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DESCRIPTION

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.

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 comprising (a) an anti-sclerostin immunoglobulin at a concentration of at least 70 mg/mL, wherein the immunoglobulin comprises amino acid sequences of SEQ ID NO: 86 and SEQ ID NO: 84; and (b) a calcium salt at a concentration ranging from 5 mM to 20 mM, and (c) a total concentration of acetate ranging from 10 mM to 90 mM acetate, wherein the formulation has an absolute viscosity of 10 cP or less. Absolute viscosity as described herein is 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] In some embodiments, the calcium salt is selected from the group consisting of calcium acetate, calcium carbonate and calcium chloride. In one embodiment, 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 disclosed is a method for reducing the viscosity of a protein formulation, the method comprising; adding calcium acetate at a concentration of between about 1 mM and about 20 mM, to an anti-sclerostin immunoglobulin formulation, wherein the formulation comprises an immunoglobulin at a concentration of from about 70 mg/mL to about 200 mg/mL, wherein the viscosity of the formulation with the calcium acetate is reduced compared to the viscosity of an 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 salt and/or 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 is 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 aspects 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 aspects 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 aspects 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 exostoses, 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. 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.

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.

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/ml 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 aspects 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 aspects 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 aspects 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 aspects 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):1126-1136 (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, theIGHG1, 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 same 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 (HCAs, 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. 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 of the invention.

[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] Antibodies and antibody fragments described herein may be 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 CH_3 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 V_{HH} domain, or H_2L_2 (referred to as "heavy-chain antibodies" or "HCAbs"); or camelized V_{HH} (See, e.g., Reichman, et al., 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). Absolute viscosity of the 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 salt, and/or acetate salt (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 salt is at a concentration of at least 5 mM, 6 mM, 7 mM, 8 mM, 9 mM or 10 mM. In certain embodiments, the concentration of calcium salt 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 5 mM to about 10 mM, or 5 mM to about 15 mM. In some embodiments, the calcium salt 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 salt 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. When the calcium salt in the formulation is calcium acetate, 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] 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. 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 salt or 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 nonlimiting 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 osmolality 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
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 pyrrolidene, 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, polyvinylpyrrolidone, 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 laurmacrogol 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 antimicrobial 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 Somatrop® (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, disclosed 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. The compound or composition may be 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 aspects, 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 formulations 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 PGE₂ 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
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 +	10	99.4	5.288	191	4.1

Sample	mM	Mg/mL	pH	Osmolarity	Viscosity (cP)
4% sucrose					
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
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

Sample	mM	Mg/mL	pH	Osmolarity	Viscosity (cP)
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 μ l 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
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 (NH₄)₂SO₄ or 1.0M MgSO₄ was added to 1 ml of antibody sample. Viscosity of the control was determined to be 30 cP. MgSO₄ was determined to significantly reduce viscosity of the sample (MgSO₄ + sample = 16 cP). (NH₄)₂SO₄ 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 CaCl₂ or 25 mM MgCl₂ was added to 1 ml of antibody sample. Viscosity of the control was determined to be 18.5 cP. CaCl₂ and MgCl₂ were determined to significantly reduce viscosity of the sample (CaCl₂ + sample = 9 cP and MgCl₂ + 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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<120> High Concentration Antibody Formulations

<130> N118386B-EP

<150> US 61/334,986

<151> 2010-05-14

<160> 248

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aaaccagggc	agcctcccaa	gctcctgatt	tatgatgcac	ccgatctggc	atctggggtc	180

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ccatcgcggt tcagtggcag tggatctggg acacagttca ctctcaccat cagcggcgtg      240
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ttcggcgagg ggaccgaggt ggtggtcaaa cgtacggatg ctgcaccaac tgtatccatc      360
ttcccaccat ccagttagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac      420
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20           25          30

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

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

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

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Gln Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gly Ala Tyr Asn Asp
85           90          95

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

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

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

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Ile Asp Ile Asp Val Ile Thr Ile Asp Gly Ser Gly Arg Gln Asp

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Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn
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Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr
165 170 175

Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His
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ggggaggggc tggaatggat cggaaccatt gattctggtg gtaggacgga ctacgcgagc	180
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agtctgacga ccggggacac ggcgcgttat ttctgtgccg gaaattggaa cttgtggggc	300
caaggcaccc tcgtcacctg ctgcagcgct tctacaaagg gcccatctgt ctatccactg	360
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aatggcaagg agttcaaatt caggggtcaac agtgcagctt tccctgcccc catcgagaaa	960
accatctcca aaaccaaaagg cagaccgaag gctccacagg tgtacaccat tccacctccc	1020
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35 40 45

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

Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Met Asp Leu Lys Met Thr
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Ser Leu Thr Thr Gly Asp Thr Ala Arg Tyr Phe Cys Ala Arg Asn Trp
85 90 95

Asn Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
100 105 110

Lys Gly Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
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Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
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Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn

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Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
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Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
225          230          235          240

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

Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
260          265          270

Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
275          280          285

Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
290          295          300

Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
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Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
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Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
340          345          350

Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
355          360          365

Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
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Asn Thr Asn Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys
385          390          395          400

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gtgactatta cctgtcaatc tagtcagagc gtgtatgata acaattggct ggcggtgtac      180
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ggtgtgccaa gccgtttcag tggcagtggc agcggtaactg actttaccct cacaatttcg      300
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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ser Ser
35           40           45

Gln Ser Val Tyr Asp Asn Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro
50           55           60

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

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85           90           95

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

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tgtgcagcaa gcggcttcag cttatcctct tactggatga attgggtgcg gcaggcacct	180
gggaagggcc tggagtgggt gggcaccatt gattccggag gccgtacaga ctacgcgtct	240
tgggcaaagg gccgtttcac catttccgcg gacaactcca aaaataccat gtacctccag	300
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Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu	
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Ser Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu	
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Glu Trp Val Gly Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser	
65 70 75 80	

Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
 85 90 95

Met Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Arg Tyr
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Val Ser Ser
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ttcagtgggc gtggatctgg gacctctcac tctctcacia tcagccgaat ggaggctgaa	240
gatgctgcca cttattactg ccagcaaagg agtacttacc caccacggt cggtgctggg	300
accaagctgg aactgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc	360

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agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg      540
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          20           25           30

Asp Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Arg Trp Ile Tyr
          35           40           45

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

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

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

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

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

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

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

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

Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
          180          185          190

Gln Glu Ala Thr His Lys Thr Ser Thr Ser Asp Ile Val Lys Ser Phe

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Cys Glu Ala Thr His Lys Thr Ser Thr Pro Ile Val Lys Ser Phe
195 200 205

Asn Arg Asn Glu Cys
210

<210> 23

<211> 1350

<212> DNA

<213> Mus musculus

<220>

<221> misc_feature

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

<400> 23

caggttactc tgaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg	60
acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt	120
cacccatcag ggaagaatct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc	180
tataaccacag tcctgaagag ccgactgact atctccaagg atacctccaa cagccaggtg	240
ttcctcaaga tcgccaatgt ggacactgca gatactgcc aataactactg tgctcgaata	300
gaggactttg attacgacga ggagtattat gctatggact actgggggtca aggaacctca	360
gtcatcgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct	420
gctgccc aaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag	480
ccagtgcagc tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct	540
gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg	600
cccagcgaga ccgtcacctg caacgttgcc caccggcca gcagcaccaa ggtggacaag	660
aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca	720
tctgtcttca tcttcccccc aaagcccaag gatgtgtctc ccattactct gactcctaag	780
gtcacgtgtg ttgtggtaga catcagcaag gatgatccc aggtccagtt cagctggttt	840
gtagatgatg tggaggtgca cacagctcag acgcaacccc gggaggagca gttcaacagc	900
actttccgct cagtcagtga acttcccac atgcaccagg actgggtcaa tggcaaggag	960
ttcaaatgca gggtaaacag tgcagcttcc cctgccccca tcgagaaaac catctccaaa	1020
accaaaggca gaccgaaggc tccacagggtg tacaccattc cacctcccaa ggagcagatg	1080
gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact	1140
gtggagtggc agtgaatgg gcagccagcg gagaactaca agaactca gccatcatg	1200
gacacagatg gctcttactt cgtctacagc aagctcaatg tgcagaagag caactgggag	1260
gcaggaaata ctttcacctg ctctgtgtta catgaggggc 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	tgaccaatc	tccagcttct	ttgactgtgt	ctctaggcct	gagggccacc	60
atctcctgca	aggccagcca	aagtgttgat	tatgatgggtg	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
atcttccac	catccagtga	gcagttaaca	tctggagggtg	cctcagtcgt	gtgcttcttg	420
aacaacttct	accccaaaga	catcaatgtc	aagtggaaga	ttgatggcag	tgaacgacaa	480
aatggcgctc	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

gagggtccagc tgcaacaatc tggacctgag ctggtgaagc ctgggacttc agtgaagatg 60

tctgtgaagg cttctggata cacattcact gactgctaca tgaactgggt gaagcagagc 120

catgggaaga gccttgaatg gattggagat attaatcctt tcaacgggtg tactacctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240

atgcagctca acagcctgac atctgacgac tctgcagtct attactgtgc aagatcccat 300

tattacttcg atggtagagt cccttgggat gctatggact actgggggtca aggaacctca 360

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gtcaccgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct      420

gctgccc aaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag      480

ccagtgcag tgacctgga ctctggatcc ctgtccagcg gtgtgcacac cttccagct      540

gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg      600

cccagcgaga ccgtcacctg caacgttgcc caccgggcca 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 actgggtcaa tggcaaggag      960

ttcaaatgca gggtaaacag tgcagcttcc cctgccccca tcgagaaaac catctccaaa     1020

accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg     1080

gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact     1140

gtggagtggc agtggaatgg gcagccagcg gagaactaca agaactca gccatcatg     1200

gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag     1260

gcaggaaata ctttcacctg ctctgtgtta catgaggggc tgcacaacca ccatactgag     1320

aagagcctct cccactctcc tggtaaata      1350

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<210> 34

<211> 449

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

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

<400> 34

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

```

```

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

```

```

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

```

```

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

```

```

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr

```

```

65           70           75           80

```

```

Met Gln Leu Asn Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Tyr Cys
          85          90          95

```

Ala Arg Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp Asp Ala Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr
 115 120 125

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

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

Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
 165 170 175

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

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

Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
 210 215 220

Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
 225 230 235 240

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

Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
 260 265 270

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

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

Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
 325 330 335

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

Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
 355 360 365

Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
 370 375 380

Trp Asn Glu Gln Pro Ala Glu Asn Trp 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

$\langle 211 \rangle$ 11

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Ab-D LCDR1

<400> 35

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

<210> 36

 $\langle 211 \rangle$ 7

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<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

$\langle 211 \rangle$ 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 gatctatggt tcaagcaact tggaagatgg ggtcccatca	180
aggttcagtg gcagtagata tgggacagat ttactctcca ccatcagcag cctggaggat	240
gaagatctgg caacttattt ctgtctacaa catagttatc tcccgtacac gttcggaggg	300
gggaccaagc tggaataaaa acgggctgat gctgcaccaa ctgtatccat cttcccacca	360
tccagtgage agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac	420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg	480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
 ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gtttag 645

<210> 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
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 tcttgtaagg cttctggata cacattcact gaccactaca tgagctgggt gaagcagagt 120
 catggaaaaa gccttgagtg gattggagat attaatccct attctggtga aactacctac 180
 aaccagaagt tcaagggcac ggccacattg actgtagaca agtcttcag tatagcctac 240
 atggagatcc gcggcctgac atctgaggac tctgcagtct attactgtgc aagagatgat 300
 tacgacgcct ctccgtttgc ttactggggc caagggactc tggtcactgt ctctgcagcc 360
 aaaacgacac ccccatctgt ctatccactg gccctggat ctgctgcca aactaactcc 420
 atggtgaccc tgggatgcct ggtcaagggc tatttccctg agccagtga 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 tgttggtgta 780
 gacatcagca aggatgatcc cgaggtccag ttcagctggt ttgtagatga tgtggaggtg 840
 cacacagctc agacgcaacc ccgggaggag cagttcaaca gcactttccg ctcagtcagt 900
 gaacttcca tcatgcacca ggactggctc aatggcaagg agttcaaatg cagggccaac 960
 agtccagctt tccctgcccc catogagaaa 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

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caaattgttc tctcccagtc tccagcaatc ctgtctacat ctccagggga gaaggtcaca      60
atgacttgca gggccagctc aagtgtatat tacatgcaact ggtaccagca gaagccagga      120
tctcccccca aacctgggat ttatgccaca tccaacctgg cttctggagt ccctgttcgc      180
ttcagtgcca gtgggtctgg gacctcttac tctctcacia tcaccagagt ggaggctgaa      240
gatgctgcca cttattactg ccagcagtgagg agtagtgacc cactcacgtt cgggtgctggg      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 agggcactca caagacatca      600
acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag                          642

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<210> 52

<211> 213

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

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

<400> 52

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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

gagggttcagg tgcagcagtc tgggccagaa cttgtgaagc caggggcctc agtcaagttg	60
tctctgcacag cttctggcct caacattaaa gactacttta tacactgggt gaagcagagg	120
cctgaacagg gcctggagtg gattggaagg cttgatcctg aggatgggtga aagtgattat	180
gccccgaagt tccaggacaa ggccattatg acagcagaca catcatccaa cacagcctat	240
cttcagctca gaagcctgac atctgaggac actgccatct attattgtga gagagaggac	300
tacgatggta cctacacctt ttttccttac tggggccaag ggactctggc cactgtctct	360
gcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact	420
aactccatgg tgaccctggg atgcctggtc aagggtatt tccctgagcc agtgacagtg	480
acctggaact ctggatccct gtccagcggc gtgcacacct tcccagctgt cctgcagtct	540
gacctctaca ctctgagcag ctccagtact gtcccctcca gcacctggcc cagcgagacc	600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc	660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcac	720
ttcccccaa agcccaagga tgtgtcacc attactctga ctctaaggc cacgtgtgtt	780
gtggttagaca tcagcaagga tgatcccag gtccagttca gctggtttgt agatgatgtg	840
gagggtgcaca cagctcagac gcaaccccg gaggagcagt tcaacagcac tttccgctca	900
gtcagtgaac tccccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg	960
gtcaacagtg cagctttccc tgccccatc gagaaaacca tctccaaaac caaaggcaga	1020
ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa	1080

```

-  - -      - - -      - - -      - - -      - -
gtcagctctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag      1140
tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc      1200
tcttacttca tctacagcaa gctcaatgtg cagaagagca actggggaggc 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

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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
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
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
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	tgactgggtt	ccagcagaag	120
tcagacacct	cccccaaacc	ctggatttat	ggcacatcca	acctggcttc	tggagtcacct	180
gttcgcttca	gtggcagtg	atctgggacc	tcttattctc	tcacaatcag	cagcatggag	240
gctgaggatg	ctgccactta	ttactgtcaa	cagtggagta	gttaccact	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	agtgtag		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

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gagggttcagc tgcagcagtc tggggctgaa cttgtgaggc caggggcctt agtcaagttg      60
tcctgcacag cttctgactt caacattaaa gacttctatc tacactggat gaggcagcgg      120
cctgaacagg gcctggactg gattggaagg attgatcctg agaatgggtga tactttatat      180
gacccgaagt tccaggacaa ggccactctt acaacagaca catcctccaa cacagcctac      240
ctgcagctca gcggcctgac atctgagacc actgccgtct attactgttc tagagaggcg      300
gattatttcc acgatggtac ctccactactg tacttcgatg tctggggcgc agggaccaca      360
atcacctgtc cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct      420
gctgccc aaa ctaactccat ggtgaccctg ggatgcctgg tcaagggtta tttccctgag      480
ccagtgcacag tgacctgga ctctggatcc ctgtccagcg gtgtgcacac cttcccagct      540
gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg      600
cccagcgaga ccgtcacctg caacgttgcc caccggcca gcagcaccaa ggtggacaag      660
aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca      720
tctgtcttca tcttcccccc aaagcccaag gatgtgtctc ccattactct gactcctaag      780
gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt      840
gtagatgatg tggagggtga cacagctcag acgcaacccc gggaggagca gttcaacagc      900
actttccgct cagtcaagtga acttcccatc atgcaccagg actgggtcaa tggcaaggag      960
ttcaaatgca ggggtcaacag tgcagctttc cctgccccca tcgagaaaac catctccaaa     1020
accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg     1080
gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact     1140
gtggagtggc agtggaatgg gcagccagcg gagaactaca agaactca gcccatcatg     1200
gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag     1260
gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag     1320
aagagcctct cccactctcc tggtaaata      1350

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<210> 64

<211> 449

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

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

<400> 64

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

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

Tyr Leu His Trp Met Arg Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35           40           45

```

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

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

Leu Gln Leu Ser Gly Leu Thr Ser Glu Thr Thr Ala Val Tyr Tyr Cys
 85 90 95

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

Asp Val Trp Gly Ala Gly Thr Thr Ile Thr Val Ser Ser Ala Lys Thr
 115 120 125

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

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

Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
 165 170 175

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

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

Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
 210 215 220

Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
 225 230 235 240

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

Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
 260 265 270

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

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

Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr

[illegible]

Lys

<210> 65
<211> 324
<212> DNA
<213> Mus musculus

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

<400> 65	
gacatccaga tgaccacagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca	60
ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcattggtt ccaacagaaa	120
cccggcaaag cacctaaatc acttatatac ggacacatcaa atctcgcatc aggcgttccct	180
tcaagatttt caggctctgg ctccaggcacc gactttactc ttacaatatc ctccctccaa	240
cccgaagact tcgcaacctt ttactgtcaa caatggctct 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 tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gattggaag attgatcctg agaatgggtga tactttatat	180
gacccgaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac	240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg	300
gattatttcc acgatggtac ctccctactgg 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 tgaccacagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca 60
 ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcattgggt ccaacagaaa 120
 cccggcaaaag cacctaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct 180
 tcaagattttt caggctctgg ctccaggcacc gactttactc ttacaatatc ctccctccaa 240
 cccgaagact tcgcaacctt ttactgtcaa caatggctct 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 caccatcag 600
 ggcctgagct cgcccgctac 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 30His Leu His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu
35 40 45Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
85 90 95Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205Ser 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

gagggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gattggaagg attgatcctg agaatgggtga tactttatat	180
gacccgaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac	240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg	300
gattatttcc acgatggtag ctccctactgg tacttcgatg tctggggccg tggcaccctg	360
gtcaccgtct ctagtgcctc caccaagggc ccatcgggtt tccccctggc gccctgctcc	420
aggagcacct ccgagagcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa	480
ccggtgacgg tgcctgga ctcaggcgct ctgaccagcg gcgtgcacac cttcccagct	540
gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcaac	600
ttcggcacc cagacctacac ctgcaacgta gatcacaagc ccagcaacac caaggtggac	660
aagacagttg agcgcgaatg ttgtgtcgag tgcccaccgt gcccagcacc acctgtggca	720
ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc	780
cctgaggtca cgtgcgtggg ggtggacgtg agccacgaag accccgaggt ccagttcaac	840
tggtagctgg acggcgtgga ggtgcataat gccaaagaaa agccacggga ggagcagttc	900
aacagcacgt tccgtgtggg cagcgtcctc accgttgtgc accaggactg gctgaacggc	960
aaggagtaca agtgcaaggt ctccaacaaa ggcctcccag ccccatcga gaaaaccatc	1020
tccaaaacca aagggcagcc ccgagaacca caggtgtaca ccctgcccc atcccgggag	1080
gagatgacca agaaccaggt cagcctgacc tgccctggta aaggcttcta cccagcgac	1140
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacacctccc	1200
atgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg	1260
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggtcttgca 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 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 caggggtctcc 60
 atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120
 gatggaactt ttaaaactct tatcttctac acatcaagat tactctcagg agtcccatca 180
 aggttcagtg gcagtgggtc tggaaacagat tattctctca ccatttataa cctggagcaa 240
 gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac ttccggaggg 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

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gagggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg      60
tcctgcaagg cttctggata tacattcact gactacaaca tgcaactgggt gaagcagaac      120
caaggaaaaga ccctagagtg gataggagaa attaatccta acagtgggtg tgctggctac      180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac      240
atagactaa agagactaa atagactaa atagactaa atagactaa atagactaa      300

```

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atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc      300
tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc      360
gtctcctcag ccaaaacgac acccccattct gtctatccac tggcccctgg atctgctgcc      420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg      480
acagtgacct ggaactctgg atccctgtcc agcgggtgtg acaccttccc agctgtcctg      540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc      600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaagggtga caagaaaatt      660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc      720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg      780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gttttagat      840
gatgtggagg tgcacacagc tcagacgcaa cccggggagg agcagttcaa cagcactttc      900
cgctcagtcg gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa      960
tgcagggtcg acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaacaaaa     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 ctctctggtaa 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 Val Ser Gln Thr Thr Thr Glu Glu Glu Glu Val Met Met Ser
85           90           95           100

```

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

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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 tgggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgttaaagtt	60
tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg	120
ccaggacaag gattggaatg gatgggagaa attaaccta atagtggagg agcaggctac	180
aatcaaaaat tcaaaggag agttacaatg acaacagaca caagcattc 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

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 ctaaaactcct catttactat acatcaagac tcctctccgg cgttccatca	180
cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca	240
gaagattttg caacctatta ctgtcaacaa ggcgatacac tcccatacac attcggcggc	300
ggcacaaaag ttgaaattaa acgtacgggtg gctgcaccat ctgtcttcat cttcccgcca	360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat	420
cccagagagg ccaaagtaca gtggaagggtg 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 tgggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgtaaagt	60
tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg	120
ccaggacaag gattggaatg gatgggagaa attaaccta atagtggagg agcaggctac	180
aatcaaaaat tcaaaggag agttacaatg acaacagaca caagcacttc aacagcatat	240
atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg	300
tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc	360
gtctctagtg cctccaccaa gggcccatcg gtcttcccc tggcgccctg ctccaggagc	420
acctccgaga gcacagcggc cctgggctgc ctgggcaagg actacttccc cgaaccggtg	480
acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta	540
cagtcctcag gactctactc cctcagcagc gtgggtgaccg tgccctccag caacttcggc	600
accagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca	660
gttgagcgca aatgttgtgt cgagtgccca ccgtgccag caccacctgt ggcaggaccg	720
tcagtcttcc tcttcccccc aaaacccaag gacacctca tgatctcccg gacctctgag	780
gtcacgtgcg tgggtggtga cgtgagccac gaagaccccg aggtccagtt caactggtac	840
gtggacggcg tggaggtgca taatgccaa acaaagccac gggaggagca gttcaacagc	900
acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag	960
tacaagtgca aggtctccaa caaaggcctc ccagccccc tccgagaaaac catctccaaa	1020
accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg	1080
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctacccag cgacatcgcc	1140
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg	1200
gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag cagggtggcag	1260
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag	1320
aagagcctct ccctgtctcc gggtaaa	1347

<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 Glv Ala Glu Val Lvs Lvs Pro Glv 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

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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 tggaataaag acgggctgat gctgcaccaa ctgtatccat cttcccacca      360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac      420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg      480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg      540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca      600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                      645

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<210> 98

<211> 214

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-6 light chain

<400> 98

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

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

Leu Asn Trp Phe Gln Gln Lys Pro Asp Gly Thr Leu Lys Leu 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 tgcaactgggt gaaacagaac	120
caaggaaaga gcctagagtg gataggagaa attaatccta acagtgggtg tagtggctac	180
aacccaaaagt tcaaaggcaa ggccacattg actgtagaca agtcttccag cacagcctac	240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattggtc	300
tacgatggca gctacgagga ctgggtacttc gatgtctggg gcgcagggac caaggtcacc	360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc	420
caaactaact ccatgggtgac cctgggatgc ctgggtcaagg gctatttccc tgagccagtg	480
acagtgaacct ggaactctgg atccctgtcc agcgggtgtgc acacdtccc agctgtcctg	540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc	600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaagggtgga caagaaaatt	660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc	720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg	780
.	840

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tgtgttggtg tagacatcag caaggatgat cccgaggtcc agttcagctg gttttagat      840
gatgtggagg tgcacacagc tcagacgcaa ccccgaggagg agcagttcaa cagcactttc      900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa      960
tgcaggggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaa      1020
ggcagaccga aggtccaca 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 ctcttggtaa atga      1344

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<210> 100

<211> 447

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-6 heavy chain

<400> 100

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

```

```

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

```

```

Asn Met His Trp Val Lys Gln Asn Gln Gly Lys 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
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	ggatgatacg	ttccgtacac	gttcggaggg	300
gggaccaagc	tggaataaaa	acgggctgat	gctgcaccaa	ctgtatccat	cttcccacca	360
tccagtgagc	agttaacatc	tgaggtgcc	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

$\langle 400 \rangle$ 109

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tctctgaagg	cttctggata	cacattcact	gactacaaca	tgcactggat	gaagcagaac	120
caaggaaaga	gcctagaatg	gataggagaa	attaatccta	acagtggctg	tgctggctac	180
aaccagcagt	tcaaaggcaa	ggccacattg	actgtagaca	agtcctccag	gacagcctac	240
atggagctcc	gcagcctgac	atctgaggac	tctgcagtct	attactgtgc	aagattgggc	300
tacgttggtg	attacgagga	ctggtacttc	gatgtctggg	gcgcagggac	cacggtcacc	360
gtctctcag	ccaaaacgac	acccccatct	gtctatccac	tggcccctgg	atctgtctgc	420
caaactaact	ccatggtgac	cctgggatgc	ctgggtcaagg	gctatttccc	tgagccagtg	480
acagtgcact	ggaactctgg	atccctgtcc	agcgggtgtc	acaccttccc	agctgtcctg	540
cagtctgacc	tctacactct	gagcagctca	gtgactgtcc	cctccagcac	ctggcccagc	600
gagaccgtca	cctgcaacgt	tgccaccocg	gccagcagca	ccaaggtgga	caagaaaatt	660
gtgcccaggg	attgtggttg	taagccttgc	atatgtacag	tcccagaagt	atcatctgtc	720
ttcatcttcc	ccccaaagcc	caaggatgtg	ctcaccatta	ctctgactcc	taaggtcacg	780
tgtgttgtgg	tagacatcag	caaggatgat	cccagggctc	agttcagctg	gtttgtagat	840
gatgtggagg	tgcacacagc	tcagacgcaa	ccccgggagg	agcagttcaa	cagcactttc	900
cgctcagtca	gtgaacttcc	catcatgcac	caggactggc	tcaatggcaa	ggagttcaaa	960
tgcagggtca	acagtgcagc	tttccttgcc	cccatogaga	aaaccatctc	caaaacccaa	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
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 $\langle 210 \rangle$ 110

<211> 447

<212> PRT

<213> Mus musculus

$\langle 220 \rangle$

<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

 $\langle 210 \rangle$ 111

$\langle 211 \rangle$ 11

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Ab-8 LCDR1

$\langle 400 \rangle$ 111

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

$\langle 210 \rangle$ 112

 $\langle 211 \rangle$ 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

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gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga caggggtctcc      60
atcagttgca gggcaagtca agacattagc aattatttaa actgggtatca gcagaaacca      120
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca      180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttaca cctggagcaa      240
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg      300
gggaccaaac tggaataaaa acgggctgat gctgcaccaa ctgtatccat cttcccacca      360
tccagtgage agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac      420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg      480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg      540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca      600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                        645

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<210> 118

<211> 214

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-8 light chain

<400> 118

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

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

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

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

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
65          70          75          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
tcttgcaagg cttctggata tacattcact gactacaaca tgcaactgggt gaagcagaac	120
caaggaaaaga ccctagactg gataggagaa attaatccta acagtgggtg tgctggctac	180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac	240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc	300
tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcaggagc cacggtcacc	360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc	420
caaactaact ccatgggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg	480
acagtgacct ggaactctgg atccctgtcc agcgggtgtg acaccttccc agctgtcctg	540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc	600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaagggtga caagaaaatt	660
gtgcccaggg atttgtggtg taagccttgc atatgtacag tcccagaagt atcatctgtc	720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg	780
tgtgttggtg tagacatcag caaggatgat cccgaggtcc agttcagctg gttttagat	840
gatgtggagg tgcacacagc tcagacgcaa ccccgaggag agcagttcaa cagcactttc	900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa	960
tgcagggtca acagtgcagc ttccctgtcc cccatcgaga aaaccatctc caaaaccaa	1020

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- - - - -
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 ctcttggtaa atga                                             1344

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<210> 120

<211> 447

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<223> Ab-8 heavy chain

<400> 120

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

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

Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu Asp Trp Ile
35          40          45

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

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

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

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

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

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

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

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

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

```

Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
 195 200 205
 His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
 210 215 220
 Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
 225 230 235 240
 Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
 245 250 255
 Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
 260 265 270
 Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
 275 280 285
 Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
 290 295 300
 Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
 305 310 315 320
 Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
 325 330 335
 Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
 340 345 350
 Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
 355 360 365
 Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
 370 375 380
 Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
 385 390 395 400
 Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
 405 410 415
 Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
 420 425 430
 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 caggggtctcc 60
 atcagttgca gggcaagtca agacattagc aattatttaa attggtatca gcagaaacca 120
 gatggaactt ttaaactcct tatcttctac acatcaagat tatttttcagg agtcccatca 180
 aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttataa cctggagcaa 240
 gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac ttccggaggg 300
 gggaccaagg tggaataaaa 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
tcttgcaagg cttctggata tacattcact gactacaaca tgcaactgggt gaagcagacc	120
caaggaaaga ccctagagtg gataggagaa attaatccta acagtgggtg tgctggctac	180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac	240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aaaattgggc	300
tacgatgata tctacgacga ctggtatttc gatgtctggg ggcagggac cacggtcacc	360
gtctcctcag ccaaaacaac agcccatcg gtctatccac tggcccctgt gtgtggagat	420
acaactggct cctcggtgac tctaggatgc ctggccaagg gttatttccc tgagccagtg	480
agcttcagct ggaattatgc atgactatgc agtcatatgc agagattgaa agctatgata	540

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acattgacct ggaactcttg accctctccc agtcatgtgc acacctcccc agctctctctg      340
cagtctggcc tctacacctt cagcagctca gtgactgtaa ccacctggcc cagccagacc      600
atcacctgca atgtggccca cccggcaagc agcaccaaag tggacaagaa aattgagccc      660
agagggtccc caacacataa accctgtcct ccatgcccag ctctaacct cttgggtgga      720
ccatccgtct tcatcttccc tccaaagatc aaggatgtac tcatgatctc cctgagcccc      780
atggtcacgt gtgtggtggt ggatgtgagc gaggatgacc cagatgtcca tgtcagctgg      840
ttcgtgaaca acgtggaagt acacacagct cagacacaaa cccatagaga ggattacaac      900
agtactatcc ggggtggtcag tgccctcccc atccagcacc aggactggat gagtggcaag      960
gagttcaaat gcaagggtcaa caacaaagcc ctcccagcgc ccatcgagag aaccatctca     1020
aaacccaaag ggccagtaag agctccacag gtatatgtct tgcctccacc agaagaagag     1080
atgactaaga aacagggtcac 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 tctcccgac tccgggtaaa                                1350

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<210> 130

<211> 450

<212> PRT

<213> Mus musculus

<400> 130

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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 cagggctctcc 60
 atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120
 gatggaactt ttaaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180
 aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttaca cctggagcaa 240
 gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300
 gggaccaaac tggaataaaa acgggctgat gctgcaccaa ctgtatccat cttcccacta 360
 tccagtgagc agttaacatc tggaggtgcc tcagtctgtg 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

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tcctgcaagg cttctggata tacattcact gactacaaca tgcaactgggt gaagcagaac 120

caaggaaaga ccctagaatg gataggagaa attaatccta acagtgggtg tgctggctac 180

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aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac      240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc      300
tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc      360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc      420
caaaactaact ccatgggtgac cctgggatgc ctgggtcaagg gctatttccc tgagccagtg      480
acagtgacct ggaactctgg atccctgtcc agcgggtgtgc acaccttccc agctgtcctg      540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc      600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaagggtga caagaaaatt      660
gtgcccaggg atttgtggtg taagccttgc atatgtacag tcccagaagt atcatctgtc      720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg      780
tgtgttggtg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat      840
gatgtggagg tgcacacagc tcagacgcaa ccccgaggag agcagttcaa cagcactttc      900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa      960
tgcaggggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaa      1020
ggcagaccga aggtccaca 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 ctcttggtaa atga                                             1344

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<210> 140

<211> 447

<212> PRT

<213> Mus musculus

<400> 140

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

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

Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu 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

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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

$\langle 211 \rangle$ 10

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Ab-11 and Ab-16 LCDR1

<400> 141

Arg Ala Ser Ser Ser Ile Ser Tyr Ile His
1 5 10

<210> 142

 $\langle 211 \rangle$ 7

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Ab-11 and Ab-16 LCDR2

<400> 142

Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 143

$\langle 211 \rangle$ 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

$\langle 211 \rangle$ 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
tctctcccca gatcctggat ttatgccaca tccaacctgg cttctggagt ccctggtcgc	180
ttcagtgcca gtgggtcttg gacctcttac tctctcacia tcagcagagt ggaggctgag	240
gatgctgcca cttattactg ccagcagtg agtagtgacc cactcacgtt cggtgctggg	300
accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc	360
agtgagcagt taacatctgg aggtgcctca gtctgtgtct 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 cttcaacagc 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

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gaagttcagc tgcaacagtc tggggcagac cttgtgcagc caggggcctc agtcaagggtg      60
tcctgcacag cttctggcct cgacattaag gactactata tacactggat gaaacagagg      120
cctgaccagg gcctggagtg gattggaagg gttgatcctg acaatggtga gactgaatct      180
gccccgaagt tccccggcaa 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 gtccagcggg gtgcacacct tcccagctgt cctgcagtct      540
gacctctaca ctctgagcag ctcaagtact gtcccctcca gcacctggcc cagcgagacc      600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc      660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcac      720
ttccccccaa agcccaagga tgtgtctacc attactctga ctctaagggt cacgtgtgtt      780
gtggtagaca tcagcaagga tgatcccag gtccagttca gctggtttgt agatgatgtg      840
gaggtgcaca cagctcagac gcaaccccg gaggagcagt tcaacagcac tttccgctca      900
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg      960
gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga     1020
ccgaaggctc cacagggtga caccattcca cctcccagg 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 ggcctctcc     1320
cactctcctg gtaaatga                                     1338

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<210> 150

<211> 445

<212> PRT

<213> Mus musculus

<400> 150

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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 tgaccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg	120
aaagccccta agctcctgat ctatgccaca tccaacctgg cttctgggggt cccatcaagg	180
ttcagcgcca gtggatctgg gacagaattc actctcacia 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

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gagggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc      60
tcttgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc      120
cctggacaag ggcttgagtg gatcggaagg gttgatcctg acaatgggtga gactgaattt      180
gccccgaagt tccccggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac      240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac      300
tacgatggtg cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct      360
agt

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<210> 154

<211> 121

<212> PRT

<213> Mus musculus

<400> 154

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

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

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

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

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

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

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

Gln Gly Thr Leu Val Thr Val Ser Ser
115    120

```

<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 cttctggggg cccatcaagg      180
ttcagcggca gtggatctgg gacagaattc actctcaca 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 agtacagtg 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
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 tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tcctgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatcggaagg gttgatcctg acaatgggtga gactgaattt	180
gccccgaagt tccccggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac	240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac	300
tacgatggtg cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct	360
agtgcctcca ccaagggccc atcggctctc cccctggcgc cctgctccag gagcacctcc	420
gagagcacag cgccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg	480
tcgtggaact caggcgtctt gaccagcggc gtgcacacct tcccagctgt cctacagtcc	540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcaccacg	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 caaaaccaa      1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag      1080
aaccaggtca gcctgacctg cctgggtcaaa ggcttctacc ccagcgacat cgccgtggag      1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc      1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg      1260
aacgtcttct catgctcgt gatgcatgag gctctgcaca accactacac gcagaagagc      1320
ctctccctgt ctccgggtaa a                                          1341

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<210> 158

<211> 447

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody sequence

<400> 158

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

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

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

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

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

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

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

Gln Gly Thr Leu Val Thr Val Ser Ser 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 acagtgggtgg ttctggttac	180
aaccagaagt tcaaaggcaa ggccacattg actgtagaca agtcctccag cacagcctac	240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc	300

tactatggta actacgagga ctggtatttc gatgtctggg gcgcaggac cacggtcacc 360
gtctcctctg ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
caactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcgggtgtg acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccaccgc gccagcagca ccaagggtga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttggtg tagacatcag caaggatgat cccgaggtcc agttcagctg gttttagatg 840
gatgtggagg tgcacacagc tcagacgcaa ccccgaggag agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc ttccctgtcc cccatcgaga aaaccatctc caaaaccaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctgagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcttggtaa 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

Asn Thr Thr Met Asn

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 tcaccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc	60
atgacctgca gggccagctc aagtgttaact tccagttact tgaactggta ccagcagaag	120
ccaggatctt cccccaaact ctggatttat agcacatcca acctggcttc aggagtcca	180
gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagtgtggag	240
gctgaggatg ctgccactta ttactgccag cagtatgatt ttttccatc gacgttcggt	300
ggaggcacca agctggaaat caagcgggct gatgctgcac caactgtatc catcttcca	360
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc	420
taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc	480
ctgaacagtt ggactgatca ggacagcaaa gacagcaoct acagcatgag cagcaccctc	540
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag	600
acatcaactt caccatcgt 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

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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 cgacaccccc atctgtctat ccaactggccc ctggatctgc tgcccaaact 420
aactccatgg tgacctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg 480
acctggaact ctggatccct gtccagcggg gtgcacacct tcccagctgt cctgcagtct 540
gacctctaca ctctgagcag ctcaagtact gtcccctcca gcacctggcc cagcgagacc 600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcac 720
ttccccccaa agcccaagga tgtgtctacc attactctga ctccctaagg cactgtgtgt 780
gtggtagaca tcagcaagga tgatcccag gtccagttca gctggtttgt agatgatgtg 840
gagggtgcaca cagctcagac gcaaccccg 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 actgggagggc aggaaatact 1260
ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320
cactctcctg gtaaa 1335

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<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

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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

Asn Phe Phe Pro Glu Asp Ile Thr Val Glu Thr Glu Thr Asn Glu Glu

Asp Phe Phe Phe Glu Asp Ile Ile Val Glu Asp Glu Asp Asp Asn Gly Glu
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 tgaccagag cccagcttc ctttccgcat ccgttggtga ccgagtaaca	60
atcacatgcc ggcctcctc ttcagttaca tcttcttctc ttaattggta tcaacaaaaa	120
ccaggaaaaag cacctaaact tcttatatac tctacatcta atctcgcatac aggagttccc	180
tctcgatttt caggatctgg atcaggcaca gaatttacac ttactatatc atcactccaa	240
ccagaagact tcgccactta ttactgcaa 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

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gaggtgcagc tgggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaagggt      60
agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc      120
cctggacaaa gacttgaatg gatgggagac attaacccctt ataacgacga cactacatac      180
aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat      240
atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact      300
gccgttatta ctactaacgc tatggattac tgggggtcaag gaaccactgt taccgtctct      360
agt                                                                 363
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<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

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gaggtgcagc tgggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaagggt      60
agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc      120
cctggacaaa gacttgaatg gatgggagac attaaccctt ataacgacga cactacatac      180
aatcataaat ttaaaggaag agttacaatt acaagagata catccgcata aaccgcctat      240
atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact      300
gccgttatta ctactaacgc tatggattac tgggggtcaag gaaccactgt taccgtctct      360
agt                                                                                   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 Asn 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 tgggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaaggtt	60
agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc	120
cctggacaaa gacttgaatg gatgggagac attaacctt ataacgacga cactacatac	180
aatcataaat ttaaaggaag agttacaatt acaagagata catccgcac caccgcctat	240
atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact	300
gccgttatta ctactaacgc tatggattac tgggggtcaag gaaccactgt taccgtctct	360
agtgcctcca ccaagggccc atcggctctt cccctggcgc cctgctccag gagcacctcc	420
gagagcacag cgccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg	480
togtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc	540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcaccacg	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 ggagtacaa	960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaa	1020
gggcagcccc gagaaccaca ggtgtacacc ctgccccat cccgggagga gatgaccaag	1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag	1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc	1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg	1260

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aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc      1320
ctctccctgt ctccgggtaa a                                                    1341
```

<210> 186

$\langle 211 \rangle$ 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

[illegible]

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 atgctaataca gtgtcacagt catattgtcc 60
 agtggagaaa ttgtgctcac ccagtctcca gcactcatgg ctgcatctcc aggggagaag 120
 gtcaccatca cctgcagtgt cagctcgagt ataagttcca gcaacttaca ctgggtcccag 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

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

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 ggcctcagt 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 tggggccaag gaacctcggc 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

113 120 125
 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

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atggatatgc gcgtagccggc gcagctgctg ggcctgctgc tgctgtggct gccgggagcg      60
cgctgcgata ttcagctgac ccagagcccg agctttctga gcgcgagcgt gggcgatcgc      120
gtgaccatta cctgcagcgt gacgagcagc attagcagca gcaacctgca ttggtatcag      180
cagaaaccgg gcaaagcgcc gaaactgctg atttatggca ccagcaacct ggcgagcggc      240
gtgccgagcc gctttagcgg cagcggcagc ggcaccgaat ttaccctgac cattagcagc      300
ctgcagccgg aagattttgc gacctattat tgccagcagt ggaccaccac ctataccttt      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 tgcaagcggg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc      120
tgcaaagcga gcggctttaa cattaagat 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
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

```

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 ctggtgctct gttttcaagg taccagatgt	60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcaac	120
atcagctgca gggcaagtca ggacattagc agttatttaa actggatatca gcagaaacca	180
gatggaactg ttaaactcct gatctactcc acatcaagat taaactcagg agtcccatca	240
aggttcagtg gcagtgggtc tgggacagat tattctctca ctattagcaa cctggcacia	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 agcagtcctgg acctgagctg gtaaagcctg gggcttcagt gaagatgtcc      120
tgcaaggctt ctgggttcac attcactgac tacattatgc actgggtgaa gcagaagcct      180
gggcagggcc ttgagtggat tggatatatt aatccttaca atgatgatac tgaatacaat      240
gagaagtca aaggcaaggc cacactgact tcagacaaat cctccagcac agcctacatg      300
gatctcagca gtctgacctc tgagggctct gcggtctatt actgtgcaag atogatttat      360
tactacgatg ccccgtttgc ttactggggc caagggactc tggtcacagt ctcgagc      417

```

<210> 212

<211> 139

<212> PRT

<213> Mus musculus

<400> 212

```

Met Gln Phe Thr Thr Thr Phe Thr Thr Thr Ser Gln Met Thr Gln

```

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 cgggtcaaggc	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 ctgcagggtgt ccactctgag      60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggg gaaggctctcc      120
tgcaaggctt ctggttttac cttcaccgac tatattatgc actgggtgcg tcaggcccct      180
gggtcaagggc ttgagtggat gggctatatc aacccttata atgatgacac cgaatacaac      240
gagaagttca agggccgtgt cagcattacc gcggacaaat ccacgagcac agcctacatg      300
gagctgagca gcctgcgctc tgaggacacg gccgtgtatt actgtgcgcg ttogatttat      360
tactacgatg ccccgtttgc ttactggggc 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 ggcgaagtca ggatattagc agctatttaa attggtatca gcagaaacca	120
gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca	180
cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct	240
gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cgggtcaaggc	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 tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc	60
tcctgcaagg cttctggttt taccttcacc gactatatta tgcaactgggt 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

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gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggatga ccgtgtcacc      60
atcacttgcc gcgcaagtca ggatattagc agctatttaa attggatatca gcagaaacca      120
gggaaagccc ctaagctcct gatctattct acttcccggt tgaatagtgg ggtcccatca      180
cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct      240
gaagattttg caacttacta ctgtcaacag gatattaaac accctacggt cggtaaggc      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 aagtcacca tcagggcctg      600
agctcgcccc tcacaaagag cttcaacagg ggagagtgt      639

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<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
 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 tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc	60
tcttgcaagg cttctgggtt 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 ccgaaccggg gacgggtgcg	480
tggaaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca	540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg caccagacc	600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc	660
aaatgttggtg tcgagtgcgc accgtgcccc gcaccacctg tggcaggacc gtcagtcttc	720
ctcttcccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacgtgc	780
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc	840
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt	900
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc	960
aggtatgag agggggggtt agggggggg atggggggg aggtatgag agggggggg	1020

```

aaggtctcca acaaaagcct cccagccccc atcgagaaaa ccacctccaa aaccaaaaggy      1020
cagccccgag aaccacaggt gtacaccctg ccccatcccc 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
tcctgtcttc cgggtaaa                                     1338

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<210> 224

<211> 446

<212> PRT

<213> Mus musculus

<400> 224

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

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

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

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

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

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

Ala Arg Ser Ile Tyr Tyr 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

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 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
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 325 330 335
 Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
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 Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
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 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380
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 385 390 395 400
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<223> Ab-21 and Ab-22 LCDR2

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Asp Tyr Tyr Met His
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<223> Ab-21 and Ab-22 HCDR2

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<211> 381

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cgcttcacag	gcagtggatc	tgggacagat	ttcactctca	ccattagcaa	tgtgcagtct	300
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<211> 128

<212> PRT

<213> Mus musculus

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		20						25					30		

Thr	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp
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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	

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<211> 411

<212> DNA

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cagctcagca gcctgacgtc tgaggacact gccgtctatt actgtgctta cgatgctggt      360
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<212> PRT

<213> Mus musculus

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

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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
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<210> 235

<211> 324

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<210> 236

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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
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<210> 237

<211> 357

<212> DNA

<213> Mus musculus

<400> 237

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<210> 238

<211> 119

<212> PRT

<213> Mus musculus

<400> 238

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                20              25              30

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

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

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

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

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<210> 239

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<223> Synthetic peptide

<400> 239

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<400> 240

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<210> 241

<211> 9

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<223> Synthetic peptide

<400> 241

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<210> 242

<211> 5

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<400> 242

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<210> 243

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<400> 243

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<210> 244

<211> 9

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<211> 657

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gagatcccag ccaggttttag tggcactggg tctgggacag acttcaccct caacatccat      240
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aatggcgctcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc      540
agcaccctca cgttgaccaa ggaacgagtat gaacgacata acagctatac ctgtgaggcc      600
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Gln Arg Ala Thr Ile Ala Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
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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

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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
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His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
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210 215

<210> 247

<211> 442

<212> PRT

<213> Mus musculus

<400> 247

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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
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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
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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

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His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser
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 385 390 395 400

Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn
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<210> 248

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<212> DNA

<213> Mus musculus

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ggtaaatga	1329

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- Remington's Pharmaceutical SciencesMack Publishing Co.199000001435-1712 [0098]

PATENTKRAV

1. Steril flydende formulering, der har en absolut viskositet på 10 cP eller mindre, omfattende: (a) et anti-sclerostin-immunoglobulin ved en koncentration på mindst 70 mg/mL; (b) et calciumsalt ved en koncentration i et interval fra 5 mM til 20 mM og (c) en total koncentration af acetat i et interval fra 10 mM til 90 mM, hvor
5 immunoglobulinet omfatter aminosyresekvenser ifølge SEQ ID NO: 86 og SEQ ID NO: 84.
2. Formulering ifølge krav 1, der har en total osmolalitet på mindre end 350 mOsm/L.
- 10 3. Formulering ifølge krav 1 eller 2, hvor immunoglobulinet er til stede ved en koncentration på mindst 120 mg/mL.
4. Formulering ifølge et hvilket som helst af krav 1-3, hvor formuleringens absolutte viskositet er 8 cP eller mindre, eller 6 cP eller mindre.
5. Formulering ifølge et hvilket som helst af krav 1-4, hvor formuleringen
15 endvidere omfatter et polyol i en mængde i intervallet fra 4 % vægt/volumen til 6 % vægt/volumen.
6. Formulering ifølge et hvilket som helst af krav 1-5, hvor formuleringen har et pH i intervallet fra 4,5 til 6, eller fra 5 til 5,5.
7. Formulering ifølge et hvilket som helst af de foregående krav til anvendelse
20 ved behandling af en patient, der undergår en ortopædisk procedure, dentalprocedure, implantationskirurgi, ledudskiftning, knogletransplantation, knoglekosmetisk kirurgi eller knoglereparation.
8. Formulering eller formulering til anvendelse ifølge et hvilket som helst af de foregående krav, hvor formuleringen omfatter en total koncentration af acetat på
25 mindst 50 mM.
9. Formulering eller formulering til anvendelse ifølge et hvilket som helst af de foregående krav, hvor immunoglobulinet er til stede ved en koncentration på 90 mg/mL eller 140 mg/mL.
10. Formulering ifølge krav 5, hvor polyolet er saccharose.

11. Formulering eller formulering til anvendelse ifølge et hvilket som helst af de foregående krav, der endvidere omfatter et overfladeaktivt middel.

12. Formulering ifølge krav 11, hvor koncentrationen af det overfladeaktive middel er fra 0,004 % vægt/volumen til 0,2 % vægt/volumen.

5 **13.** Formulering ifølge krav 11, hvor det overfladeaktive middel er polysorbat 20.

14. Formulering eller formulering til anvendelse ifølge et hvilket som helst af de foregående krav, hvor acetatbufferen omfatter natriumacetat.

10 **15.** Formulering til anvendelse ifølge krav 7, hvor knoglereparationen er frakturheling, ikke-sammenvoksningsheling, forsinket sammenvoksningsheling eller ansigtsrekonstruktion.

16. Formulering eller formulering til anvendelse ifølge et hvilket som helst af de foregående krav, hvor viskositeten vurderes ved 25 °C eller mellem 2-8 °C.

15 **17.** Formulering eller formulering til anvendelse ifølge et hvilket som helst af de foregående krav, hvor immunoglobulinet omfatter aminosyresekvenserne ifølge SEQ ID NO: 88 og 90.