> 234

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Met Gly Trp Asn Trp Ile Ile Phe Phe Leu Met Ala Val Val Thr Gly
1               5                   10                  15

Val Asn Ser Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg
            20                  25                  30
```

```
Pro Gly Ala Leu Val Lys Leu Ser Cys Lys Ala Ser Gly Phe Asn Ile
        35                  40                  45

Lys Asp Tyr Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp
65                  70                  75                  80

Pro Lys Phe Gln Gly Lys Ala Ser Ile Thr Thr Asp Thr Ser Ser Asn
                85                  90                  95

Thr Ala Tyr Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp
        115                 120                 125

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135
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<210> 235

<211> 324

<212> DNA

<213> Mus musculus

<400> 235

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gatatccaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc       60

attacctgca aagcgagcca ggatgtgttt accgcggtgg cgtggtatca gcagaaaccg      120

ggcaaagcgc cgaaactgct gatttattgg gcgagcaccc gccataccgg cgtgccgagt      180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg      240

gaagattttg cgacctatta ttgccagcag tatagcagct atccgctgac ctttggcggc      300

ggcaccaaag tggaaattaa acgt                                             324
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<210> 236

<211> 108

<212> PRT

<213> Mus musculus

<400> 236

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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
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<210> 237

<211> 357

<212> DNA

<213> Mus musculus

<400> 237

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gaagtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg       60

agctgcaaag cgagcggctt taacattaaa gattattata tgcattgggt gcgccaggcg      120

ccgggccagg gcctggaatg gatcggcccc attgatccgg aaaacggcga tattatttat      180

gatccgaaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat      240

atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gtatgatgcg      300

ggcgatccgg cgtggtttac ctattgggcc cagggcaccc tggtgaccgt ctcgagc         357
```

<210> 238

<211> 119

<212> PRT

<213> Mus musculus

<400> 238

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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 Glu Trp Ile
        35                  40                  45

Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
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<210> 239
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 239

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 Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Thr Ser Tyr Met Asn

 1               5                  10                  15
```

<210> 240
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 240

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Ala Ala Ser Asn Leu Glu Ser
1               5
```

<210> 241
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 241

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Gln Gln Ser Asn Glu Asp Pro Phe Thr
1               5
```

<210> 242
<211> 5
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 242
Thr Tyr Trp Met Asn
1 5

<210> 243
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 243
Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp Gln Lys Phe Lys
1 5 10 15

Asp

<210> 244
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 244
Ser Gly Glu Trp Gly Ser Met Asp Tyr
1 5

<210> 245
<211> 657
<212> DNA
<213> Mus musculus

<400> 245
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atcgcctgca aggccagcca aagtgttgat tatgatggta ctagttatat gaattggtac 120

caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 180

gagatcccag ccaggtttag tggcactgcg tctgggacag acttcaccct caacatccat 240

cctgtggagg aggaggatat cacaacctat tactgtcagc aaagtaatga ggatccgttc 300

acgttcggag gggggaccaa gttggaaata aaacgggctg atgctgcacc aactgtatcc 360

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 480

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 540

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600

actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag 657

<210> 246

<211> 218

<212> PRT

<213> Mus musculus

<400> 246

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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

Gly Thr Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro

        35                  40                  45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Glu Ile Pro Ala
    50                  55                  60

Arg Phe Ser Gly Thr Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Glu Glu Asp Ile Thr Thr Tyr Tyr Cys Gln Gln Ser Asn
                85                  90                  95

Glu Asp Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
        115                 120                 125

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

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145                 150                 155                 160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
            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> 247

<211> 442

<212> PRT

<213> Mus musculus

<400> 247

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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 Ser Thr Ala Tyr
65                  70                  75                  80

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                 160

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                 240

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                 320

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                 400

Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn
                405                 410                 415

Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr
            420                 425                 430

Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440
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<210> 248

<211> 1329

<212> DNA

<213> Mus musculus

<400> 248

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tcctgtaagg cttctggcta catcttcacc acctactgga tgaactgggt gaaacagagg     120

cctggacaag gccttgagtg gattggcatg attcatcctt ccgcaagtga aattaggttg     180
```

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gatcagaaat tcaaggacaa ggccacattg actcttgaca aatcctccag cacagcctat      240
atgcacctca gcggcccgac atctgtggat tctgcggtct attactgtgc aagatcaggg      300
gaatgggggt ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctcagccaaa      360
acgacacccc catctgtcta tccactggcc cctggatctg ctgcccaaac taactccatg      420
gtgaccctgg gatgcctggt caagggctat ttccctgagc cagtgacagt gacctggaac      480
tctggatccc tgtccagcgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac      540
actctgagca gctcagtgac tgtcccctcc agcacctggc ccagcgagac cgtcacctgc      600
aacgttgccc acccggccag cagcaccaag gtggacaaga aaattgtgcc cagggattgt      660
ggttgtaagc cttgcatatg tacagtccca gaagtatcat ctgtcttcat cttccccca       720
aagcccaagg atgtgctcac cattactctg actcctaagg tcacgtgtgt tgtggtagac      780
atcagcaagg atgatcccga ggtccagttc agctggtttg tagatgatgt ggaggtgcac      840
acagctcaga cgcaaccccg ggaggagcag ttcaacagca ctttccgctc agtcagtgaa      900
cttcccatca tgcaccagga ctggctcaat ggcaaggagt tcaaatgcag ggtcaacagt      960
gcagctttcc ctgccccat cgagaaaacc atctccaaaa ccaaaggcag accgaaggct      1020
ccacaggtgt acaccattcc acctcccaag gagcagatgg ccaaggataa agtcagtctg      1080
acctgcatga taacagactt cttccctgaa gacattactg tggagtggca gtggaatggg      1140
cagccagcgg agaactacaa gaacactcag cccatcatgg acacagatgg ctcttactc       1200
atctacagca agctcaatgt gcagaagagc aactgggagg caggaaatac tttcacctgc      1260
tctgtgttac atgagggcct gcacaaccac catactgaga agagcctctc ccactctcct      1320
ggtaaatga                                                              1329
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PATENTKRAV

1. Steril flydende formulering, der har en absolut viskositet på 10 cP eller mindre, hvilken formulering omfatter:
(a) et anti-sclerostin-immunoglobulin ved en koncentration på mindst 70 mg/mL og
(b) calciumacetat ved en koncentration i intervallet fra 1 mM til 20 mM, hvor anti-sclerostin-immunoglobulinet omfatter aminosyresekvenser ifølge SEQ ID NO: 86 og SEQ ID NO: 84.

2. Formulering ifølge krav 1, hvor formuleringen omfatter en total koncentration af acetat på mellem 10 mM og 90 mM.

3. Formulering ifølge krav 1 eller krav 2, hvor formuleringen omfatter en total koncentration af acetat på mellem 30 mM og 90 mM eller mellem 30 mM og 75 mM.

4. Formulering ifølge krav 2 eller krav 3, hvor koncentrationen af calciumsalt er mindst 5 mM og ikke større end 15 mM, og koncentrationen af acetat er mindst 50 mM.

5. Formulering ifølge et hvilket som helst af kravene 1-4, hvor immunoglobulinet er ved en koncentration på fra 70 mg/mL til 200 mg/mL.

6. Formulering ifølge et hvilket som helst af kravene 1-5, der har en total osmolalitet på mindre end 350 mOsm/L.

7. Formulering ifølge et hvilket som helst af kravene 1-5, hvor immunoglobulinet er til stede ved en koncentration på mindst 120 mg/mL.

8. Formuleringen of c1aim 7, hvor immunoglobulinet er til stede ved en koncentration på 140 mg/ml.

9. Formulering ifølge et hvilket som helst af kravene 1-5, hvor immunoglobulinet er til stede ved en koncentration på 90 mg/ml.

10. Formulering ifølge et hvilket som helst af kravene 1-5, hvor formuleringens absolutte viskositet er 8 cP eller mindre.

11. Formulering ifølge krav 10, hvor formuleringens absolutte viskositet er 6 cP eller mindre.

12. Formulering ifølge et hvilket som helst af kravene 1-11, hvor formuleringen endvidere omfatter en polyol i en mængde i intervallet fra 4 % vægt/volumen til 6 % vægt/volumen.

13. Formulering ifølge krav 12, hvor polyolen er saccharose.

14. Formulering ifølge et hvilket som helst af kravene 1-13, hvor formuleringen har et pH i intervallet fra 4,5 til 6.

15. Formulering ifølge krav 14, hvor formuleringen har et pH i intervallet fra 5 til 5,5.

16. Fremgangsmåde til reduktion af en proteinformulerings viskositet, hvilken fremgangsmåde omfatter tilsætning af calciumacetat ved en koncentration på mellem 1 mM og 20 mM til en anti-sclerostin-immunoglobulinformulering,
hvor formuleringen omfatter et immunoglobulin ved en koncentration på fra 70 mg/mL til 200 mg/mL, hvor anti-sclerostin-immunoglobulinet omfatter aminosyresekvenser ifølge SEQ ID NO: 86 og SEQ ID NO: 84, og hvor formuleringens viskositet med calciumacetatet er reduceret sammenlignet med antistofformuleringens viskositet uden calciumacetatet.

17. Formulering ifølge et hvilket som helst af kravene 1-15, hvor immunoglobulinet har tungkæder fra SEQ ID NO: 90 og letkæder fra SEQ ID NO: 88.

18. Formulering ifølge krav 17, der endvidere omfatter et overfladeaktivt middel.

19. Formulering ifølge krav 18, hvor koncentrationen af det overfladeaktive middel er fra 0,004 % vægt/volumen til 0,2 % vægt/volumen.

20. Formulering ifølge et hvilket som helst af kravene 1-15 og 17, hvor calciumacetatet reducerer formuleringens absolutte viskositet med mindst 10 % sammenlignet med antistofformuleringens viskositet uden calciumacetatet.

21. Formulering ifølge krav 19, hvor det overfladeaktive middel er polysorbat 20.

22. Formulering ifølge et hvilket som helst af kravene 1-15 og 17-21 til anvendelse i en fremgangsmåde til forbedring af resultatet af en ortopædisk procedure, en dental procedure,

implantationskirurgi, ledudskiftning, knogletransplantation, kosmetisk knoglekirurgi eller knoglereparation, eller til anvendelse i en fremgangsmåde til behandling af osteoporose eller osteopeni.

23. Formulering til anvendelse i fremgangsmåden ifølge krav 22, hvor knoglereparationen er frakturheling, nonunion-heling, forsinket union-heling eller ansigtsrekonstruktion.