(19) Europäisches
Patentamt
European
Patent Office
Office européen
des brevets

(11) EP 2 556 841 B9

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Claims EN 1

(48) Corrigendum issued on:
06.09.2017 Bulletin 2017/36

(45) Date of publication and mention
of the grant of the patent:
11.05.2016 Bulletin 2016/19

(21) Application number: **12180292.0**

(22) Date of filing: **17.09.2008**

(51) Int Cl.:
A61K 39/395 ^(2006.01)^ ***A61P 19/08*** ^(2006.01)^
C07K 16/18 ^(2006.01)^

---

(54) **Method for inhibiting bone resorption**

Verfahren zur Hemmung von Knochenresorption

Procédé d’inhibition de la résorption osseuse

---

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT RO SE SI SK TR

(30) Priority: **17.09.2007 US 973024 P**

(43) Date of publication of application:
13.02.2013 Bulletin 2013/07

(60) Divisional application:
16162068.7 / 3 085 386

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
08832690.5 / 2 195 026

(73) Proprietor: **Amgen, Inc**
Thousand Oaks, CA 91320-1799 (US)

(72) Inventors:
- **Padhi, Ian, Desmond**
  Newbury Park, CA 91320 (US)
- **Jang, Graham, Richard**
  Thousand Oaks,
  California 91360 (US)

(74) Representative: **J A Kemp**
14 South Square
Gray’s Inn
London WC1R 5JJ (GB)

(56) References cited:
WO-A2-2006/119107

- **ANONYMOUS: "Amgen presents denosumab and sclerostin antibody data at American Society for Bone and Mineral Research Annual Meeting", AMGEN MEDIA PRESS RELEASE, 2006, pages 1-3, XP002517455, Retrieved from the Internet: URL:www.amgen.com/media/media_pr_detail.jsp?releaseID=907028 [retrieved on 2009-02-26]**
- **LÖWIK ET AL: "Wnt signaling is involved in the inhibitory action of sclerostin on BMP-stimulated bone formation", JOURNAL OF MUSCULOSKELETAL AND NEURONAL INTERACTIONS, vol. 6, 2006, page 357, XP002517456,**
- **GAZZERRO ET AL: "Potential drug targets within bone morphogenetic protein signaling pathways", CURRENT OPINION IN PHARMACOLOGY, vol. 7, May 2007 (2007-05), pages 325-333, XP022078332,**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 2 556 841 B9

Printed by Jouve, 75001 PARIS (FR)

(Cont. next page)

- **PADHI ET AL: "Anti-sclerostin antibody increases markers of bone formation in healthy postmenopausal women", Oasis, Online Abstract Submission and Invitation System, 18 September 2007 (2007-09-18), page 1, XP002517555, Retrieved from the Internet: URL:www.abstractsonline.com/viewer/SearchResults.asp [retrieved on 2009-03-03]**
- **ANONYMOUS: "UCB on track", UCB NEWS, 14 December 2007 (2007-12-14), pages 1/3-3/3, XP002517457, Retrieved from the Internet: URL:http://hugin.info/133973/R/1176122/233395.pdf [retrieved on 2009-03-03]**
- **PADHI ET AL: "OC35 - Effects of anti-sclerostin monoclonal antibody in healthy postmenopausal women", OSTEOPOROSIS INTERNATIONAL / SUPPLEMENT 1, vol. 19, 20 March 2008 (2008-03-20), page S19, XP002517556,**
- **MALONE ET AL: "Bone anabolism achieved by reducing sclerostin bioavailability with an anti-sclerostin antibody", 37TH INTERNATIONAL SUN VALLEY WORKSHOP ON SKELETAL TISSUE BIOLOGY, AUGUST 5TH-8TH, 2007 37TH INTERNATIONAL SUN VALLEY WORKSHOP ON SKELETAL TISSUE BIOLOGY, AUGUST 5TH-8TH, 2007, pages 2-3, XP002517458, Retrieved from the Internet: URL:www.sunvalleyworkshop.org/Poster%20Pre sentations%20&%20Abstracts%202007.pdf [retrieved on 2009-02-26]**
- **OMINSKY ET AL: "Sclerostin monoclonal antibody treatment increases bone strength in aged osteopenic ovariectomized rats", JOURNAL OF BONE AND MINERAL RESEARCH, vol. 21 (suppl. 1), 2006, page S44, XP002689214,**
- **PADHI ET AL: "Anti-sclerostin antibody increases markers of bone formation in healthy postmenopausal women", JOURNAL OF BONE AND MINERAL RESEARCH, vol. 22 (Suppl. 1), September 2007 (2007-09), page S37, XP002689215,**
- **LI ET AL: "Treatment with an anti-sclerostin antibody increases bone mass by stimulating bone formation without increasing bone resorption in aged male rats", JOURNAL OF BONE AND MINERAL RESEARCH, vol. 22 (suppl. 1), September 2007 (2007-09), page S36, XP002689216,**
- **REB: "Antikörper gegen Sclerostin", MEDICAL TRIBUNE, vol. 39, March 2007 (2007-03), page 12, XP002689219,**

Description

TECHNICAL FIELD OF THE INVENTION

[0001] The invention generally relates to methods of using sclerostin binding agents to modulate bone density.

BACKGROUND OF THE INVENTION

[0002] Loss of bone mineral content can be caused by a wide variety of conditions and may result in significant medical problems. For example, osteoporosis is a debilitating disease in humans and is characterized by marked decreases in skeletal bone mass and mineral density, structural deterioration of bone, including degradation of bone microarchitecture and corresponding increases in bone fragility (i.e., decreases in bone strength), and susceptibility to fracture in afflicted individuals. Osteoporosis in humans is generally preceded by clinical osteopenia, a condition found in approximately 25 million people in the United States. Another 7-8 million patients in the United States have been diagnosed with clinical osteoporosis. The frequency of osteoporosis in the human population increases with age. Among Caucasians, osteoporosis is predominant in women who, in the United States, comprise 80% of the osteoporosis patient pool. The increased fragility and susceptibility to fracture of skeletal bone in the aged is aggravated by the greater risk of accidental falls in this population. Fractured hips, wrists, and vertebrae are among the most common injuries associated with osteoporosis. Hip fractures in particular are extremely uncomfortable and expensive for the patient, and for women, correlate with high rates of mortality and morbidity.

[0003] The following documents are acknowledged:

- an Amgen press release of 19 September 2006 which is concerned with the presentation of Denosumab and Sclerostin Antibody Data at the American Society for Bone and Mineral Research Annual Meeting; the Data Suggesting the Potential for Targeting the Key Proteins, RANK Ligand and Sclerostin, for Bone Loss Conditions;

- Li et al (2007) J Bone Mineral Research, 22, Supplement 1: S36, which is concerned with treatment with an anti-sclerostin antibody increasing bone mass by stimulating bone formation with increasing bone resorption in aged male rats;

- Padhi et al (2007) J Bone Mineral Research, 22: Supplement: S37, which is concerned with anti-sclerostin antibody increases markers of bone formation in healthy postmenopausal women; and

- Padhi et al (2007) Oasis Abstract, which is concerned with anti-sclerostin antibody increasing markers of bone formation in healthy postmenopausal women.

SUMMARY OF THE INVENTION

[0004] The invention is directed to methods of using a sclerostin inhibitor for inhibiting bone resorption in humans. The method comprises administering to a human an amount of sclerostin inhibitor that is effective to reduce the level of a marker of bone resorption and optionally increase the level of a marker of bone formation. In some embodiments, bone resorption is inhibited and bone formation is increased for at least about 7 days, 2 weeks, 3 weeks, 4 weeks, 1 month, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 2 months, 3 months or longer. In related embodiments, the invention provides a method of increasing bone mineral density or treating a bone-related disorder. The invention further provides a method of ameliorating the effects of an osteoclast-related disorder. The method comprises administering to a human a sclerostin inhibitor that reduces the level of a marker of bone resorption compared to bone marker levels absent treatment. The sclerostin inhibitor also increases the level of a marker of bone formation by at least about 10% compared to bone marker levels absent treatment. The sclerostin inhibitor can be administered via a single dose or in multiple doses. For example, the sclerostin inhibitor can be administered in a short-term therapy regimen to, e.g., increase bone formation, and/or can be administered long-term to prevent loss of bone mineral density in a maintenance therapeutic regimen.

[0005] In any of the methods disclosed herein, the level of one or more markers of bone resorption is reduced by at least about 5%, 10%, 15%, 20%, 30%, 40%, 50% or more for at least 2 weeks, 3 weeks, 30 days, 1 month, 6 weeks, 2 months or longer, compared to pre-treatment levels or normal levels for that patient population. By way of non-limiting example, the level of the marker of bone resorption by 3 weeks after treatment is decreased by, e.g., at least about 20% compared to pre-treatment levels or normal levels for that patient population. In any of the preceding methods, the level of the marker of bone formation is increased by at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 100% or more for at least about 2 weeks, 3 weeks, 30 days, 1 month, 6 weeks, 2 months or longer, compared to pre-treatment levels or normal levels for that patient population. By way of non-limiting example, the level of the marker of bone formation by 3 weeks after treatment is increased by, e.g., at least about 20% compared to pre-treatment levels or normal levels for that patient population. In one exemplary embodiment, the marker of bone resorption is serum level of C-telopeptide of type I collagen (CTX). In other exemplary embodiments, the marker of bone formation is bone-specific alkaline phosphatase (BSAP), osteocalcin (OstCa), and/or N-terminal extension of procollagen type 1 (P1NP).

[0006] The invention also provides a method of treating a bone-related disorder, wherein the method comprises administering to a human one or more amounts of a sclerostin inhibitor effective to increase bone mineral density for the total body (e.g., head, trunk, arms, and legs) or at the hip (e.g., total hip and/or femoral neck), spine (e.g., lumbar spine), wrist, finger, shin bone and/or heel by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 8%, about 10%, about 12%, about 15%, about 18%, about 20%, about 25%, or 30% or more. In some embodiments, the bone mineral density of the human before treatment is characteristic of osteoporosis or osteopenia, and one or more doses of sclerostin inhibitor are administered in an amount and for a time effective to improve bone mineral density such that the bone mineral density is no longer characteristic of osteoporosis and/or osteopenia. For example, one or more doses may be administered for an initial time period to increase bone mineral density to within 2.5, or one, standard deviations of the density normal for a young adult (i.e., a T-score ≥ -2.5 or a T-score ≥ -1, as defined below). In exemplary embodiments, the initial time period is about 3 months or less, 6 months or less, 9 months or less, 1 year or less, 18 months or less, or longer. The method may further comprise subsequently administering one or more amounts of a sclerostin inhibitor effective to maintain bone mineral density, optionally for a maintenance time period of at least about 6 months, 1 year, 2 years or longer (e.g., over the life-time of the subject).

[0007] The invention further provides a method of treating a bone-related disorder in a human by administering one or more doses between about 0.1 to about 20 mg/kg, or about 0.1 to about 12 mg/kg, or about 0.5 to about 12 mg/kg, or about 1 to about 10 mg/kg, or about 1 to about 8 mg/kg, or about 2 to about 8 mg/kg, or about 3 to about 8 mg/kg. In some embodiments, doses may be administered at an interval of about once 2 weeks or longer, once every month or longer, or once every 2 months or longer, or once every 3 months or longer, or once every 4 months or longer, or once every 5 months or longer, or once every 6 months or longer, or once every 9 months or longer, or once every year or longer. The sclerostin inhibitor may be used in the preparation of a medicament for administration using any of the dosing and timing regimens described herein. Optionally, the sclerostin inhibitor is presented in a container, such as a single dose or multidose vial, containing a dose of sclerostin inhibitor for administration (e.g., about 70 to about 450 mg of sclerostin inhibitor). In one exemplary embodiment, a vial may contain about 70 mg or 75 mg of sclerostin inhibitor, e.g. anti-sclerostin antibody, and would be suitable for administering a single dose of about 1 mg/kg. In other embodiments, a vial may contain about 140 mg or 150 mg; or about 210 mg or 220 mg or 250 mg; or about 280 mg or 290 mg or 300 mg; or about 350 mg or 360 mg; or about 420 mg or 430 mg or 440 mg or 450 mg of sclerostin inhibitor, e.g., anti-sclerostin antibody.

[0008] Additionally, the invention provides a method of treating a bone-related disorder in a human suffering from or at risk of hypocalcemia or hypercalcemia, a human in which treatment with a parathyroid hormone or analog thereof is contraindicated, or a human in which treatment with a bisphosphonate is contraindicated. The method comprises administering to the human an amount of a sclerostin inhibitor effective to increase the level of a marker of bone formation and/or reduce the level of a marker of bone resorption, without resulting in hypocalcemia or hypercalcemia (e.g., clinically-significant hypocalcemia or hypercalcemia).

[0009] The invention also provides a method of monitoring anti-sclerostin therapy, i.e., the physiological response to a sclerostin inhibitor. The method comprises the steps of administering one or more doses of a sclerostin inhibitor, and detecting the level of one or more markers of bone resorption, wherein a reduction of at least about 5%, about 10%, about 15%, about 20%, about 30%, about 40%, about 50% or more in the level of a marker of bone resorption, compared to pre-treatment levels or normal levels for that patient population, is indicative of effective treatment. The method optionally further comprises the step of detecting the level of one or more markers of bone formation, wherein an increase of at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% in the level of a marker of bone formation, compared to pre-treatment levels or normal levels for that patient population, is indicative of effective treatment. In certain embodiments, the increase in bone formation marker levels is about 20%. The method may further comprise the step of adjusting the dose of a sclerostin inhibitor to a different amount, e.g., higher if the change in bone resorption and/or bone formation is less than desired, or lower if the change in bone resorption and/or bone formation is more than desired.

[0010] In a different aspect, the invention provides selected sclerostin inhibitors that reduce the level of a marker of bone resorption by at least about 5%, about 10%, about 15%, about 20%, about 30%, about 40%, about 50% or more and increase the level of a marker of bone formation by at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 100%, or more, for at least about 1 week, about 2 weeks, about 1 month, about 6 weeks, about 2 months, about 10 weeks, or about 3 months. In a related aspect, the invention provides a method of selecting such sclerostin inhibitors by administering a candidate sclerostin inhibitor to an animal and selecting a candidate sclerostin inhibitor that changes the level of a marker of bone resorption and/or formation to the desired extent.

[0011] In any of the preceding methods or embodiments of the invention, the sclerostin inhibitor may be a sclerostin binding agent. The use of sclerostin binding agents disclosed in U.S. Patent Publication No. 20070110747, e.g., in any of the methods disclosed herein or for preparation of medicaments for administration according to any of the methods disclosed herein, is specifically contemplated. In this regard, the invention includes use of a sclerostin binding agent in preparation of a medicament for inhibiting bone resorption in an amount from about 1 mg/kg to about 10 mg/kg, wherein the amount is effective to reduce serum level of C-telopeptide of type I collagen (CTX) by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins. The invention also includes use of a sclerostin binding agent in preparation of a medicament for increasing bone mineral density in an amount from about 1 mg/kg to about 10 mg/kg, wherein the amount is effective to (a) reduce serum level of CTX by at least 20% compared to pre-treatment or normal levels, by 3 weeks after treatment begins, and (b) increase serum level of a bone formation marker selected from the group consisting of serum level of bone-specific alkaline phosphatase (BSAP), serum level of amino-terminal extension of peptide of procollagen type 1 (PINP), and serum level of osteocalcin (OstCa), by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins.

[0012] The invention further includes use of a sclerostin binding agent in preparation of a medicament for treating a bone-related disorder in an amount from about 1 mg/kg to about 10 mg/kg for a first period of time, wherein the amount is effective to increase bone mineral density at the hip, spine, wrist, finger, shin bone and/or heel by at least about 3%, followed by an amount of from about 1 mg/kg to about 10 mg/kg for a second period of time effective to maintain bone mineral density. Use of a sclerostin binding agent in preparation of a medicament for treating a bone-related disorder in a human suffering from or at risk of hypocalcemia or hypercalcemia in an amount from about 1 mg/kg to about 10 mg/kg, also is contemplated, as well as use of a sclerostin binding agent in preparation of a medicament for treating a bone-related disorder in (a) a human in which treatment with a parathyroid hormone or analog thereof is contraindicated or (b) a human in which treatment with bisphosphonate is contraindicated.

[0013] The invention also includes containers comprising anti-sclerostin antibody or fragment thereof. In one embodiment, the container comprises anti-sclerostin antibody or fragment thereof and instructions for administering the antibody or fragment thereof in an amount effective to (a) reduce serum level of C-telopeptide of type I collagen (CTX) by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins, and (b) increase serum level bone-specific alkaline phosphatase (BSAP), serum level of amino-terminal extension of peptide of procollagen type 1 (PINP), or serum level of osteocalcin (OstCa) by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins. Alternatively or in addition, the container comprises an amount of anti-sclerostin antibody from about 70 mg to about 450 mg. The invention further provides a container comprising anti-sclerostin antibody or fragment thereof and instructions for administering the antibody or fragment thereof for treating a bone-related disorder in an amount from about 1 mg/kg to about 10 mg/kg every two or four weeks. In addition, the invention provides a container comprising anti-sclerostin antibody or fragment thereof and instructions for administering the antibody or fragment thereof for treating a bone-related disorder in an amount from about 1 mg/kg to about 10 mg/kg for a period of about 3 months.

BRIEF DESCRIPTION OF THE FIGURES

[0014]

Figure 1 is a graph of percent change of N-terminal extension of procollagen type 1 (P1NP) levels compared to baseline and placebo P1NP levels versus time (day) post-administration of various single doses of a sclerostin binding agent in healthy, postmenopausal women.

Figure 2 is a graph of percent change of bone-specific alkaline phosphatase (BSAP) levels compared to baseline and placebo BSAP levels versus time (day) post-administration of various single doses of a sclerostin binding agent in healthy, postmenopausal women.

Figure 3 is a graph of percent change of osteocalcin levels compared to baseline and placebo osteocalcin levels versus time (day) post-administration of various single doses of a sclerostin binding agent in healthy, postmenopausal women.

Figure 4 is a graph of percent change of serum C-terminal telopeptide of type 1 collagen (CTX) levels compared to baseline and placebo serum CTX levels versus time (day) post-administration of various single doses of a sclerostin binding agent in healthy, postmenopausal women.

Figure 5 are graphs of percent change of osteocalcin, BSAP, P1NP, and CTX levels compared to baseline and placebo levels versus time (day) post-administration of a single dose of 5 mg/kg or 10 mg/kg of sclerostin binding agent in healthy, postmenopausal women.

Figure 6 is a graph of percent change of serum calcium levels compared to baseline and placebo serum calcium levels versus time (day) post-administration of various single doses of a sclerostin binding agent in healthy, postmenopausal women.

Figure 7 are graphs of percent change of bone mineral density compared to baseline and placebo versus time (day) post-administration of various single doses of sclerostin binding agent in healthy, postmenopausal women.

DETAILED DESCRIPTION OF THE INVENTION

[0015] The invention is predicated, at least in part, on the surprising discovery that blocking or inhibiting the biological activity of human sclerostin triggers multiple physiological responses linked to increased bone mineral density (BMD), including significant inhibition of bone resorption. Most currently available therapies only inhibit bone resorption without increasing bone formation. Some currently available therapies for disorders associated with reduced BMD only increase bone formation without significantly reducing bone resorption. For example, when bone formation is triggered by some current drugs, bone resorption may also increase (albeit potentially at a lower rate than before therapy). In contrast, agents that interfere with sclerostin activity both enhance bone formation *and* reduce bone resorption. In other words, sclerostin inhibitors "uncouple" bone formation and bone resorption to more effectively build bone. The materials and methods of the invention are superior to existing therapies whose therapeutic efficacy is limited and which are accompanied by potentially serious adverse side effects.

[0016] In this regard, the invention provides a method of inhibiting bone resorption, e.g., bone resorption mediated by osteoclasts, bone cells that dissolve bone mineral matrices. The invention further provides a method of ameliorating the effects of an osteoclast-related disorder, i.e., a disorder caused by abnormally increased osteoclast activity that, in some embodiments, manifests as abnormally high bone resorption. The inventive method comprises administering to a human an amount of sclerostin binding agent that reduces the level of a marker of bone resorption and, optionally, increases the level of a marker of bone formation.

[0017] Activity of a sclerostin inhibitor, e.g., a sclerostin binding agent, (further described below) may be measured in a variety of ways. Sclerostin binding agent-mediated increases in bone mineral content or bone density may be measured using single- and dual-energy X-ray absorptometry, ultrasound, computed tomography, radiography, and magnetic resonance imaging. The amount of bone mass may also be calculated from body weights or by using other methods (see Guinness-Hey, Metab. Bone Dis. Relat. Res., 5:177-181 (1984)). Animals and particular animal models are used in the art for testing the effect of the pharmaceutical compositions and methods on, for example, parameters of bone loss, bone resorption, bone formation, bone strength, or bone mineralization that mimic conditions of human disease such as osteoporosis and osteopenia. Examples of such models include the ovariectomized rat model (Kalu, Bone and Mineral, 15:175-192 (1991); Frost and Jee, Bone and Mineral, 18:227-236 (1992); and Jee and Yao, J. Musculoskel. Neuron. Interact.,1:193-207 (2001)). The methods for measuring sclerostin binding agent activity described herein also may be used to determine the efficacy of other sclerostin inhibitors.

[0018] In humans, bone mineral density can be determined clinically using dual x-ray absorptiometry (DXA) of, for example, the hip and spine. Other techniques include quantitative computed tomography (QCT), ultrasonography, single-energy x-ray absorptiometry (SXA), and radiographic absorptiometry. Common central skeletal sites for measurement include the spine and hip; peripheral sites include the forearm, finger, wrist and heel. Except for ultrasonography, the American Medical Association notes that BMD techniques typically involve the use of x-rays and are based on the principle that attenuation of the radiation depends on thickness and composition of the tissues in the radiation path. All techniques involve the comparison of results to a normative database.

[0019] Alternatively, a physiological response to one or more sclerostin binding agents can be gauged by monitoring bone marker levels. Bone markers are products created during the bone remodeling process and are released by bone, osteoblasts, and/or osteoclasts. Fluctuations in bone resorption and/or bone formation "marker" levels imply changes in bone remodeling/modeling. The International Osteoporosis Foundation (IOF) recommends using bone markers to monitor bone density therapies (see, e.g., Delmas et al., Osteoporos Int., Suppl. 6:S2-17 (2000). Markers indicative of bone resorption (or osteoclast activity) include, for example, C-telopeptide (e.g., C-terminal telopeptide of type 1 collagen (CTX) or serum cross-linked C-telopeptide), N-telopeptide (N-terminal telopeptide of type 1 collagen (NTX)), deoxypyridinoline (DPD), pyridinoline, urinary hydroxyproline, galactosyl hydroxylysine, and tartrate-resistant acid phosphatase (e.g., serum tartrate-resistant acid phosphatase isoform 5b). Bone formation/mineralization markers include, but are not limited to, bone-specific alkaline phosphatase (BSAP), peptides released from N- and C-terminal extension of type I procollagen (P1NP, PICP), and osteocalcin (OstCa). Several kits are commercially-available to detect and quantify markers in clinical samples, such as urine and blood.

[0020] Upon administration, the sclerostin binding agent preferably reduces the level of one or more markers of bone resorption, such as the serum level of C-telopeptide of type I collagen (CTX). Accordingly, the invention further provides a method of monitoring anti-sclerostin therapy, i.e., the physiological response to a sclerostin binding agent or other sclerostin inhibitor. The method comprises administering a sclerostin binding agent, then measuring the level of one or more markers of bone resorption. In addition, the method can comprise measuring the level of one or more markers of bone formation before administration of a sclerostin binding agent. The level of bone resorption marker during and/or after treatment with the sclerostin binding agent may be compared to a pre-treatment level, or alternatively may be compared to a standard range typical of that patient population. One of ordinary skill in the art can readily determine a suitable standard range by testing a representative number of patients of like age, gender, disease level, and/or other characteristics of the patient population. The level of bone resorption marker can be reduced by at least about 5% (e.g., about 10%, about 20%, or about 30%) by a single dose of sclerostin binding agent. In some embodiments, the dose of sclerostin binding agent reduces the level of bone resorption marker at least about 40% (e.g., about 50%, about 60%, or about 70%) compared to the level of the bone resorption marker prior to administering the sclerostin binding agent. In addition, the bone resorption marker level may be reduced for at least about 3 days (e.g., about 7 days, about 2 weeks, about 3 weeks, about 1 month, about 5 weeks, about 6 weeks, about 7 weeks, about 2 months, about 9 weeks, about 10 weeks, about 11 weeks, or about 3 months) after administration of a single dose of the sclerostin binding agent.

[0021] In addition to decreasing the level of bone resorption markers, the amount of sclerostin binding agent administered to a patient also can increase the level of one or more markers of bone formation, such as the serum level of BSAP, the serum level of P1NP, and/or the serum level of OstCa. A single dose of sclerostin binding agent can increase the level of a bone formation marker by, for example, at least about 5% (e.g., about 10%, about 20%, or about 30%). In some embodiments, the dose of sclerostin binding agent elevates the level of a bone formation marker at least about 40% (e.g., about 50%, about 60%, or about 70%). In other embodiments, the dose of sclerostin binding agent increases the level of one or more bone formation markers by at least about 75% (e.g., about 80%, about 90%, about 100%, or about 110%). In yet other embodiments, the dose of sclerostin binding agent increases the level of a bone formation marker by at least about 120% (e.g., about 130%, about 140%, about 150%, about 160% or about 170%). In alternative embodiments, the sclerostin binding agent increases the level of bone formation marker by least about 180% (e.g., about 190% or about 200%). Bone formation marker levels ideally remain elevated (compared to bone formation marker levels pre-treatment or to a standard range typical of that patient population) for at least about 3 days (e.g., about 7 days, about 2 weeks, about 3 weeks, about 1 month, about 5 weeks, about 6 weeks, about 7 weeks, about 2 months, about 9 weeks, about 10 weeks, about 11 weeks, or about 3 months) after administration of a single dose of the sclerostin binding agent.

[0022] The invention also provides a method of increasing bone mineral density (BMD), wherein an amount of sclerostin binding agent that (a) reduces the level of a marker of bone resorption and (b) increases the level of a marker of bone formation is administered to a human. BMD generally correlates with skeletal fragility and osteoporosis. Typically, BMD is can be measured "total body" (e.g., head, trunk, arms, and legs) or at the hip (e.g., total hip and/or femoral neck), spine (e.g., lumbar spine), wrist, finger, shin bone and/or heel. In osteoporosis diagnosis, a patient's BMD is compared to the peak density of a 30-year old healthy adult (i.e., a "young adult"), creating the so-called "T-score." A patient's BMD also may be compared to an "age-matched" bone density (see, e.g., World Health Organization Scientific Group on the Prevention and Management of Osteoporosis, "Prevention and management of osteoporosis: report of a WHO scientific group." WHO Technical Report Series; 921, Geneva, Switzerland (2000)). The difference between a patient's BMD and that of a healthy, young adult is conventionally referred to in terms of the multiple of a "standard deviation," which typically equals about 10% to about 12% decrease in bone density. The World Health Organization proposed four diagnostic categories based on BMD T-scores. A BMD value within 1 standard deviation of the young adult reference mean (T-score $\geq$ -1) is "normal." Low bone mass (osteopenia) is indicated by a BMD value more than 1 standard deviation below the young adult mean, but less than 2 standard deviations (T-score < -1 and > -2.5). A T-score of more than 2.5 standard deviations below the norm supports a diagnosis of osteoporosis. If a patient additionally suffers from one or more fragility fractures, the patient qualifies as having severe osteoporosis.

[0023] The sclerostin inhibitor, e.g., a sclerostin binding agent, may be administered to a patient to improve bone mineral density regardless of the patient's T-score. The sclerostin binding agent may be administered at a dose and for a time period effective to increase BMD in the patient by at least about 1% (about 2%, about 3%, about 4%, about 5%, or about 6%). In some embodiments, BMD is increased by at least about 8% (e.g., at least about 10%, about 12%, about 15%, or about 18%). In other embodiments, BMD is increased by the sclerostin binding agent at least about 20% (e.g., at least about 22%, about 25%, or about 28%) at the hip, spine, wrist, finger, shin bone, and/or heel. In yet other embodiments, BMD is increased at least about 30% (e.g., at least about 32%, about 35%, about 38%, or about 40%). In other words, the BMD can be increased to the range of about 1 to about 2.5 standard deviations (preferably a range of about 0 to about 1 standard deviations) below the normal BMD of a healthy young adult.

[0024] Alterations in bone remodeling can lead to fluctuations in mineral concentrations throughout the body. Bone is one of the principal regulators of calcium levels in the bloodstream. Osteoclast-mediated bone resorption releases stored calcium into the systemic circulation, while osteoblast-mediated bone formation removes calcium from circulation to incorporate into bone tissue. In normal bone remodeling, these processes cycle to maintain healthy, strong bone and maintain free calcium levels at about 8.5 mg/dL to about 10.5 mg/dL (e.g., about 2.2 mmol/L to about 2.6 mmol/L). Bone disorders, other illnesses, and even certain therapies can disrupt systemic calcium levels with dire consequences. Hypercalcemia is associated with high levels of calcium in the blood (e.g., greater than 12 mg/dL or 3 mmol/L). Extraordinarily high calcium levels leads to, for example, fatigue, confusion, constipation, decreased appetite, frequent urination, heart problems, and bone pain. Hypocalcemia is an electrolyte imbalance indicated by an abnormally low level of calcium in the blood (e.g., less than about 9 mg/dL or 2.2 mmol/L). Calcium levels of < 7.5 mg/dL (< 1.87 mmol/L) or less are considered severe hypocalcemia and may be accompanied by clinical symptoms.

[0025] Common symptoms of hypocalcemia include nerve and muscle spasms and cramps, numbness, tingling in the extremities, confusion, and heart irregularities. Extreme variations in system calcium can lead to coma and death.

[0026] Several ailments and pharmaceutical therapies alter system calcium levels. Hypercalcemia and hypocalcemia can result from, for example, chronic kidney disease, renal failure, primary or secondary hyperparathyroidism, pseudohyperparathyroidism, hypoparathyroidism, pseudohypoparathyroidism, magnesium depletion, alcoholism, bisphosphonate therapy, severe hypermagnesemia, vitamin D deficiency, hyperphosphatemia, acute pancreatitis, hungry bone syndrome, chelation, osteoblastic metastases, sepsis, surgery, chemotherapy, neoplasia syndrome, familial hypocalciuric hypercalcemia, sarcoidosis, tuberculosis, berylliosis, histoplasmosis, Candidiasis, Coccidioidomycosis, histiocytosis X, Hodgkin's or Non-Hodgkin's lymphoma, Crohn's disease, Wegener's granulomatosis, leukemia, pneumonia, silicone-induced granulomas, immobilization, or drug therapy, such as administration of thiazide diuretics, lithium, estrogens, fluorides, glucose, and insulin. In addition, serum calcium fluctuations are a side effect of many existing bone-related therapies, such as bisphosphonate and parathyroid hormone therapy. Because of the potentially life-threatening consequences of calcium imbalance, patients susceptible to hypocalcemia or hypercalcemia may need to forego certain therapy options.

[0027] Remarkably, sclerostin inhibitors, e.g., sclerostin binding agents, have been shown to promote bone formation and inhibit (or slow) bone resorption with minimal fluctuations in systemic calcium levels (e.g., calcium levels fluctuate 10% or less from baseline serum calcium levels). Accordingly, the materials and method of the invention are particularly advantageous in treating patients that are susceptible or sensitive to unstable calcium levels. The amount of sclerostin binding agent administered to a human in the context of this aspect of the invention is an amount that does not result in hypocalcemia or hypercalcemia (e.g., clinically-significant hypocalcemia or hypercalcemia). In addition, the invention provides a method of treating a bone-related disorder in a human suffering from or at risk of hypocalcemia or hypercalcemia or a human in which treatment with bisphosphonate, a parathyroid hormone, or parathyroid hormone analog is contraindicated. The method comprises administering to the human an amount of a sclerostin binding agent effective to increase the level of a marker of bone formation, such as serum levels of BSAP, P1NP, and/or OstCa and/or reduce the level of a marker of bone resorption, such as CTX.

[0028] The inventive method is useful for treating or preventing bone-related disorders, such as bone-related disorders associated with abnormal osteoblast or osteoclast activity. Indeed, the sclerostin inhibitor (e.g., sclerostin binding agent) can be administered to a human 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, mucopolysacchandoses, 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.

[0029] The inventive method need not cure the patient of the disorder or completely protect against the onset of a bone-related disorder to achieve a beneficial biological response. The method may be used prophylactically, meaning to protect, in whole or in part, against a bone-related disorder or symptom thereof. The method also may be used therapeutically to ameliorate, in whole or in part, a bone-related disorder or symptom thereof, or to protect, in whole or in part, against further progression of a bone-related disorder or symptom thereof. Indeed, the materials and methods of the invention are particularly useful for increasing bone mineral density and maintaining the increased BMD over a period of time. In this regard, the invention provides a method of treating a bone-related disorder, which method comprises (a) administering one or more amounts of a sclerostin binding agent effective to increase BMD measured for the total body (e.g., head, trunk, arms, and legs) or at the hip (e.g., total hip and/or femoral neck), spine (e.g., lumbar spine), wrist, finger, shin bone and/or heel by about 1%, about 2%, about 3%, about 6%, about 8%, about 10%, about 12%, about 15%, about 18%, about 20%, about 25%, or 30% or more. One or more administrations of a pharmaceutical composition comprising the sclerostin binding agent 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). The method further includes (b) subsequently administering one or more amounts of a sclerostin binding agent effective to maintain bone mineral density. By "maintain bone mineral density" is meant that the increased BMD resulting from step (a) does not fall more than about 1% to about 5% over the course of step (b) (e.g., 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.

[0030] The sclerostin binding agent is preferably administered to a patient in a physiologically-acceptable (e.g., pharmaceutical) composition, which can include carrier, excipients, or diluents. It will be appreciated that the sclerostin binding agents described herein may be used in the preparation of a medicament for administration using any of the dosage and timing regimens disclosed herein. Pharmaceutical compositions and methods of treatment are disclosed in U.S. Patent Publication No. 20050106683. "Physiologically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human. In addition, the composition administered to a subject may contain more than one sclerostin inhibitor (e.g., a sclerostin binding agent and a synthetic chemical sclerostin inhibitor) or a sclerostin inhibitor in combination with one or more therapeutics having different mechanisms of action.

[0031] The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including e.g., subcutaneous, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art and discussed in U.S. Patent Publication No. 20070110747. For example, in certain circumstances, it will be desirable to deliver a pharmaceutical composition comprising a sclerostin binding agent subcutaneously, parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U.S. Patent Nos. 5,543,158; 5,641,515; and 5,399,363. Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U.S. Patent No. 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists.

[0032] In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous, and intraperitoneal administration. For example, one dose may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion (see, for example, Remington's Pharmaceutical Sciences, 15th ed., Mack Pub. Co., Easton, PA, pp. 1035-1038 and 1570-1580). Some variation in dosage and frequency of administration may occur depending on the condition of the subject being treated; age, height, weight, and overall health of the patient; and the existence of any side effects. In addition, a pharmaceutical composition comprising a sclerostin binding agent may be placed within containers (e.g., vials), along with packaging material that provides instructions regarding the use of such pharmaceutical compositions. Generally, such instructions will include a tangible expression describing the reagent concentration, as well as within certain embodiments, relative amounts of excipient ingredients or diluents (e.g., water, saline or PBS) that may be necessary to reconstitute the pharmaceutical composition.

[0033] The sclerostin binding agent is administered in an amount that reduces the level of a bone resorption marker and/or increases the level of a bone formation marker and/or increases bone density. The dose of sclerostin binding agent administered may range from about 0.5 mg/kg to about 20 mg/kg (e.g., 12 mg/kg) of body weight. For example, the dose of sclerostin binding agent may range from about 1 mg/kg to about 10 mg/kg (e.g., about 2 mg/kg or about 9 mg/kg), about 1 mg/kg to about 3 mg/kg, or about 3 mg/kg to about 8 mg/kg (e.g., about 4 mg/kg, 5 mg/kg, 6 mg/kg, or 7 mg/kg).

[0034] In addition, it may be advantageous to administer multiple doses of a sclerostin binding agent or space out the administration of doses, depending on the therapeutic regimen selected for a particular patient. The sclerostin binding agent 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 sclerostin binding agent 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.

[0035] The inventive method comprises administering an amount of a "sclerostin inhibitor." As used herein, the term "sclerostin inhibitor" means any molecule that inhibits the biological activity of sclerostin on bone, as measured by changes to bone mineralization, bone density, effect on osteoblasts and/or osteoclasts, markers of bone formation, markers of bone resorption, markers of osteoblast activity, and/or markers of osteoclast activity. Such inhibitors may act by binding to sclerostin or its receptor or binding partner. Inhibitors in this category include "sclerostin binding agents," such as, e.g., antibodies or peptide-based molecules. "Sclerostin inhibitors" also refers to small organic chemical compounds, optionally of less than about 1000 Daltons in molecular weight that bind sclerostin and inhibit its activity. Inhibitors may alternatively act by inhibiting expression of sclerostin. Inhibitors in this category include polynucleotides or oligonucleotides that bind to sclerostin DNA or mRNA and inhibit sclerostin expression, including an antisense oligonucleotide, inhibitory RNA, DNA enzyme, ribozyme, an aptamer or pharmaceutically acceptable salts thereof that inhibit the expression of sclerostin.

[0036] A "sclerostin binding agent" specifically binds to sclerostin or portions thereof to block or impair binding of human sclerostin to one or more ligands. Sclerostin, the product of the SOST gene, is absent in sclerosteosis, a skeletal disease characterized by bone overgrowth and strong dense bones (Brunkow et al., Am. J. Hum. Genet., 68:577-589 (2001); Balemans et al., Hum. Mol. Genet., 10:537-543 (2001)). The amino acid sequence of human sclerostin is reported by Brunkow et al. and is disclosed in U.S. Patent Publication No. 20070110747 as SEQ ID NO: 1. Recombinant human sclerostin/SOST is commercially available from R&D Systems (Minneapolis, Minn., USA; 2006 Catalog #1406-ST-025). Additionally, recombinant mouse sclerostin/SOST is commercially available from R&D Systems (Minneapolis, Minn., USA; 2006 Catalog #1589-ST-025). Research grade sclerostin-binding monoclonal antibodies are commercially available from R&D Systems (Minneapolis, Minn., USA; mouse monoclonal: 2006 Catalog # MAB1406; rat monoclonal: 2006 Catalog # MAB1589). U.S. Patent Nos. 6,395,511 and 6,803,453, and U.S. Patent Publication Nos. 20040009535 and 20050106683 refer to anti-sclerostin antibodies generally. Examples of sclerostin binding agents suitable for use in the context of the invention also are described in U.S. Patent Publication Nos. 20070110747 and 20070072797. Additional information regarding materials and methods for generating sclerostin binding agents can be found in U.S. Patent Publication No. 20040158045.

[0037] The sclerostin binding agent of the invention preferably is an antibody. 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)). Antibody polypeptides, including fibronectin polypeptide monobodies, also are disclosed in U.S. Patent No. 6,703,199. Other antibody polypeptides are disclosed in U.S. Patent Publication No. 20050238646. Anti-sclerostin antibodies may bind to sclerostin of SEQ NO: 1, or a naturally occurring variant thereof, with an affinity of less than or equal to 1×10^{-7}M, less than or equal to 1×10^{-8}M, less than or equal to 1×10^{-9}M, less than or equal to 1×10^{-1}M, less than or equal to 1×10^{-11}M, or less than or equal to 1×10^{-12}M. Affinity may be determined by an affinity ELISA assay. In certain embodiments, affinity may be determined by a BIAcore assay. In certain embodiments, affinity may be determined by a kinetic method. In certain embodiments, affinity may be determined by an equilibrium/solution method.

[0038] An antibody fragment may be any synthetic or genetically engineered protein. For example, antibody fragments include isolated fragments consisting of the light chain variable region, "Fv" fragments consisting of the variable regions of the heavy and light chains, recombinant single chain polypeptide molecules in which light and heavy variable regions are connected by a peptide linker (scFv proteins).

[0039] Another form of an antibody fragment is a peptide comprising one or more complementarity determining regions (CDRs) of an antibody. CDRs (also termed "minimal recognition units" or "hypervariable region") can be obtained by constructing polynucleotides that encode the CDR of interest. Such polynucleotides are prepared, for example, by using the polymerase chain reaction to synthesize the variable region using mRNA of antibody-producing cells as a template (see, for example, Larrick et al., Methods: A Companion to Methods in Enzymology, 2:106 (1991); Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in Monoclonal Antibodies Production, Engineering and Clinical Application, Ritter et al. (eds.), page 166, Cambridge University Press (1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in Monoclonal Antibodies: Principles and Applications, Birch et al., (eds.), page 137, Wiley-Liss, Inc. (1995)).

[0040] In one embodiment of the invention, the sclerostin binding agent cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747) to sclerostin. Alternatively or in addition, the sclerostin binding agent is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747). The terms "cross-block," "cross-blocked," and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or other binding agent to interfere with the binding of other antibodies or binding agents to sclerostin. The extent to which an antibody or other binding agent is able to interfere with the binding of another to sclerostin, and therefore whether it can be said to cross-block, can be determined using competition binding assays. In some aspects of the invention, a cross-blocking antibody or fragment thereof reduces sclerostin binding of a reference antibody between about 40% and about 100%, such as about 60% and about 100%, specifically between 70% and 100%, and more specifically between 80% and 100%. A particularly suitable quantitative assay for detecting cross-blocking uses a Biacore machine which measures the extent of interactions using surface plasmon resonance technology. Another suitable quantitative cross-blocking assay uses an ELISA-based approach to measure competition between antibodies or other binding agents in terms of their binding to sclerostin.

[0041] Suitable sclerostin binding agents include antibodies and portions thereof described in U.S. Patent Publication No. 20070110747, such as one or more of CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and CDR-L3 as specifically disclosed therein. At least one of the regions of CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 may have at least one amino acid substitution, provided that the binding agent retains the binding specificity of the non-substituted CDR. The non-CDR portion of the binding agent may be a non-protein molecule, wherein the binding agent cross-blocks the binding of an antibody disclosed herein to sclerostin and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be a non-protein molecule in which the binding agent exhibits a similar binding pattern to human sclerostin peptides in a human sclerostin peptide epitope competition binding assay as that exhibited by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21. Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747), and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be composed of amino acids, wherein the binding agent is a recombinant binding protein or a synthetic peptide, and the recombinant binding protein cross-blocks the binding of an antibody to sclerostin and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be composed of amino acids, wherein the binding agent is a recombinant binding protein, and the recombinant binding protein exhibits a similar binding pattern to human sclerostin peptides in the human sclerostin peptide epitope competition binding assay (described in U.S. Patent Publication No. 20070110747) as that exhibited by at least one of the antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (described in U.S. Patent Publication No. 20070110747), and/or neutralizes sclerostin. Preferably, the sclerostin binding agent is 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 of U.S. Patent Publication No. 20070110747.

[0042] In addition, the sclerostin binding agent can comprise at least one CDR sequence having at least 75% identity (e.g., 100% identity) to a CDR selected from SEQ ID NOs: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 78, 79, 80, 81, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 351, 352, 353, 358, 359, and 360 disclosed in U.S. Patent Publication No. 20070110747. Preferably, the sclerostin binding agent comprises at least one CDR sequence having at least 75% identity to a CDR selected from SEQ ID NOs: 245, 246, 247, 78, 79, 80, 269, 270, 271, 239, 240, and 24, all of which is described in U.S. Patent Publication No. 20070110747. As described in U.S. Patent Publication No. 20070110747, the sclerostin binding agent can comprise: a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs:45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; 1) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs: 113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs:116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270, and 271; r) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; or s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360.

[0043] The sclerostin binding agent also can comprise at least one CDR sequence having at least 75% identity to a CDR selected from CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 wherein CDR-H1 has the sequence given in SEQ ID NO: 245 or SEQ ID NO: 269, CDR-H2 has the sequence given in SEQ ID NO: 246 or SEQ ID NO: 270, CDR-H3 has the sequence given in SEQ NO: 247 or SEQ ID NO: 271, CDR-L1 has the sequence given in SEQ ID NO: 78 or SEQ ID NO: 239, CDR-L2 has the sequence given in SEQ ID NO: 79 or SEQ ID NO: 240 and CDR-L3 has the sequence given in SEQ ID NO: 80 or SEQ ID NO 241, all of which is described in U.S. Patent Publication No. 20070110747.

[0044] Alternatively, the sclerostin binding agent can have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 137 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 245, 246, and 247, respectively, and a light chain comprising CDR's L1, L2 and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 133 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 78, 79, and 80, respectively (as described in U.S. Patent Publication No. 20070110747).

[0045] The sclerostin binding agent may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 145 or 392 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 245, 246, and 247, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 141 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 78, 79, and 80, respectively (as described in U.S. Patent Publication No. 20070110747).

[0046] The sclerostin binding agent may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 335 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 334 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 239, 240, and 241, respectively (as described in U.S. Patent Publication No. 20070110747).

[0047] Alternatively, the sclerostin binding agent has a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 331 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 330 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 239, 240, and 241, respectively (as described in U.S. Patent Publication No. 20070110747).

[0048] The sclerostin binding agent may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 345 or 396 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 341 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 239, 240, and 241, respectively (as described in U.S. Patent Publication No. 20070110747).

[0049] Alternatively, the sclerostin binding agent has a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 137, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 133; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 145 or 392, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 141; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 335, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 334; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 331, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 330; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 345 or 396, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 341 (as described in U.S. Patent Publication No. 20070110747).

[0050] Sclerostin binding agents for use in the inventive method preferably modulate sclerostin function in the cell-based assay described in U.S. Patent Publication No. 20070110747 and/or the *in vivo* assay described in U.S. Patent Publication No. 20070110747 and/or bind to one or more of the epitopes described in U.S. Patent Publication No. 20070110747 and/or cross-block the binding of one of the antibodies described in U.S. Patent Publication No. 20070110747 and/or are cross-blocked from binding sclerostin by one of the antibodies described in U.S. Patent Publication No. 20070110747.

[0051] Alternatively, the inventive method can comprise administering a sclerostin inhibitor other than a sclerostin binding agent described herein. Such agents can act directly or indirectly on SOST or sclerostin, Sclerostin inhibitors contemplated for use in the inventive method include those described in U.S. Patent Publication No. 20030229041. For example, agents useful for modulating SOST expression and sclerostin activity include, but are not limited to, steroids (such as those corresponding to Formula 1 of U.S. Patent Publication No. 20030229041), alkaloids, teipenoids, peptoids, and synthetic chemicals. In some embodiments, the SOST antagonist or agonist can bind to a glucocorticoid receptor. For example, dexamethasone tends to abolish the stimulatory effect of BMP-4 and BMP-6 on SOST expression. Other chemical entities including glucocorticoid analogs, bile salts (such as those corresponding to Formula 3 of U.S. Patent Publication No. 20030229041), and prostaglandins (such as those corresponding to Formula 2 of U.S. Patent Publication No. 20030229041) also modulate the effects of bone morphogenetic proteins on SOST expression, and are contemplated for use in the inventive method.

[0052] The sclerostin inhibitor may also be other small molecule therapeutics that act directly or indirectly on SOST or sclerostin to decrease the level of at least one bone resorptive marker and/or increase the level of at least one bone formation marker *in vivo.* The term "small molecule" includes a compound or molecular complex, either synthetic, naturally derived, or partially synthetic, and which preferably has a molecular weight of less than 5,000 Daltons (e.g., between about 100 and 1,500 Daltons). Agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including spatially addressable parallel solid phase or solution phase libraries, synthetic library methods requiring deconvolution, the "one-bead one-compound" library method, and synthetic library methods using affinity chromatography selection (see, e.g., Lam, Anticancer Drug Des., 12:145 (1997) and U.S. Patent Nos. 5,738,996; 5,807,683; and 7,261,892). Methods of developing and screening sclerostin inhibitors are further described in U.S. Patent Publication No. 20030229041.

[0053] Sclerostin expression inhibitors that may be used according to the methods of the invention include inhibitor oligonucleotides or polynucleotides, including pharmaceutically acceptable salts thereof, e.g., sodium salts. Nonlimiting examples include: antisense oligonucleotides (Eckstein, Antisense Nucleic Acid Drug Dev., 10: 117-121 (2000); Crooke, Methods Enzymol., 313: 3-45 (2000); Guvalcova et al., J. Biol. Chem., 270: 2620-2627 (1995); Manoharan, Biochim. Biophys. Acta, 1489: 117-130 (1999); Baker et al., J. Biol. Chem., 272: 11994-12000 (1997); Kurreck, Eur. J. Biochem., 270: 1628-1644 (2003); Sieralcowska et al., Proc. Natl. Acad. Sci. USA, 93: 12840-12844 (1996); Marwick, J. Am. Med. Assoc., 280: 871 (1998); Tomita and Morishita, Curr. Pharm. Des.,10: 797-803 (2004); Gleave and Monia, Nat. Rev. Cancer, 5: 468-479 (2005) and Patil, AAPS J., 7: E61-E77 (2005)), triplex oligonucleotides (Francois et al., Nucleic Acids Res., 16: 11431-11440 (1988) and Moser and Dervan, Science, 238: 645-650 (1987)), ribozymes/deoxyribozymes (DNAzymes) (Kruger et al., Tetrahymena. Cell, 31: 147-157 (1982); Uhlenbeck, Nature, 328: 596-600 (1987); Sigurdsson and Eckstein, Trends Biotechnol., 13: 286-289 (1995); Kumar et al., Gene Ther., 12: 1486-1493 (2005); Breaker and Joyce, Chem. Biol., 1: 223-229 (1994); Khachigian, Curr. Pharm. Biotechnol., 5: 337-339 (2004); Khachigian, Biochem. Pharmacol, 68: 1023-1025 (2004) and Trulzsch and Wood, J. Neurochem., 88: 257-265 (2004)), small-interfering RNAs/RNAi (Fire et al., Nature, 391: 806-811 (1998); Montgomery et al., Proc. Natl. Acad. Sci. U.S.A., 95: 15502-15507 (1998); Cullen, Nat. Immunol., 3: 597-599 (2002); Hannon, Nature, 418: 244-251 (2002); Bernstein et al., Nature, 409: 363-366 (2001); Nykanen et al., Cell, 107: 309-321 (2001); Gilmore et al., J. Drug Target., 12: 315-340 (2004); Reynolds et al., Nat. Biotechnol, 22: 326-330 (2004); Soutschek et al., Nature, 432173-178 (2004); Ralph et al., Nat. Med., 11: 429-433 (2005); Xia et al., Nat. Med., 10816-820 (2004) and Miller et al,, Nucleic Acids Res., 32: 661-668 (2004)), aptamers (Ellington and Szostak, Nature, 346: 818-822 (1990); Doudna et al., Proc. Natl. Acad. Sci. U.S.A., 92: 2355-2359 (1995); Tuerk and Gold, Science, 249: 505-510 (1990); White et al., Mol. Ther., 4: 567-573 (2001); Rusconi et al., Nature, 419: 90-94 (2002); Nimjee et al., Mol. Ther., 14: 408-415 (2006); Gragoudas et al., N. Engl. J. Med., 351: 3805-2816 (2004); Vinores, Curr. Opin. Mol. Ther., 5673-679 (2003) and Kourlas and Schiller et al., Clin. Ther., 28: 36-44 (2006)) or decoy oligonucleotides (Morishita et al., Proc. Natl. Acad. Sci. U.S.A., 92: 5855-5859 (1995); Alexander et al., J. Am. Med. Assoc., 294: 2446-2454 (2005); Mann and Dzau, J. Clin. Invest.,106: 1071-1075 (2000) and Nimjee et al., Annu. Rev. Med., 56: 555-583 (2005)). Commercial providers such as Ambion Inc. (Austin, TX), Darmacon Inc. (Lafayette, CO), InvivoGen (San Diego, CA), and Molecular Research Laboratories, LLC (Herndon, VA) generate custom siRNA molecules. In addition, commercial kits are available to produce custom siRNA molecules, such as SILENCER™ siRNA Construction Kit (Ambion Inc., Austin, TX) or psiRNA System (InvivoGen, San Diego, CA).

[0054] Inhibitory oligonucleotides which are stable, have a high resistance to nucleases, possess suitable pharmacokinetics to allow them to traffic to target tissue site at non-toxic doses, and have the ability to cross through plasma membranes are contemplated for use as a therapeutic. Inhibitory oligonucleotides may be complementary to the coding portion of a target gene, 3' or 5' untranslated regions, or intronic sequences in a gene, or alternatively coding or intron sequences in the target mRNA. Intron sequences are generally less conserved and thus may provide greater specificity. In one embodiment, the inhibitory oligonucleotide inhibits expression of a gene product of one species but not its homologue in another species; in other embodiments, the inhibitory oligonucleotide inhibits expression of a gene in two species, e.g. human and primate, or human and murine.

[0055] The constitutive expression of antisense oligonucleotides in cells has been shown to inhibit gene expression, possibly via the blockage of translation or prevention of splicing. In certain embodiments, the inhibitory oligonucleotide is capable of hybridizing to at least 8, 9, 10, 11, or 12 consecutive bases of the sclerostin gene or mRNA (or the reverse strand thereof) under moderate or high stringency conditions. Suitable inhibitory oligonucleotides may be single stranded and contain a segment, e.g. at least 12, 15 or 18 bases in length, that is sufficiently complementary to, and specific for, an mRNA or DNA molecule such that it hybridizes to the mRNA or DNA molecule and inhibits transcription, splicing or translation. Generally complementarity over a length of less than 30 bases is more than sufficient.

[0056] Typically, stringent conditions will be those in which the salt concentration is less than about 1.5 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short nucleic acids (e.g., 10 to 50 nucleotides) and at least about 60°C for longer nucleic acids (e.g., greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. Exemplary low stringency conditions include hybridization with a buffer solution of 30% to 35% formamide, 1 M NaCl, 1% SDS (sodium dodecyl sulphate) at 37°C, and a wash in 1X to 2X SSC (20X SSC = 3.0 M NaCl/0.3 M trisodium citrate) at 50°C to 55°C. Exemplary moderate stringency conditions include hybridization in 40% to 45% formamide, 1.0 M NaCl, 1% SDS at 37°C, and a wash in 0.5X to 1X SSC at 55°C to 60°C. Exemplary high stringency conditions include hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.1X SSC at 60°C to 65°C. Duration of hybridization is generally less than about 24 hours, usually about 4 hours to about 12 hours.

[0057] In some cases, depending on the length of the complementary region, one, two or more mismatches may be tolerated without affecting inhibitory function. In certain embodiments, the inhibitory oligonucleotide is an antisense oligonucleotide, an inhibitory RNA (including siRNA or RNAi, or shRNA), a DNA enzyme, a ribozyme (optionally a hammerhead ribozyme), an aptamer, or pharmaceutically acceptable salts thereof. In one embodiment, the oligonucleotide is complementary to at least 10 bases of the nucleotide sequence encoding SEQ ID NO: 1 of U.S. Patent Publication No. 20040158045. In one embodiment, the oligonucleotide targets the nucleotides located in the vicinity of the 3' untranslated region of the sclerostin mRNA.

[0058] The specific sequence utilized in design of the oligonucleotides may be any contiguous sequence of nucleotides contained within the expressed gene message of the target. Factors that govern a target site for the inhibitory oligonucleotide sequence include the length of the oligonucleotide, binding affinity, and accessibility of the target sequence. Sequences may be screened *in vitro* for potency of their inhibitory activity by measuring inhibition of target protein translation and target related phenotype, e.g., inhibition of cell proliferation in cells in culture. In general it is known that most regions of the RNA (5' and 3' untranslated regions, AUG initiation, coding, splice junctions and introns) can be targeted using antisense oligonucleotides. Programs and algorithms, known in the art, may be used to select appropriate target sequences. In addition, optimal sequences may be selected utilizing programs designed to predict the secondary structure of a specified single stranded nucleic acid sequence and allowing selection of those sequences likely to occur in exposed single stranded regions of a folded mRNA. Methods and compositions for designing appropriate oligonucleotides may be found, for example, in U.S. Patent No. 6,251,588.

[0059] Phosphorothioate antisense oligonucleotides may be used. Modifications of the phosphodiester linkage as well as of the heterocycle or the sugar may provide an increase in efficiency. Phophorothioate is used to modify the phosphodiester linkage. An N3'-P5' phosphoramidate linkage has been described as stabilizing oligonucleotides to nucleases and increasing the binding to RNA. Peptide nucleic acid (PNA) linkage is a complete replacement of the ribose and phosphodiester backbone and is stable to nucleases, increases the binding affinity to RNA, and does not allow cleavage by RNAse H. Its basic structure is also amenable to modifications that may allow its optimization as an antisense component. With respect to modifications of the heterocycle, certain heterocycle modifications have proven to augment antisense effects without interfering with RNAse H activity. An example of such modification is C-5 thiazole modification. Finally, modification of the sugar may also be considered. 2'-O-propyl and 2'-methoxyethoxy ribose modifications stabilize oligonucleotides to nucleases in cell culture and *in vivo.*

[0060] Most mRNAs have been shown to contain a number of secondary and tertiary structures. Secondary structural elements in RNA are formed largely by Watson-Crick type interactions between different regions of the same RNA molecule. Important secondary structural elements include intramolecular double stranded regions, hairpin loops, bulges in duplex RNA and internal loops. Tertiary structural elements are formed when secondary structural elements come in contact with each other or with single stranded regions to produce a more complex three dimensional structure. A number of researchers have measured the binding energies of a large number of RNA duplex structures and have derived a set of rules which can be used to predict the secondary structure of RNA (see, e.g., Jaeger et al., Proc. Natl. Acad. Sci. USA, 86:7706 (1989); and Turner et al., Annu. Rev. Biophys. Biophys. Chem. 17:167 (1988)). The rules are useful in identification of RNA structural elements and, in particular, for identifying single stranded RNA regions which may represent segments of the mRNA to target for siRNA, ribozyme, or antisense technologies.

[0061] Short interfering (si) RNA technology (also known as RNAi) generally involves degradation of an mRNA of a particular sequence induced by double-stranded RNA (dsRNA) that is homologous to that sequence, thereby "interfering" with expression of the corresponding gene. Any selected gene may be repressed by introducing a dsRNA which corresponds to all or a substantial part of the mRNA for that gene. It appears that when a long dsRNA is expressed, it is initially processed by a ribonuclease III into shorter dsRNA oligonucleotides of as few as 21 to 22 base pairs in length.

Accordingly, siRNA may be affected by introduction or expression of relatively short homologous dsRNAs. Exemplary siRNAs have sense and antisense strands of about 21 nucleotides that form approximately 19 nucleotides of double stranded RNA with overhangs of two nucleotides at each 3' end. Indeed the use of relatively short homologous dsRNAs may have certain advantages.

[0062] Mammalian cells have at least two pathways that are affected by double-stranded RNA (dsRNA). In the sequence-specific siRNA pathway, the initiating dsRNA is first broken into short interfering RNAs, as described above. Short interfering RNAs are thought to provide the sequence information that allows a specific messenger RNA to be targeted for degradation. In contrast, the nonspecific pathway is triggered by dsRNA of any sequence, as long as it is at least about 30 base pairs in length.

[0063] The nonspecific effects occur because dsRNA activates two enzymes: PKR, which in its active form phosphorylates the translation initiation factor eIF2 to shut down all protein synthesis, and 2', 5' oligoadenylate synthetase (2', 5'-AS), which synthesizes a molecule that activates RNase L, a nonspecific enzyme that targets all mRNAs. The nonspecific pathway may represent a host response to stress or viral infection, and, in general, the effects of the nonspecific pathway are preferably minimized. Significantly, longer dsRNAs appear to be required to induce the nonspecific pathway and, accordingly, dsRNAs shorter than about 30 bases pairs are contemplated to effect gene repression by RNAi (see Hunter et al., J. Biol. Chem., 250: 409-17 (1975); Manche et al., Mol. Cell. Biol. 12: 5239-48 (1992); Minks et al., J. Biol. Chem., 254: 10180-3 (1979); and Elbashir et al., Nature, 411: 494-8 (2001)).

[0064] siRNA has proven to be an effective means of decreasing gene expression in a variety of cell types. siRNA typically decreases expression of a gene to lower levels than that achieved using antisense techniques, and frequently eliminates expression entirely (see Bass, Nature, 411: 428-9 (2001)). In mammalian cells, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments (Elbashir et al., Nature, 411:494-8 (2001)).

[0065] The double stranded oligonucleotides used to effect RNAi are preferably less than 30 base pairs in length, for example, about 25, 24, 23, 22, 21, 20, 19, 18, or 17 base pairs or less in length, and contain a segment sufficiently complementary to the target mRNA to allow hybridization to the target mRNA. Optionally the dsRNA oligonucleotides may include 3' overhang ends. Exemplary 2-nucleotide 3' overhangs may be composed of ribonucleotide residues of any type and may even be composed of 2'-deoxythymidine resides, which lowers the cost of RNA synthesis and may enhance nuclease resistance of siRNAs in the cell culture medium and within transfected cells (see Elbashi et al., *supra*). Exemplary dsRNAs may be synthesized chemically or produced *in vitro* or *in vivo* using appropriate expression vectors (see, e.g., Elbashir et al., Genes Dev., 15:188-200 (2001)). Longer RNAs may be transcribed from promoters, such as T7 RNA polymerase promoters, known in the art.

[0066] Longer dsRNAs of 50, 75, 100, or even 500 base pairs or more also may be utilized in certain embodiments of the invention. Exemplary concentrations of dsRNAs for effecting RNAi are about 0.05 nM, 0.1 nM, 0.5 nM, 1.0 nM, 1.5 nM, 25 nM, or 100 nM, although other concentrations may be utilized depending upon the nature of the cells treated, the gene target and other factors readily discernable to the skilled artisan.

[0067] Further compositions, methods and applications of siRNA technology are provided in U.S. Patent Nos. 6,278,039; 5,723,750; and 5,244,805.

[0068] Compared to siRNA, shRNA offers advantages in silencing longevity and delivery options. See, e.g., Hannon et al., Nature, 431:371-378 (2004) for review. Vectors that produce shRNAs, which are processed intracellularly into short duplex RNAs having siRNA-like properties have been reported (Brummelkamp et al., Science, 296: 550-553 (2000); Paddison et al., Genes Dev., 16: 948-958 (2002)). Such vectors provide a renewable source of a gene-silencing reagent that can mediate persistent gene silencing after stable integration of the vector into the host-cell genome. Furthermore, the core silencing 'hairpin' cassette can be readily inserted into retroviral, lentiviral, or adenoviral vectors, facilitating delivery of shRNAs into a broad range of cell types (Brummelkamp et al., Cancer Cell, 2:243-247 (2002); Dirac et al., J. Biol. Chem., 278:11731-11734 (2003); Michiels et al., Nat. Biotechnol., 20:1154-1157 (2002); Stegmeie et al., Proc. Natl. Acad. Sci. USA, 102:13212-13217 (2005); Khvorova et al., Cell, 115:209-216 (2003)) in any of the innumerable ways that have been devised for delivery of DNA constructs that allow ectopic mRNA expression.

[0069] A hairpin can be organized in either a left-handed hairpin (i.e., 5'-antisense-loop-sense-3') or a right-handed hairpin (i.e., 5'-sense-loop-antisense-3'). The siRNA may also contain overhangs at either the 5' or 3' end of either the sense strand or the antisense strand, depending upon the organization of the hairpin. Preferably, if there are any overhangs, they are on the 3' end of the hairpin and comprise between 1 to 6 bases. The overhangs can be unmodified, or can contain one or more specificity or stabilizing modifications, such as a halogen or O-alkyl modification of the 2' position, or internucleotide modifications such as phosphorothioate, phosphorodithioate, or methylphosphonate modifications. The overhangs can be ribonucleic acid, deoxyribonucleic acid, or a combination of ribonucleic acid and deoxyribonucleic acid.

[0070] Additionally, a hairpin can further comprise a phosphate group on the 5'-most nucleotide. The phosphorylation of the 5'-most nucleotide refers to the presence of one or more phosphate groups attached to the 5' carbon of the sugar moiety of the 5'-terminal nucleotide. Preferably, there is only one phosphate group on the 5' end of the region that will form the antisense strand following Dicer processing. In one exemplary embodiment, a right-handed hairpin can include a 5' end (i.e., the free 5' end of the sense region) that does not have a 5' phosphate group, or can have the 5' carbon of the free 5'-most nucleotide of the sense region being modified in such a way that prevents phosphorylation. This can be achieved by a variety of methods including, but not limited to, addition of a phosphorylation blocking group (e.g., a 5'-O-alkyl group), or elimination of the 5'-OH functional group (e.g., the 5'-most nucleotide is a 5'-deoxy nucleotide). In cases where the hairpin is a left-handed hairpin, preferably the 5' carbon position of the 5'-most nucleotide is phosphorylated.

[0071] Hairpins that have stem lengths longer than 26 base pairs can be processed by Dicer such that some portions are not part of the resulting siRNA that facilitates mRNA degradation. Accordingly the first region, which may comprise sense nucleotides, and the second region, which may comprise antisense nucleotides, may also contain a stretch of nucleotides that are complementary (or at least substantially complementary to each other), but are or are not the same as or complementary to the target mRNA. While the stem of the shRNA can be composed of complementary or partially complementary antisense and sense strands exclusive of overhangs, the shRNA can also include the following: (1) the portion of the molecule that is distal to the eventual Dicer cut site contains a region that is substantially complementary/homologous to the target mRNA; and (2) the region of the stem that is proximal to the Dicer cut site (i.e., the region adjacent to the loop) is unrelated or only partially related (e.g., complementary/homologous) to the target mRNA. The nucleotide content of this second region can be chosen based on a number of parameters including but not limited to thermodynamic traits or profiles.

[0072] Modified shRNAs can retain the modifications in the post-Dicer processed duplex. In exemplary embodiments, in cases in which the hairpin is a right handed hairpin (e.g., 5'-S-loop-AS-3') containing 2-6 nucleotide overhangs on the 3' end of the molecule, 2'-O-methyl modifications can be added to nucleotides at position 2, positions 1 and 2, or positions 1, 2, and 3 at the 5' end of the hairpin. Also, Dicer processing of hairpins with this configuration can retain the 5' end of the sense strand intact, thus preserving the pattern of chemical modification in the post-Dicer processed duplex. Presence of a 3' overhang in this configuration can be particularly advantageous since blunt ended molecules containing the prescribed modification pattern can be further processed by Dicer in such a way that the nucleotides carrying the 2' modifications are removed. In cases where the 3' overhang is present/retained, the resulting duplex carrying the sense-modified nucleotides can have highly favorable traits with respect to silencing specificity and functionality. Examples of exemplary modification patterns are described in detail in U.S. Patent Publication No. 20050223427 and International Patent Publication Nos. WO 2004/090105 and WO 2005/078094.

[0073] shRNA may comprise sequences that were selected at random, or according to any rational design selection procedure. For example, rational design algorithms are described in International Patent Publication No. WO 2004/045543 and U.S. Patent Publication No. 20050255487. Additionally, it may be desirable to select sequences in whole or in part based on average internal stability profiles ("AISPs") or regional internal stability profiles ("RISPs") that may facilitate access or processing by cellular machinery.

[0074] Ribozymes are enzymatic RNA molecules capable of catalyzing specific cleavage of mRNA, thus preventing translation. (For a review, see Rossi, Current Biology, 4:469-471 (1994)). The mechanism of ribozymes action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by an endonucleolytic cleavage event. The ribozyme molecules preferably include (1) one or more sequences complementary to a target mRNA, and (2) the well known catalytic sequence responsible for mRNA cleavage or a functionally equivalent sequence (see, e.g., U.S. Patent No. 5,093 ,246).

[0075] While ribozymes that cleave mRNA at site-specific recognition sequences can be used to destroy target mRNAs, hammerhead ribozymes may alternatively be used. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. Preferably, the target mRNA has the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988); and International Patent Publication. No. WO 89/05852.

[0076] Gene targeting ribozymes may contain a hybridizing region complementary to two regions of a target mRNA, each of which is at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleotides (but which need not both be the same length).

[0077] Hammerhead ribozyme sequences can be embedded in a stable RNA such as a transfer RNA (tRNA) to increase cleavage *efficiency in vivo* (Perriman et al., Proc. Natl. Acad. Sci, USA, 92:6175-79 (1995); de Feyter and Gaudron, Methods in Molecular Biology, Vol. 74, Chapter 43, "Expressing Ribozymes in Plants," Turner, P. C. (ed.), Humana Press Inc., Totowa, N.J.). In particular, RNA polymerase III-mediated expression of tRNA fusion ribozymes are well known in the art (see Kawasaki et al., Nature, 393:284-9 (1998); Kuwabara et al., Nature Biotechnol., 16:961-5 (1998); and Kuwabara et al., Mol. Cell, 2:617-27 (1998); Koseki et al., J. Virol., 73:1868-77 (1999); Kuwabara et al., Proc. Natl. Acad. Sci. USA, 96:1886-91 (1999); Tanabe et al., Nature, 406:473-4 (2000)). There are typically a number of potential hammerhead ribozyme cleavage sites within a given target cDNA sequence. Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the target mRNA- to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts. Furthermore, the use of any cleavage recognition site located in the target sequence encoding different portions of the target mRNA would allow the selective targeting of one or the other target genes.

[0078] Ribozymes for use in the inventive method also include RNA endoribonucleases ("Cech-type ribozymes") such as the one which occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) and which has been extensively described in Zaug et al., Science, 224:574-578 (1984); Zaug, et al., Science, 231:470-475 (1986); Zaug et al., Nature, 324:429-433 (1986); International Patent Publication No. WO 88/04300; and Been et al., Cell, 47:207-216 (1986)). The Cech-type ribozymes have an eight base pair active site which hybridizes to a target RNA sequence whereafter cleavage of the target RNA takes place. In one embodiment, the inventive method employs those Cech-type Ribozymes which target eight base-pair active site sequences that are present in a target gene or nucleic acid sequence.

[0079] Ribozymes can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and can be chemically synthesized or produced through an expression vector. Because ribozymes, unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency. Additionally, in certain embodiments, a ribozyme may be designed by first identifying a sequence portion sufficient to cause effective knockdown by RNAi. Portions of the same sequence may then be incorporated into a ribozyme.

[0080] Alternatively, target gene expression can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of the gene (i.e., the promoter and/or enhancers) to form triple helical structures that prevent transcription of the gene in target cells in the body. (See generally Helene, C., Anticancer Drug Des., 6:569-84 (1991); Helene et al., Ann. N.Y. Acad. Sci., 660:27-36 (1992); and Maher, L. J., Bioassays, 14:807-15 (1992)).

[0081] Nucleic acid molecules to be used in triple helix formation for the inhibition of transcription are preferably single stranded and composed of deoxyribonucleotides. The base composition of these oligonucleotides should promote triple helix formation via Hoogsteen base pairing rules, which generally require sizable stretches of either purines or pyrimidines to be present on one strand of a duplex. Nucleotide sequences may be pyrimidine-based, which will result in TAT and CGC triplets across the three associated strands of the resulting triple helix. The pyrimidine-rich molecules provide base complementarity to a purine-rich region of a single strand of the duplex in a parallel orientation to that strand. In addition, nucleic acid molecules may be chosen that are purine-rich, for example, containing a stretch of G residues. These molecules will form a triple helix with a DNA duplex that is rich in GC pairs, in which the majority of the purine residues are located on a single strand of the targeted duplex, resulting in CGC triplets across the three strands in the triplex.

[0082] Alternatively, the target sequences that can be targeted for triple helix formation may be increased by creating a so-called "switchback" nucleic acid molecule. Switchback molecules are synthesized in an alternating 5’-3’, 3’-5’ manner, such that they base pair with first one strand of a duplex and then the other, eliminating the necessity for a sizable stretch of either purines or pyrimidines to be present on one strand of a duplex.

[0083] Alternatively, DNA enzymes may be used to inhibit expression of target gene, such as the sclerostin gene. DNA enzymes incorporate some of the mechanistic features of both antisense and ribozyme technologies. DNA enzymes are designed so that they recognize a particular target nucleic acid sequence, much like an antisense oligonucleotide. They are, however, also catalytic and specifically cleave the target nucleic acid.

[0084] DNA enzymes include two basic types identified by Santoro and Joyce (see, for example, U.S. Patent No. 6,110,462). The 10-23 DNA enzyme comprises a loop structure which connect two arms. The two arms provide specificity by recognizing the particular target nucleic acid sequence while the loop structure provides catalytic function under physiological conditions.

[0085] Preferably, the unique or substantially unique sequence is a G/C rich segment of approximately 18 to 22 nucleotides. High G/C content helps insure a stronger interaction between the DNA enzyme and the target sequence. The specific antisense recognition sequence that will target the enzyme to the message may be divided between the two arms of the DNA enzyme.

[0086] Methods of making and administering DNA enzymes can be found, for example, in U.S. Patent No. 6,110,462. Additionally, one of skill in the art will recognize that, like antisense oligonucleotide, DNA enzymes can be optionally modified to improve stability and improve resistance to degradation.

[0087] Inhibitory oligonucleotides can be administered directly or delivered to cells by transformation or transfection via a vector, including viral vectors or plasmids, into which has been placed DNA encoding the inhibitory oligonucleotide with the appropriate regulatory sequences, including a promoter, to result in expression of the inhibitory oligonucleotide in the desired cell. Known methods include standard transient transfection, stable transfection and delivery using viruses ranging from retroviruses to adenoviruses. Delivery of nucleic acid inhibitors by replicating or replication-deficient vectors is contemplated. Expression can also be driven by either constitutive or inducible promoter systems (Paddison et al., Methods Mol. Biol., 265:85-100 (2004)). In other embodiments, expression may be under the control of tissue or development-specific promoters.

[0088] For example, vectors may be introduced by transfection using carrier compositions such as Lipofectamine 2000 (Life Technologies) or Oligofectamine (Life Technologies). Transfection efficiency may be checked using fluorescence microscopy for mammalian cell lines after co-transfection of hGFP-encoding pAD3 (Kehlenback et al., J. Cell Biol., 141:863-74 (1998)).

[0089] The delivery route will be the one that provides the best inhibitory effect as measured according to the criteria described above. Delivery mediated by cationic liposomes, delivery by retroviral vectors and direct delivery are efficient.

[0090] The effectiveness of the inhibitory oligonucleotide may be assessed by any of a number of assays, including reverse transcriptase polymerase chain reaction or Northern blot analysis to determine the level of existing human sclerostin mRNA, or Western blot analysis using antibodies which recognize the human sclerostin protein, after sufficient time for turnover of the endogenous pool after new protein synthesis is repressed.

[0091] The invention is further described in the following example. The example serves only to illustrate the invention and are not intended to limit the scope of the invention in any way.

EXAMPLE

[0092] This example describes *in vivo* studies wherein a sclerostin binding agent reduced the level of a marker of bone resorption and increased the level of one or more markers of bone formation.

[0093] A single-center, randomized, double-blind, placebo-controlled, ascending single-dose study in healthy men and postmenopausal women was conducted. Approximately 72 subjects enrolled in one of six dose cohorts. For cohorts 1, 2, 3a, 4, 5 and 6a, eight healthy postmenopausal women were randomized to receive a sclerostin binding agent or placebo via subcutaneous injection in a 3:1 ratio at dose levels of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg, or 10 mg/kg, respectively. In cohorts 3b and 6b, 8 healthy males received the sclerostin binding agent or a placebo intravenously and subcutaneously in a 3:3:1:1 ratio (sclerostin binding agent intravenously: sclerostin binding agent subcutaneously: placebo intravenously: placebo subcutaneously) at a dose level of 1 mg/kg or 10 mg/kg (reduced to 5 mg/kg), respectively. For cohorts 3c and 6c, four healthy postmenopausal women were randomized to receive the sclerostin binding agent or placebo intravenously in a 3:1 ratio at a dose level of 1 mg/kg or 10 mg/kg (reduced to 5 mg/kg), respectively.

[0094] The anti-sclerostin therapy was monitored by measuring the levels of bone resorption markers and bone formation markers prior to administration, then at least every week for 12 weeks post-administration. P1NP and BSAP levels were monitored following a single-dose subcutaneous administration of sclerostin binding agent in healthy, postmenopausal women (see Figures 1 and 2). Subjects dosed at 0.1 mg/kg and 0.3 mg/kg enjoyed the least elevation of P1NP or BSAP levels (e.g., levels increased less than 20%).

[0095] P1NP levels in subjects given 1 mg/kg increased approximately 20% by Day 10 and gradually tapered off to baseline around Day 56, while BSAP levels peaked at Day 14 at about 30% above baseline. P1NP and BSAP levels in subjects given 3 mg/kg peaked at Day 21 at approximately 100% (P1NP) and 60% (BSAP) increase from baseline, and returned to baseline about Day 56. In subjects administered 5 mg/kg, the level of P1NP rose to about 140% above baseline at Day 14 post-administration, and remained elevated at Day 77. In other words, the level of P1NP increased about 140% by two weeks post-treatment. BSAP rose to about 115% above baseline and remained elevated at Day 84. Similarly, administration of 10 mg/kg triggered a 180% increase in P1NP levels at about Day 28. P1NP levels remained elevated throughout the monitoring period. Subjects administered 10 mg/kg demonstrated a peak increase of BSAP levels at Day 21 (125% baseline for 3 weeks post-administration), which also remained elevated at Day 84. The results of the study are illustrated in Figures 1 and 2.

[0096] Osteocalcin also was monitored following a single-dose, subcutaneous administration of sclerostin binding agent in healthy, postmenopausal women (see Figure 3). Subjects given less than 1 mg/kg experienced little elevation of Osteocalcin. Osteocalcin levels fluctuated in patients administered 1 mg/kg, peaking at about 30% above baseline at Days 21 and 35. Osteocalcin levels peaked at about 100% above baseline at Day 21 in subjects administered 3 mg/kg, and levels remained elevated until about Day 56. Likewise, administration of 5 mg/kg sclerostin binding agent resulted in a 140% increase in osteocalcin levels at day 28, which levels remained at Day 84. Subjects dosed at 10 mg/kg demonstrated a peak osteocalcin level of about 180% above baseline at Day 35. Osteocalcin levels remained elevated above baseline until at least about Day 77.

[0097] Levels of the bone resorptive marker sCTx also were monitored (see Figure 4). Subjects administered placebo and 0.1 mg/kg demonstrated modest decreases in sCTx levels (e.g., less than 20%). Administration of 0.3 mg/kg of sclerostin binding agent reduced sCTx levels by about 20% by Day 21 (i.e., sCTX levels were reduced about 20% by two weeks after treatment). Levels fluctuated in subjects dosed at 1 mg/kg but reached about 30% below baseline at Days 10, 28, and 49. Levels in subjects administered 3 mg/kg, 5 mg/kg, and 10 mg/kg fell lowest at Day 14 to about 35%, 55%, and 55% below baseline, respectively, and levels remained below baseline when monitored thereafter. A comparison of the levels of all monitored biomarkers is provided in Figure 5.

[0098] Serum ionized calcium levels were monitored following a single, subcutaneous dose of sclerostin binding agent in healthy, postmenopausal women (see Figure 6). Remarkably, ionized calcium levels did not fluctuate dramatically at any dosage. Indeed, all subjects (including those receiving placebo) experienced a modest transient decrease in serum ionized calcium of approximately 5% during the monitoring period.

[0099] Finally, bone mineral density was measured in the spine and hip of healthy, postmenopausal women receiving 1 mg/kg, 3 mg/kg, 5 mg/kg, or 10 mg/kg sclerostin binding agent (see Figure 7). Significant increases in BMD were observed in the spine, for example, at Days 28, 56, and 84, particularly in patients receiving 5 mg/kg and 10 mg/kg. BMD in the hip increased less than that of the spine, but BMD was elevated at Day 56 in patients administered 3 mg/kg, 5 mg/kg, and 10 mg/kg. BMD was further elevated at Day 84 in patients dosed at 5 mg/kg and 10 mg/kg.

[0100] This example illustrates the ability of the inventive method to reduce levels of a marker of bone resorption, elevate levels of markers of bone formation, and increase bone mineral density without dramatic alterations in serum calcium. The therapeutic effect of a single dose of sclerostin binding agent is long-lived, with increased bone formation marker levels and decreased bone resorptive marker levels continuing to be observed at 84 days (12 weeks) post treatment. Furthermore, data described herein suggests that the therapeutic efficacy of the invention have significant advantages compared to other treatments by "uncoupling" bone formation and bone resorption to maximize bone formation and mineralization *in vivo.*

[0101] **NUMBERED FURTHER ASPECTS,** Not part of the claimed subject-matter unless thus claimed.

(1) A method for inhibiting bone resorption in a subject, the method comprising administering to the subject a sclerostin binding agent in an amount from about 1 mg/kg to about 10 mg/kg,
wherein the amount is effective to reduce serum level of C-telopeptide of type I collagen (CTX) by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins,
and wherein bone resorption is inhibited.

(2) The method of (1), wherein the amount of sclerostin binding agent increases a marker of bone formation selected from the group consisting of serum level of bone-specific alkaline phosphatase (BSAP), serum level of amino-terminal extension of peptide of procollagen type 1 (PINP), and serum level of osteocalcin (OstCa), by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins.

(3) The method of (1), wherein the amount of sclerostin binding agent does not result in hypocalcemia or hypercalcemia.

(4) A method for increasing bone mineral density in a subject, the method comprising administering to the subject a sclerostin binding agent in an amount from about 1 mg/kg to about 10 mg/kg,
wherein the amount is effective to (a) reduce serum level of CTX by at least 20% compared to pre-treatment or normal levels, by 3 weeks after treatment begins, and (b) increase serum level of a bone formation marker selected from the group consisting of serum level of bone-specific alkaline phosphatase (BSAP), serum level of amino-terminal extension of peptide of procollagen type 1 (PINP), and serum level of osteocalcin (OstCa), by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins,
and wherein bone mineral density is increased.

(5) The method of (4), wherein hip, spine, wrist, finger, shin bone and/or heel bone mineral density is increased by at least about 1%.

(6) The method of (5), wherein bone mineral density in the spine is increased by at least about 1%.

(7) The method of (4), wherein bone mineral density is increased to the range of about 1 to 2.5 standard deviations below the normal bone mineral density of a healthy young adult.

(8) The method of (4), wherein bone mineral density is increased to the range of about 0 to 1 standard deviations below the normal bone mineral density of a healthy young adult.

(9) A method for treating a bone-related disorder in a subject, the method comprising

   (a) administering to the subject a sclerostin binding agent in an amount from about 1 mg/kg to about 10 mg/kg for a first period of time, wherein the amount is effective to increase bone mineral density at the hip, spine, wrist, finger, shin bone and/or heel by at least about 3%, and
   (b) administering to the subject a sclerostin binding agent in an amount of from about 1 mg/kg to about 10 mg/kg for a second period of time effective to maintain bone mineral density.

(10) The method of (9), wherein the first period of time is 3 months or less.

(11) The method of claim (9), wherein the second period of time is at least 6 months.

(12) The method of claim (9), wherein bone mineral density in the spine is increased by at least about 3%.

(13) A method of treating a bone-related disorder in a human suffering from or at risk of hypocalcemia or hypercalcemia, the method comprising administering to the human a sclerostin binding agent in a therapeutically effective amount from about 1 mg/kg to about 10 mg/kg.

(14) The method of (13), wherein the hypocalcemia or hypercalcemia results from chronic kidney disease, renal failure, primary or secondary hyperparathyroidism, pseudohyperparathyroidism, hypoparathyroidism, pseudohypoparathyroidism, magnesium depletion, severe hypermagnesemia, vitamin D deficiency, hyperphosphatemia,

acute pancreatitis, hungry bone syndrome, chelation, osteoblastic metastases, sepsis, surgery, chemotherapy, neoplasia syndrome, hypoparathyroidism, familial hypocalciuric hypercalcemia, sarcoidosis, tuberculosis, berylliosis, histoplasmosis, Candidiasis, Coccidioidomycosis, histiocytosis X, Hodgkin's or Non-Hodgkin's lymphoma, Crohn's disease, Wegener's granulomatosis, pneumonia, silicone-induced granulomas, administration of thiazide diuretics or lithium, or immobilization.

(15) A method of treating a bone-related disorder in (a) a human in which treatment with a parathyroid hormone or analog thereof is contraindicated or (b) a human in which treatment with bisphosphonate is contraindicated, the method comprising administering to the human a therapeutically effective amount of a sclerostin binding agent from about 1 mg/kg to about 10 mg/kg.

(16) The method any one of (1) to (15), wherein an amount of sclerostin binding agent is administered to the subject once every two weeks.

(17) The method of any one of (1) to (15), wherein an amount of sclerostin binding agent is adminstered to the subject once a month.

(18) The method of any one of (1) to (17), where the sclerostin binding agent cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 to sclerostin.

(19) The method of any one of (1) to (18), wherein the sclerostin binding agent is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24.

(20) The method of any one of (1) to (17), wherein the sclerostin binding agent is an antibody or fragment thereof that demonstrates a binding affinity for sclerostin of SEQ ID NO: 1 of less than or equal to 1 x 10-7 M.

(21) The method of (20), wherein the antibody or fragment thereof comprises:

a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs:45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; 1) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs:113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ ID NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs: 116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270, and 271; r) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; or s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360.

(22) The method of (21), wherein the antibody or fragment thereof comprises CDRH-1, CDR-H2, CDR-H3, CDR-L1 CDR-L2 and CDR-L3 wherein (a) CDR-H1 is SEQ ID NO:245, CDR-H2 is SEQ ID NO:246, CDR-H3 is SEQ ID NO:247, CDR-L1 is SEQ ID NO:78, CDR-L2 is SEQ ID NO:79 and CDR-L3 is SEQ ID NO:80; or (b) CDR-H1 is SEQ ID NO:269, CDR-H2 is SEQ ID NO:270, CDR-H3 is SEQ ID NO:271, CDR-L1 is SEQ ID NO:239, CDR-L2 is SEQ ID NO:240 and CDR-L3 is SEQ ID NO:241.

(23) The method of any one of (20) to (22), wherein the antibody is a human antibody, a humanized antibody, a monoclonal antibody, or a chimeric antibody.

(24) Use of a sclerostin binding agent in preparation of a medicament for inhibiting bone resorption in an amount from about 1 mg/kg to about 10 mg/kg, wherein the amount is effective to reduce serum level of C-telopeptide of type I collagen (CTX) by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins.

(25) The use of (24), wherein the amount of sclerostin binding agent increases a marker of bone formation selected from the group consisting of serum level of bone-specific alkaline phosphatase (BSAP), serum level of amino-terminal extension of peptide of procollagen type 1 (PINP), and serum level of osteocalcin (OstCa), by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins.

(26) The use of (24) or (25), wherein the amount of sclerostin binding agent does not result in hypocalcemia or hypercalcemia.

(27) Use of a sclerostin binding agent in preparation of a medicament for increasing bone mineral density in an amount from about 1 mg/kg to about 10 mg/kg, wherein the amount is effective to (a) reduce serum level of CTX by at least 20% compared to pre-treatment or normal levels, by 3 weeks after treatment begins, and (b) increase serum level of a bone formation marker selected from the group consisting of serum level of bone-specific alkaline phosphatase (BSAP), serum level of amino-terminal extension of peptide of procollagen type 1 (PINP), and serum level of osteocalcin (OstCa), by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins.

(28) The use of (27), wherein hip, spine, wrist, finger, shin bone and/or heel bone mineral density is increased by at least about 1%.

(29) The use of (28), wherein bone mineral density in the spine is increased by at least about 1%.

(30) The use of any one of (27) to (29), wherein bone mineral density is increased to the range of about 1 to 2.5 standard deviations below the normal bone mineral density of a healthy young adult.

(31) The use of any one of (27) to (29), wherein bone mineral density is increased to the range of about 0 to 1 standard deviations below the normal bone mineral density of a healthy young adult.

(32) Use of a sclerostin binding agent in preparation of a medicament for treating a bone-related disorder in an amount from about 1 mg/kg to about 10 mg/kg for a first period of time, wherein the amount is effective to increase bone mineral density at the hip, spine, wrist, finger, shin bone and/or heel by at least about 3%, followed by an amount of from about 1 mg/kg to about 10 mg/kg for a second period of time effective to maintain bone mineral density.

(33) The use of (32), wherein the first period of time is 3 months or less.

(34) The use of (32) or (33), wherein the second period of time is at least 6 months.

(35) The use of any one of (32) to (34), wherein bone mineral density in the spine is increased by at least about 3%.

(36) Use of a sclerostin binding agent in preparation of a medicament for treating a bone-related disorder in a human suffering from or at risk of hypocalcemia or hypercalcemia in an amount from about 1 mg/kg to about 10 mg/kg.

(37) The use of (36), wherein the hypocalcemia or hypercalcemia results from chronic kidney disease, renal failure, primary or secondary hyperparathyroidism, pseudohyperparathyroidism, hypoparathyroidism, pseudohypoparathyroidism, magnesium depletion, severe hypermagnesemia, vitamin D deficiency, hyperphosphatemia, acute pancreatitis, hungry bone syndrome, chelation, osteoblastic metastases, sepsis, surgery, chemotherapy, neoplasia syndrome, hypoparathyroidism, familial hypocalciuric hypercalcemia, sarcoidosis, tuberculosis, berylliosis, histoplasmosis, Candidiasis, Coccidioidomycosis, histiocytosis X, Hodgkin's or Non-Hodgkin's lymphoma, Crohn's disease, Wegener's granulomatosis, pneumonia, silicone-induced granulomas, administration of thiazide diuretics or lithium, or immobilization.

(38) Use of a sclerostin binding agent in preparation of a medicament for treating a bone-related disorder in (a) a human in which treatment with a parathyroid hormone or analog thereof is contraindicated or (b) a human in which treatment with bisphosphonate is contraindicated.

(39) The use of any one of (32) to (38) in which the bone-related disorder is 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 Pisease, Turner Syndrome, Down Syndrome, Klinefelter Syndrome, leprosy, Perthes' Disease, adolescent idiopathic scoliosis, infantile onset multi-system inflammatory disease, Winchester Syndrome, Menkes Disease, Wilson's Disease, ischemic bone disease (such as Legg-Calve-Perthes disease, regional migratory osteoporosis), anemic states, conditions caused by steroids, glucocorticoid-induced bone loss, heparin-induced bone loss, bone marrow disorders, scurvy, malnutrition, calcium deficiency, 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.

(40) The use of any one of (24) to (39), where the sclerostin binding agent cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 to sclerostin.

(41) The use of any one of (24) to (39), wherein the sclerostin binding agent is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24.

(42) The use of any one of (24) to (39), wherein the sclerostin binding agent is an antibody or fragment thereof that demonstrates a binding affinity for sclerostin of SEQ ID NO: 1 of less than or equal to 1 x 10-7 M.

(43) The use of (42), wherein the antibody or fragment thereof comprises: a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs:45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; 1) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs:113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ ID NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs: 116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270, and 271; r) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; or s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360.

(44) The use of (43), wherein the antibody or fragment thereof comprises CDRH-1, CDR-H2, CDR-H3, CDR-L1 CDR-L2 and CDR-L3 wherein (a) CDR-H1 is SEQ ID NO:245, CDR-H2 is SEQ ID NO:246, CDR-H3 is SEQ ID NO:247, CDR-L1 is SEQ ID NO:78, CDR-L2 is SEQ ID NO:79 and CDR-L3 is SEQ ID NO:80; or (b) CDR-H1 is SEQ ID NO:269, CDR-H2 is SEQ ID NO:270, CDR-H3 is SEQ ID NO:271, CDR-L1 is SEQ ID NO:239, CDR-L2 is SEQ ID NO:240 and CDR-L3 is SEQ ID NO:241.

(45) The use of any one of (42) to (44), wherein the antibody is a human antibody, a humanized antibody, a monoclonal antibody, or a chimeric antibody.

(46) A container comprising anti-sclerostin antibody or fragment thereof and instructions for administering the antibody or fragment thereof in an amount effective to (a) reduce serum level of C-telopeptide of type I collagen (CTX) by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins, and (b) increase serum level bone-specific alkaline phosphatase (BSAP), serum level of amino-terminal extension of peptide of procollagen type 1 (PINP), or serum level of osteocalcin (OstCa) by at least 20%, compared to pre-treatment or normal levels, by 3 weeks after treatment begins.

(47) A container comprising an amount of anti-sclerostin antibody from about 70 mg to about 450 mg.

(48) A container comprising anti-sclerostin antibody or fragment thereof and instructions for administering the antibody or fragment thereof for treating a bone-related disorder in an amount from about 1 mg/kg to about 10 mg/kg every two or four weeks.

(49) A container comprising anti-sclerostin antibody or fragment thereof and instructions for administering the antibody or fragment thereof for treating a bone-related disorder in an amount from about 1 mg/kg to about 10 mg/kg for a period of about 3 months.

SEQUENCE LISTING

[0102]

<110> Amgen Inc. Padhi, et al.

<120> Methods of Inhibiting Bone Resorption

<130> 31173/43242A

<150> 60/973,024
<151> 2007-09-17

<160> 396

<170> PatentIn version 3.5

<210> 1
<211> 190
<212> PRT
<213> Homo sapiens

<400> 1

```
Gln Gly Trp Gln Ala Phe Lys Asn Asp Ala Thr Glu Ile Ile Pro Glu
1               5                   10                  15

Leu Gly Glu Tyr Pro Glu Pro Pro Pro Glu Leu Glu Asn Asn Lys Thr
            20                  25                  30

Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro His His Pro Phe Glu
        35                  40                  45

Thr Lys Asp Val Ser Glu Tyr Ser Cys Arg Glu Leu His Phe Thr Arg
    50                  55                  60

Tyr Val Thr Asp Gly Pro Cys Arg Ser Ala Lys Pro Val Thr Glu Leu
65                  70                  75                  80

Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile
                85                  90                  95

Gly Arg Gly Lys Trp Trp Arg Pro Ser Gly Pro Asp Phe Arg Cys Ile
            100                 105                 110

Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu Leu Cys Pro Gly Gly
        115                 120                 125

Glu Ala Pro Arg Ala Arg Lys Val Arg Leu Val Ala Ser Cys Lys Cys
    130                 135                 140

Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu Leu Lys Asp Phe Gly
145                 150                 155                 160

Thr Glu Ala Ala Arg Pro Gln Lys Gly Arg Lys Pro Arg Pro Arg Ala
                165                 170                 175
```

```
Arg Ser Ala Lys Ala Asn Gln Ala Glu Leu Glu Asn Ala Tyr
            180                 185                 190
```

<210> 2
<211> 14
<212> PRT
<213> Homo sapiens

<400> 2

```
Asp Val Ser Glu Tyr Ser Cys Arg Glu Leu His Phe Thr Arg
1               5                   10
```

<210> 3
<211> 16
<212> PRT
<213> Homo sapiens

<400> 3

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

<210> 4
<211> 16
<212> PRT
<213> Homo sapiens

<400> 4

```
Trp Trp Arg Pro Ser Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr
1               5                   10                  15
```

<210> 5
<211> 12
<212> PRT
<213> Homo sapiens

<400> 5

```
Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg
1               5                   10
```

<210> 6
<211> 26
<212> PRT
<213> Homo sapiens

<400> 6

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

Trp Arg Pro Ser Gly Pro Asp Phe Arg Cys
            20                  25
```

<210> 7
<211> 214
<212> PRT
<213> Mus musculus

<400> 7

```
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> 8
<211> 645
<212> DNA
<213> Mus musculus

<400> 8

```
gatgtccaga tgattcagtc tccatcctcc ctgtctgcat ctttgggaga catagtcacc      60

atgacttgcc aggcaagtca gggcactagc attaatttaa actggtttca gcaaaaacca     120

gggaaggctc ctaagctcct gatctatggt tcaagcaact tggaagatgg ggtcccatca     180

aggttcagtg gcagtagata tgggacagat ttcactctca ccatcagcag cctggaggat     240

gaagatctgg caacttattt ctgtctacaa catagttatc tcccgtacac 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> 9
<211> 236
<212> PRT
<213> Mus musculus

<400> 9

```
Met Asn Thr Arg Ala Pro Ala Glu Phe Leu Gly Phe Leu Leu Leu Trp
1               5                   10                  15

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

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

Gln Gly Thr Ser Ile Asn Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys
    50                  55                  60

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

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

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

His Ser Tyr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125
```

```
Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser
    130                 135                 140

Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu
                165                 170                 175

Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr
        195                 200                 205

Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr
    210                 215                 220

Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230                 235
```

<210> 10
<211> 711
<212> DNA
<213> Mus musculus

<400> 10

```
atgaacacga gggcccctgc tgagttcctt gggttcctgt tgctctggtt tttaggtgcc       60
agatgtgatg tccagatgat tcagtctcca tcctccctgt ctgcatcttt gggagacata      120
gtcaccatga cttgccaggc aagtcagggc actagcatta atttaaactg gtttcagcaa      180
aaaccaggga aggctcctaa gctcctgatc tatggttcaa gcaacttgga agatggggtc      240
ccatcaaggt tcagtggcag tagatatggg acagatttca ctctcaccat cagcagcctg      300
gaggatgaag atctggcaac ttatttctgt ctacaacata gttatctccc gtacacgttc      360
ggaggggggga ccaagctgga aataaaacgg gctgatgctg caccaactgt atccatcttc      420
ccaccatcca gtgagcagtt aacatctgga ggtgcctcag tcgtgtgctt cttgaacaac      480
ttctacccca aagacatcaa tgtcaagtgg aagattgatg gcagtgaacg acaaaatggc      540
gtcctgaaca gttggactga tcaggacagc aaagacagca cctacagcat gagcagcacc      600
ctcacgttga ccaaggacga gtatgaacga cataacagct atacctgtga ggccactcac      660
aagacatcaa cttcacccat tgtcaagagc ttcaacagga atgagtgtta g              711
```

<210> 11
<211> 443

<212> PRT
<213> Mus musculus

<400> 11

```
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> 12
<211> 1332
<212> DNA
<213> Mus musculus

<400> 12

gaggtccagc tgcaacagtc tggacctgaa ctggtgacgc ctggggcttc agtgaagata 60

tcttgtaagg cttctggata cacattcact gaccactaca tgagctgggt gaagcagagt 120

catggaaaaa gccttgagtg gattggagat attaatccct attctggtga aactacctac 180

aaccagaagt tcaagggcac ggccacattg actgtagaca agtcttccag tatagcctac 240

atggagatcc gcggcctgac atctgaggac tctgcagtct attactgtgc aagagatgat 300

tacgacgcct ctccgtttgc ttactggggc caagggactc tggtcactgt ctctgcagcc 360

aaaacgacac ccccatctgt ctatccactg gcccctggat ctgctgccca aactaactcc 420

atggtgaccc tgggatgcct ggtcaagggc tatttccctg agccagtgac agtgacctgg 480

aactctggat ccctgtccag cggtgtgcac accttcccag ctgtcctgca gtctgacctc 540

tacactctga gcagctcagt gactgtcccc tccagcacct ggcccagcga gaccgtcacc 600

tgcaacgttg cccacccggc cagcagcacc aaggtggaca agaaaattgt gcccagggat 660

tgtggttgta agccttgcat atgtacagtc ccagaagtat catctgtctt catcttcccc 720

ccaaagccca aggatgtgct caccattact ctgactccta aggtcacgtg tgttgtggta 780

gacatcagca aggatgatcc cgaggtccag ttcagctggt ttgtagatga tgtggaggtg 840

cacacagctc agacgcaacc ccgggaggag cagttcaaca gcactttccg ctcagtcagt 900

gaacttccca tcatgcacca ggactggctc aatggcaagg agttcaaatg cagggtcaac 960

agtccagctt tccctgcccc catcgagaaa accatctcca aaaccaaagg cagaccgaag 1020

gctccacagg tgtacaccat tccacctccc aaggagcaga tggccaagga taaagtcagt 1080

ctgacctgca tgataacaga cttcttccct gaagacatta ctgtggagtg gcagtggaat 1140

gggcagccag cggagaacta caagaacact cagcccatca tggacacaga tggctcttac 1200

ttcatctaca gcaagctcaa tgtgcagaag agcaactggg aggcaggaaa tactttcacc 1260

tgctctgtgt tacatgaggg cctgcacaac caccatactg agaagagcct ctcccactct 1320

cctggtaaat ga 1332

<210> 13
<211> 462
<212> PRT
<213> Mus musculus

<400> 13

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

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Thr
            20                  25                  30

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

Thr Asp His Tyr Met Ser Trp Val Lys Gln Ser His Gly Lys Ser Leu
    50                  55                  60

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

Gln Lys Phe Lys Gly Thr Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
```

```
                85                  90                  95

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

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

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

Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met
145                 150                 155                 160

Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175

Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
            180                 185                 190

Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
        195                 200                 205

Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
    210                 215                 220

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

Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe
                245                 250                 255

Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro
            260                 265                 270

Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val
        275                 280                 285

Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr
    290                 295                 300

Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu
305                 310                 315                 320

Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys
                325                 330                 335

Arg Val Asn Ser Pro Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350
```

```
Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro
        355                 360                 365

Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile
    370                 375                 380

Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly
385                 390                 395                 400

Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp
                405                 410                 415

Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp
            420                 425                 430

Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His
        435                 440                 445

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

<210> 14
<211> 1389
<212> DNA
<213> Mus musculus

<400> 14

```
atgagatgca ggtggatctt tctctttctc ctgtcaggaa ctgcaggtgt cctctctgag      60
gtccagctgc aacagtctgg acctgaactg gtgacgcctg gggcttcagt gaagatatct     120
tgtaaggctt ctggatacac attcactgac cactacatga gctgggtgaa gcagagtcat     180
ggaaaaagcc ttgagtggat tggagatatt aatccctatt ctggtgaaac tacctacaac     240
cagaagttca agggcacggc cacattgact gtagacaagt cttccagtat agcctacatg     300
gagatccgcg gcctgacatc tgaggactct gcagtctatt actgtgcaag agatgattac     360
gacgcctctc cgtttgctta ctggggccaa gggactctgg tcactgtctc tgcagccaaa     420
acgacacccc catctgtcta tccactggcc cctggatctg ctgcccaaac taactccatg     480
gtgaccctgg gatgcctggt caagggctat ttccctgagc cagtgacagt gacctggaac     540
tctggatccc tgtccagcgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac     600
actctgagca gctcagtgac tgtcccctcc agcacctggc ccagcgagac cgtcacctgc     660
aacgttgccc acccggccag cagcaccaag gtggacaaga aaattgtgcc cagggattgt     720
ggttgtaagc cttgcatatg tacagtccca gaagtatcat ctgtcttcat cttcccccca     780
aagcccaagg atgtgctcac cattactctg actcctaagg tcacgtgtgt tgtggtagac     840
atcagcaagg atgatcccga ggtccagttc agctggtttg tagatgatgt ggaggtgcac     900

acagctcaga cgcaaccccg ggaggagcag ttcaacagca ctttccgctc agtcagtgaa     960
cttcccatca tgcaccagga ctggctcaat ggcaaggagt tcaaatgcag ggtcaacagt    1020
ccagctttcc ctgcccccat cgagaaaacc atctccaaaa ccaaaggcag accgaaggct    1080
ccacaggtgt acaccattcc acctcccaag gagcagatgg ccaaggataa agtcagtctg    1140
acctgcatga taacagactt cttccctgaa gacattactg tggagtggca gtggaatggg    1200
cagccagcgg agaactacaa gaacactcag cccatcatgg acacagatgg ctcttacttc    1260
atctacagca agctcaatgt gcagaagagc aactgggagg caggaaatac tttcacctgc    1320
tctgtgttac atgagggcct gcacaaccac catactgaga agagcctctc ccactctcct    1380
ggtaaatga                                                            1389
```

<210> 15
<211> 218
<212> PRT
<213> Mus musculus

<400> 15

```
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> 16
<211> 657
<212> DNA
<213> Mus musculus

<400> 16

```
gacattgtgc tgacccaatc tccagcttct ttgactgtgt ctctaggcct gagggccacc        60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtac       120

cagcagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct       180

gggatcccag ccaggtttag tggcaatggg tctgggacag acttcaccct caacatccat       240

cctgtggagg aggaggatgc tgtaacctat tactgtcaac aaagtaatga ggatccgtgg       300

acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc       360

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg       420

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa       480

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc       540

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc       600

actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag          657
```

<210> 17
<211> 238
<212> PRT
<213> Mus musculus

<400> 17

```
Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Thr
            20                  25                  30

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

```
Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
    50                  55                  60

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

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

Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Val Thr Tyr Tyr Cys
            100                 105                 110

Gln Gln Ser Asn Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
        115                 120                 125

Glu Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro
    130                 135                 140

Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu
145                 150                 155                 160

Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly
                165                 170                 175

Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser
            180                 185                 190

Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp
        195                 200                 205

Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr
    210                 215                 220

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

<210> 18
<211> 717
<212> DNA
<213> Mus musculus

<400> 18

atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60
gacattgtgc tgacccaatc tccagcttct ttgactgtgt ctctaggcct gagggccacc 120
atctcctgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtac 180
cagcagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 240
gggatcccag ccaggtttag tggcaatggg tctgggacag acttcaccct caacatccat 300
cctgtggagg aggaggatgc tgtaacctat tactgtcaac aaagtaatga ggatccgtgg 360
acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc 420
atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 480
aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 540
aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 600
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 660
actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag 717

<210> 19
<211> 449
<212> PRT
<213> Mus musculus

<400> 19

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys
```

<210> 20
<211> 1350
<212> DNA
<213> Mus musculus

<400> 20

```
gaggtccagc tgcaacaatc tggacctgag ctggtgaagc ctgggacttc agtgaagatg      60

tcctgtaagg cttctggata cacattcact gactgctaca tgaactgggt gaagcagagc     120

catgggaaga gccttgaatg gattggagat attaatcctt tcaacggtgg tactacctac     180

aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac     240

atgcagctca acagcctgac atctgacgac tctgcagtct attactgtgc aagatcccat     300

tattacttcg atggtagagt cccttgggat gctatggact actggggtca aggaacctca     360

gtcaccgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct     420

gctgcccaaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag     480

ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct     540

gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg     600

cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag     660

aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca     720

tctgtcttca tcttcccccc aaagcccaag gatgtgctca ccattactct gactcctaag     780

gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt     840

gtagatgatg tggaggtgca cacagctcag acgcaacccc gggaggagca gttcaacagc     900

actttccgct cagtcagtga acttcccatc atgcaccagg actggctcaa tggcaaggag     960

ttcaaatgca gggtcaacag tgcagctttc cctgccccca tcgagaaaac catctccaaa    1020

accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg    1080

gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact    1140

gtggagtggc agtggaatgg gcagccagcg gagaactaca agaacactca gcccatcatg    1200

gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag    1260

gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag    1320

aagagcctct cccactctcc tggtaaatga                                     1350
```

<210> 21
<211> 468
<212> PRT
<213> Mus musculus

<400> 21

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

Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys
                20                  25                  30

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

Thr Asp Cys Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu
        50                  55                  60

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

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85                  90                  95

Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Asp Asp Ser Ala Val
                100                 105                 110

Tyr Tyr Cys Ala Arg Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp
            115                 120                 125

Asp Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        130                 135                 140

Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
145                 150                 155                 160

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
                165                 170                 175

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
                180                 185                 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
            195                 200                 205

Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
        210                 215                 220

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
225                 230                 235                 240

Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
                245                 250                 255
```

```
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
            260                 265                 270

Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
        275                 280                 285

Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
    290                 295                 300

Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320

Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
        355                 360                 365

Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
    370                 375                 380

Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
385                 390                 395                 400

Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
                405                 410                 415

Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
            420                 425                 430

Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
        435                 440                 445

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

Ser Pro Gly Lys
465
```

<210> 22
<211> 1407
<212> DNA
<213> Mus musculus

<400> 22

```
atgggatgga actggatctt tctcttcctc ttgtcaggaa ctgcaggtgt ctactctgag      60

gtccagctgc aacaatctgg acctgagctg gtgaagcctg ggacttcagt gaagatgtcc     120
tgtaaggctt ctggatacac attcactgac tgctacatga actgggtgaa gcagagccat     180
gggaagagcc ttgaatggat tggagatatt aatcctttca acggtggtac tacctacaac     240
cagaagttca agggcaaggc cacattgact gtagacaaat cctccagcac agcctacatg     300
cagctcaaca gcctgacatc tgacgactct gcagtctatt actgtgcaag atcccattat     360
tacttcgatg gtagagtccc ttgggatgct atggactact ggggtcaagg aacctcagtc     420
accgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct     480
gcccaaacta actccatggt gaccctggga tgcctggtca agggctattt ccctgagcca     540
gtgacagtga cctggaactc tggatccctg tccagcggtg tgcacacctt cccagctgtc     600
ctgcagtctg acctctacac tctgagcagc tcagtgactg tcccctccag cacctggccc     660
agcgagaccg tcacctgcaa cgttgcccac ccggccagca gcaccaaggt ggacaagaaa     720
attgtgccca gggattgtgg ttgtaagcct tgcatatgta cagtcccaga agtatcatct     780
gtcttcatct tccccccaaa gcccaaggat gtgctcacca ttactctgac tcctaaggtc     840
acgtgtgttg tggtagacat cagcaaggat gatcccgagg tccagttcag ctggtttgta     900
gatgatgtgg aggtgcacac agctcagacg caaccccggg aggagcagtt caacagcact     960
ttccgctcag tcagtgaact tcccatcatg caccaggact ggctcaatgg caaggagttc    1020
aaatgcaggg tcaacagtgc agctttccct gcccccatcg agaaaaccat ctccaaaacc    1080
aaaggcagac cgaaggctcc acaggtgtac accattccac ctcccaagga gcagatggcc    1140
aaggataaag tcagtctgac ctgcatgata acagacttct tccctgaaga cattactgtg    1200
gagtggcagt ggaatgggca gccagcggag aactacaaga acactcagcc catcatggac    1260
acagatggct cttacttcat ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca    1320
ggaaatactt tcacctgctc tgtgttacat gagggcctgc acaaccacca tactgagaag    1380
agcctctccc actctcctgg taaatga                                        1407
```

<210> 23
<211> 217
<212> PRT
<213> Rabbit-Mouse Chimera

<400> 23

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

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

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

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

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

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

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

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

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

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

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
            180                 185                 190

Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile
        195                 200                 205

Val Lys Ser Phe Asn Arg Asn Glu Cys
    210                 215
```

<210> 24
<211> 654
<212> DNA
<213> Rabbit-Mouse Chimera

<400> 24

gcgcaagtgc tgacccagac tccagcctcc gtgtctgcag ctgtgggagg cacagtcacc 60
atcaattgcc agtccagtca gagtgtttat gataacaact ggttagcctg gtttcagcag 120
aaaccagggc agcctcccaa gctcctgatt tatgatgcat ccgatctggc atctggggtc 180
ccatcgcggt tcagtggcag tggatctggg acacagttca ctctcaccat cagcggcgtg 240
cagtgtgccg atgctgccac ttactactgt caaggcgctt ataatgatgt tatttatgct 300
ttcggcggag ggaccgaggt ggtggtcaaa cgtacggatg ctgcaccaac tgtatccatc 360
ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac 420

aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat 480
ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc 540
accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact 600
cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg ttag 654

<210> 25
<211> 239
<212> PRT
<213> Rabbit-Mouse Chimera

<400> 25

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

Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ala Ser
            20                  25                  30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser
        35                  40                  45

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

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

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

Leu Thr Ile Ser Gly Val Gln Cys Ala Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Gln Gly Ala Tyr Asn Asp Val Ile Tyr Ala Phe Gly Gly Gly Thr Glu
        115                 120                 125

Val Val Val Lys Arg Thr Asp Ala Ala Pro Thr Val Ser Ile Phe Pro
    130                 135                 140

Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp
                165                 170                 175

Gly Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys
        195                 200                 205

Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys
    210                 215                 220

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

<210> 26
<211> 720

<212> DNA
<213> Rabbit-Mouse Chimera

<400> 26

```
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc      60

acatttgcgc aagtgctgac ccagactcca gcctccgtgt ctgcagctgt gggaggcaca     120

gtcaccatca attgccagtc cagtcagagt gtttatgata acaactggtt agcctggttt     180

cagcagaaac cagggcagcc tcccaagctc ctgatttatg atgcatccga tctggcatct     240

ggggtcccat cgcggttcag tggcagtgga tctgggacac agttcactct caccatcagc     300

ggcgtgcagt gtgccgatgc tgccacttac tactgtcaag gcgcttataa tgatgttatt     360

tatgctttcg gcggagggac cgaggtggtg gtcaaacgta cggatgctgc accaactgta     420

tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc     480

ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga     540

caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg     600

agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag     660

gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgttag     720
```

<210> 27
<211> 433
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody

<400> 27

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


Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser Ser Tyr Trp
            20                  25                  30
```

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

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

Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Met Asp Leu Lys Met Thr
65                  70                  75                  80

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

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

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

Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
    130                 135                 140

Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
145                 150                 155                 160

Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
                165                 170                 175

Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
            180                 185                 190

Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
        195                 200                 205

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

Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
225                 230                 235                 240

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

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

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

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

Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
305                 310                 315                 320

Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
                325                 330                 335

Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
            340                 345                 350

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

Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
    370                 375                 380

Asn Thr Asn Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys
385                 390                 395                 400

Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
                405                 410                 415

Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
            420                 425                 430

Lys
```

<210> 28
<211> 1302
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody

<400> 28

```
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc      60
tgcacagcct ctggattctc cctcagtagt tattggatga actgggtccg ccaggctcca     120
ggggaggggc tggaatggat cggaaccatt gattctggtg gtaggacgga ctacgcgagc     180
tgggcaaaag gccgattcac catctccaga acctcgacta cgatggatct gaaaatgacc     240
agtctgacga ccggggacac ggcccgttat ttctgtgcca gaaattggaa cttgtggggc     300
caaggcaccc tcgtcaccgt ctcgagcgct tctacaaagg gcccatctgt ctatccactg     360

gcccctggat ctgctgccca aactaactcc atggtgaccc tgggatgcct ggtcaagggc     420
tatttccctg agccagtgac agtgacctgg aactctggat ccctgtccag cggtgtgcac     480
accttcccag ctgtcctgca gtctgacctc tacactctga gcagctcagt gactgtcccc     540
tccagcacct ggcccagcga gaccgtcacc tgcaacgttg cccacccggc cagcagcacc     600
aaggtggaca agaaaattgt gcccagggat tgtggttgta agccttgcat atgtacagtc     660
ccagaagtat catctgtctt catcttcccc ccaaagccca aggatgtgct caccattact     720
ctgactccta aggtcacgtg tgttgtggta gacatcagca aggatgatcc cgaggtccag     780
ttcagctggt ttgtagatga tgtggaggtg cacacagctc agacgcaacc ccgggaggag     840
cagttcaaca gcactttccg ctcagtcagt gaacttccca tcatgcacca ggactggctc     900
aatggcaagg agttcaaatg cagggtcaac agtgcagctt tccctgcccc catcgagaaa     960
accatctcca aaaccaaagg cagaccgaag gctccacagg tgtacaccat tccacctccc    1020
aaggagcaga tggccaagga taaagtcagt ctgacctgca tgataacaga cttcttccct    1080
gaagacatta ctgtggagtg gcagtggaat gggcagccag cggagaacta caagaacact    1140
cagcccatca tggacacaga tggctcttac ttcgtctaca gcaagctcaa tgtgcagaag    1200
agcaactggg aggcaggaaa tactttcacc tgctctgtgt tacatgaggg cctgcacaac    1260
caccatactg agaagagcct ctcccactct cctggtaaat ga                       1302
```

<210> 29
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody

<400> 29

```
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                   10                  15

Val His Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
        35                  40                  45

Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
    50                  55                  60
```

```
Trp Ile Gly Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Met Asp Leu
                85                  90                  95

Lys Met Thr Ser Leu Thr Thr Gly Asp Thr Ala Arg Tyr Phe Cys Ala
            100                 105                 110

Arg Asn Trp Asn Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125

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

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
145                 150                 155                 160

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
                165                 170                 175

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

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

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
    210                 215                 220

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

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

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

Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
        275                 280                 285

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

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

Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
```

```
                325                 330                 335

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

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

Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
    370                 375                 380

Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
385                 390                 395                 400

Pro Ile Met Asn Thr Asn Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
                405                 410                 415

Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
            420                 425                 430

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

Ser Pro Gly Lys
    450
```

<210> 30
<211> 1359
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody

<400> 30

atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccactgtcag 60
tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120
acagcctctg gattctccct cagtagttat tggatgaact gggtccgcca ggctccaggg 180
gaggggctgg aatggatcgg aaccattgat tctggtggta ggacggacta cgcgagctgg 240
gcaaaaggcc gattcaccat ctccagaacc tcgactacga tggatctgaa aatgaccagt 300
ctgacgaccg gggacacggc ccgttatttc tgtgccagaa attggaactt gtggggccaa 360
ggcaccctcg tcaccgtctc gagcgcttct acaaagggcc catctgtcta tccactggcc 420
cctggatctg ctgcccaaac taactccatg gtgaccctgg gatgcctggt caagggctat 480

ttccctgagc cagtgacagt gacctggaac tctggatccc tgtccagcgg tgtgcacacc 540
ttcccagctg tcctgcagtc tgacctctac actctgagca gctcagtgac tgtcccctcc 600
agcacctggc ccagcgagac cgtcacctgc aacgttgccc acccggccag cagcaccaag 660
gtggacaaga aaattgtgcc cagggattgt ggttgtaagc cttgcatatg tacagtccca 720
gaagtatcat ctgtcttcat cttcccccca aagcccaagg atgtgctcac cattactctg 780
actcctaagg tcacgtgtgt tgtggtagac atcagcaagg atgatcccga ggtccagttc 840
agctggtttg tagatgatgt ggaggtgcac acagctcaga cgcaaccccg ggaggagcag 900
ttcaacagca ctttccgctc agtcagtgaa cttcccatca tgcaccagga ctggctcaat 960
ggcaaggagt tcaaatgcag ggtcaacagt gcagctttcc ctgcccccat cgagaaaacc 1020
atctccaaaa ccaaaggcag accgaaggct ccacaggtgt acaccattcc acctcccaag 1080
gagcagatgg ccaaggataa agtcagtctg acctgcatga taacagactt cttccctgaa 1140
gacattactg tggagtggca gtggaatggg cagccagcgg agaactacaa gaacactcag 1200
cccatcatgg acacagatgg ctcttacttc gtctacagca agctcaatgt gcagaagagc 1260
aactgggagg caggaaatac tttcacctgc tctgtgttac atgagggcct gcacaaccac 1320
catactgaga agagcctctc ccactctcct ggtaaatga 1359

<210> 31
<211> 213
<212> PRT
<213> Mus musculus

<400> 31

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

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

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

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

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

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> 32
<211> 642
<212> DNA
<213> Mus musculus

<400> 32

caaattgttc tcacccagtc tccaacaatc gtgtctgcat ctccagggga gaaggtcacc 60
ctaatctgca gtgccagttc aagtgtaagt ttcgtggact ggttccagca gaagccaggc 120
acttctccca aacgctggat ttacagaaca tccaacctgg gttttggagt ccctgctcgc 180
ttcagtggcg gtggatctgg gacctctcac tctctcacaa tcagccgaat ggaggctgaa 240
gatgctgcca cttattactg ccagcaaagg agtacttacc cacccacgtt cggtgctggg 300
accaagctgg aactgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 360
agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480
agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg 540
accaaggacg agtatgaacg acataacagc tatacctgtg aggccactca caagacatca 600
acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag 642

<210> 33
<211> 235
<212> PRT
<213> Mus musculus

<400> 33

```
Met His Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1               5                   10                  15

Val Ile Val Ser Arg Gly Gln Ile Val Leu Thr Gln Ser Pro Thr Ile
            20                  25                  30

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

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

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

Ala Arg Phe Ser Gly Gly Gly Ser Gly Thr Ser His Ser Leu Thr Ile
                85                  90                  95

Ser Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg
            100                 105                 110

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

Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
    130                 135                 140

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
                165                 170                 175

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
        195                 200                 205

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
    210                 215                 220

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230                 235
```

<210> 34
<211> 708

<212> DNA
<213> Mus musculus

<400> 34

atgcattttc aagtgcagat tttcagcttc ctgctaatca gtgcctcagt catagtgtcc 60

agagggcaaa ttgttctcac ccagtctcca acaatcgtgt ctgcatctcc aggggagaag 120

gtcaccctaa tctgcagtgc cagttcaagt gtaagtttcg tggactggtt ccagcagaag 180

ccaggcactt ctcccaaacg ctggatttac agaacatcca acctgggttt tggagtccct 240

gctcgcttca gtggcggtgg atctgggacc tctcactctc tcacaatcag ccgaatggag 300

gctgaagatg ctgccactta ttactgccag caaaggagta cttacccacc cacgttcggt 360

gctgggacca agctggaact gaaacgggct gatgctgcac caactgtatc catcttccca 420

ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 480

taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 540

ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 600

acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660

acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 708

<210> 35
<211> 449
<212> PRT
<213> Mus musculus

<400> 35

```
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> 36
<211> 1350
<212> DNA
<213> Mus musculus

<400> 36

caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cacccatcag ggaagaatct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataacccag tcctgaagag ccgactgact atctccaagg atacctccaa cagccaggta 240

ttcctcaaga tcgccaatgt ggacactgca gatactgcca catactactg tgctcgaata 300

gaggactttg attacgacga ggagtattat gctatggact actggggtca aggaacctca 360

gtcatcgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct 420

gctgcccaaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag 480

ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct 540

gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg 600

cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag 660

aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca 720

tctgtcttca tcttcccccc aaagcccaag gatgtgctca ccattactct gactcctaag 780

gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt 840

gtagatgatg tggaggtgca cacagctcag acgcaacccc gggaggagca gttcaacagc 900

actttccgct cagtcagtga acttcccatc atgcaccagg actggctcaa tggcaaggag 960

ttcaaatgca gggtcaacag tgcagctttc cctgccccca tcgagaaaac catctccaaa 1020

accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg 1080

gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact 1140

gtggagtggc agtggaatgg gcagccagcg gagaactaca agaacactca gcccatcatg 1200

gacacagatg gctcttactt cgtctacagc aagctcaatg tgcagaagag caactgggag 1260

gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag 1320

aagagcctct cccactctcc tggtaaatga 1350

<210> 37
<211> 468
<212> PRT
<213> Mus musculus

<400> 37

```
Met Gly Arg Leu Thr Ser Ser Phe Leu Leu Leu Ile Val Pro Ala Tyr
1               5                   10                  15

Val Leu Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln
            20                  25                  30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
        35                  40                  45

Ser Thr Ser Gly Met Gly Val Gly Trp Ile Arg His Pro Ser Gly Lys
    50                  55                  60

Asn Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr
65                  70                  75                  80

Asn Pro Val Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Asn
                85                  90                  95

Ser Gln Val Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Thr Ala
            100                 105                 110

Thr Tyr Tyr Cys Ala Arg Ile Glu Asp Phe Asp Tyr Asp Glu Glu Tyr
        115                 120                 125

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Ile Val Ser Ser
    130                 135                 140

Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
145                 150                 155                 160

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
                165                 170                 175

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
            180                 185                 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
        195                 200                 205
```

```
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
    210                 215                 220

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
225                 230                 235                 240

Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
                245                 250                 255

Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
            260                 265                 270

Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
        275                 280                 285

Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
    290                 295                 300

Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320

Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
        355                 360                 365

Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
    370                 375                 380

Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
385                 390                 395                 400

Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
                405                 410                 415

Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
            420                 425                 430

Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
        435                 440                 445

Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
    450                 455                 460
```

Ser Pro Gly Lys
465

<210> 38
<211> 1407
<212> DNA
<213> Mus musculus

<400> 38

atgggcaggc ttacttcttc attcctgcta ctgattgtcc ctgcatatgt cctgtcccag 60

gttactctga aagagtctgg ccctgggata ttgcagccct cccagaccct cagtctgact 120

tgttctttct ctgggttttc actgagcact tctggtatgg gtgtaggctg gattcgtcac 180

ccatcaggga agaatctgga gtggctggca cacatttggt gggatgatgt caagcgctat 240

aacccagtcc tgaagagccg actgactatc tccaaggata cctccaacag ccaggtattc 300

ctcaagatcg ccaatgtgga cactgcagat actgccacat actactgtgc tcgaatagag 360

gactttgatt acgacgagga gtattatgct atggactact ggggtcaagg aacctcagtc 420

atcgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct 480

gcccaaacta actccatggt gaccctggga tgcctggtca agggctattt ccctgagcca 540

gtgacagtga cctggaactc tggatccctg tccagcggtg tgcacacctt cccagctgtc 600

ctgcagtctg acctctacac tctgagcagc tcagtgactg tcccctccag cacctggccc 660

agcgagaccg tcacctgcaa cgttgcccac ccggccagca gcaccaaggt ggacaagaaa 720

attgtgccca gggattgtgg ttgtaagcct tgcatatgta cagtcccaga agtatcatct 780

gtcttcatct tccccccaaa gcccaaggat gtgctcacca ttactctgac tcctaaggtc 840

acgtgtgttg tggtagacat cagcaaggat gatcccgagg tccagttcag ctggtttgta 900

gatgatgtgg aggtgcacac agctcagacg caaccccggg aggagcagtt caacagcact 960

ttccgctcag tcagtgaact tcccatcatg caccaggact ggctcaatgg caaggagttc 1020

aaatgcaggg tcaacagtgc agctttccct gcccccatcg agaaaaccat ctccaaaacc 1080

aaaggcagac cgaaggctcc acaggtgtac accattccac ctcccaagga gcagatggcc 1140

aaggataaag tcagtctgac ctgcatgata acagacttct tccctgaaga cattactgtg 1200

gagtggcagt ggaatgggca gccagcggag aactacaaga acactcagcc catcatggac 1260

acagatggct cttacttcgt ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca 1320

ggaaatactt tcacctgctc tgtgttacat gagggcctgc acaaccacca tactgagaag 1380

agcctctccc actctcctgg taaatga 1407

<210> 39

<211> 5
<212> PRT
<213> Mus musculus

<400> 39

```
Asp His Tyr Met Ser
1               5
```

<210> 40
<211> 17
<212> PRT
<213> Mus musculus

<400> 40

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

Gly
```

<210> 41
<211> 10
<212> PRT
<213> Mus musculus

<400> 41

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

<210> 42
<211> 11
<212> PRT
<213> Mus musculus

<400> 42

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

<210> 43
<211> 7
<212> PRT
<213> Mus musculus

<400> 43

```
Gly Ser Ser Asn Leu Glu Asp
1               5
```

<210> 44

<211> 9
<212> PRT
<213> Mus musculus

<400> 44

```
Leu Gln His Ser Tyr Leu Pro Tyr Thr
1               5
```

<210> 45
<211> 5
<212> PRT
<213> Mus musculus

<400> 45

```
Asp Cys Tyr Met Asn
1               5
```

<210> 46
<211> 17
<212> PRT
<213> Mus musculus

<400> 46

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


Gly
```

<210> 47
<211> 16
<212> PRT
<213> Mus musculus

<400> 47

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

<210> 48
<211> 15
<212> PRT
<213> Mus musculus

<400> 48

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

<210> 49

<211> 7
<212> PRT
<213> Mus musculus

<400> 49

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

<210> 50
<211> 9
<212> PRT
<213> Mus musculus

<400> 50

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

<210> 51
<211> 5
<212> PRT
<213> Rabbit-Mouse Chimera

<400> 51

```
Ser Tyr Trp Met Asn
1               5
```

<210> 52
<211> 16
<212> PRT
<213> Rabbit-Mouse Chimera

<400> 52

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

<210> 53
<211> 4
<212> PRT
<213> Rabbit-Mouse Chimera

<400> 53

```
Asn Trp Asn Leu
1
```

<210> 54
<211> 13
<212> PRT
<213> Rabbit-Mouse Chimera

<400> 54

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

<210> 55
<211> 7
<212> PRT
<213> Rabbit-Mouse Chimera

<400> 55

```
Asp Ala Ser Asp Leu Ala Ser
1               5
```

<210> 56
<211> 10
<212> PRT
<213> Rabbit-Mouse Chimera

<400> 56

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

<210> 57
<211> 7
<212> PRT
<213> Mus musculus

<400> 57

```
Thr Ser Gly Met Gly Val Gly
1               5
```

<210> 58
<211> 16
<212> PRT
<213> Mus musculus

<400> 58

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

<210> 59
<211> 14
<212> PRT
<213> Mus musculus

<400> 59

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

<210> 60
<211> 10
<212> PRT
<213> Mus musculus

<400> 60

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

<210> 61
<211> 7
<212> PRT
<213> Mus musculus

<400> 61

```
Arg Thr Ser Asn Leu Gly Phe
1               5
```

<210> 62
<211> 9
<212> PRT
<213> Mus musculus

<400> 62

```
Gln Gln Arg Ser Thr Tyr Pro Pro Thr
1               5
```

<210> 63
<211> 20
<212> PRT
<213> Homo sapiens

<400> 63

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

Trp Arg Pro Ser
            20
```

<210> 64
<211> 20
<212> PRT
<213> Homo sapiens

<400> 64

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

Arg Pro Ser Gly
            20
```

<210> 65
<211> 20
<212> PRT
<213> Homo sapiens

<400> 65

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

Pro Ser Gly Pro
            20
```

<210> 66
<211> 20
<212> PRT
<213> Homo sapiens

<400> 66

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

Ser Gly Pro Asp
            20
```

<210> 67
<211> 20
<212> PRT
<213> Homo sapiens

<400> 67

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

Gly Pro Asp Phe
            20
```

<210> 68
<211> 20
<212> PRT
<213> Homo sapiens

<400> 68

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

Pro Asp Phe Arg
            20
```

<210> 69
<211> 20
<212> PRT
<213> Homo sapiens

<400> 69

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

Asp Phe Arg Cys
            20
```

<210> 70
<211> 14
<212> PRT
<213> Homo sapiens

<400> 70

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

<210> 71
<211> 7
<212> PRT
<213> Homo sapiens

<400> 71

```
Leu Val Ala Ser Cys Lys Cys

    1               5
```

<210> 72
<211> 8
<212> PRT
<213> Homo sapiens

<400> 72

```
Cys Arg Glu Leu His Phe Thr Arg
1               5
```

<210> 73
<211> 7

<212> PRT
<213> Homo sapiens

<400> 73

```
Cys Ile Pro Asp Arg Tyr Arg
1               5
```

<210> 74
<211> 399
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 74

```
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc      60

acatttgctc aagttctgac ccagagtcca agcagtctct ccgccagcgt aggcgatcgt     120

gtgactatta cctgtcaatc tagtcagagc gtgtatgata acaattggct ggcgtggtac     180

cagcaaaaac cgggcaaagc ccccgaagctg ctcatctatg acgcgtccga tctggctagc    240

ggtgtgccaa gccgtttcag tggcagtggc agcggtactg actttaccct cacaatttcg     300

tctctccagc cggaagattt cgccacttac tattgtcaag gtgcttacaa cgatgtgatt     360

tatgccttcg gtcagggcac taaagtagaa atcaaacgt                            399
```

<210> 75
<211> 133
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 75

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

Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Ser Pro Ser Ser
            20                  25                  30

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

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

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

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

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

Gln Gly Ala Tyr Asn Asp Val Ile Tyr Ala Phe Gly Gln Gly Thr Lys
        115                 120                 125

Val Glu Ile Lys Arg
    130
```

<210> 76
<211> 393
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 76

```
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccactgtgag        60

gtgcagctgt tggagtctgg aggcgggctt gtccagcctg gagggagcct gcgtctctct       120

tgtgcagcaa gcggcttcag cttatcctct tactggatga attgggtgcg gcaggcacct       180

gggaagggcc tggagtgggt gggcaccatt gattccggag gccgtacaga ctacgcgtct       240

tgggcaaagg gccgtttcac catttcccgc gacaactcca aaaataccat gtacctccag       300

atgaactctc tccgcgcaga ggacacagca cgttattact gtgcacgcaa ctggaatctg       360


tggggtcaag gtactcttgt aacagtctcg agc                                    393
```

<210> 77
<211> 131
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 77

```
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                   10                  15

Val His Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu
        35                  40                  45

Ser Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

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

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

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

Tyr Cys Ala Arg Asn Trp Asn Leu Trp Gly Gln Gly Thr Leu Val Thr
        115                 120                 125

Val Ser Ser
    130
```

<210> 78
<211> 11
<212> PRT
<213> Mus musculus

<400> 78

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

<210> 79
<211> 7
<212> PRT
<213> Mus musculus

<400> 79

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

<210> 80
<211> 9

<212> PRT
<213> Mus musculus

<400> 80

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

<210> 81
<211> 11
<212> PRT
<213> Mus musculus

<400> 81

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

<210> 82
<211> 24
<212> PRT
<213> Rattus norvegicus

<400> 82

```
Gln Gly Trp Gln Ala Phe Lys Asn Asp Ala Thr Glu Ile Ile Pro Gly
1               5                   10                  15

Leu Arg Glu Tyr Pro Glu Pro Pro
            20
```

<210> 83
<211> 20
<212> PRT
<213> Rattus norvegicus

<400> 83

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

Leu Glu Asn Asn
            20
```

<210> 84
<211> 20
<212> PRT
<213> Rattus norvegicus

<400> 84

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


Glu Asn Gly Gly
            20
```

<210> 85
<211> 20
<212> PRT
<213> Rattus norvegicus

<400> 85

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


Ser Glu Tyr Ser
            20
```

<210> 86
<211> 14
<212> PRT
<213> Rattus norvegicus

<400> 86

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

<210> 87
<211> 25
<212> PRT
<213> Rattus norvegicus

<400> 87

```
Cys Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro Ser Arg
1               5                   10                  15


Ser Ala Lys Pro Val Thr Glu Leu Val
            20                  25
```

<210> 88
<211> 23
<212> PRT
<213> Rattus norvegicus

<400> 88

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

Gly Pro Arg Ala Arg Leu Leu
20

<210> 89
<211> 25
<212> PRT
<213> Rattus norvegicus

<400> 89

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

Trp Arg Pro Asn Gly Pro Asp Phe Arg
20 25

<210> 90
<211> 20
<212> PRT
<213> Rattus norvegicus

<400> 90

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

Ser Arg Lys Val
20

<210> 91
<211> 16
<212> PRT
<213> Rattus norvegicus

<400> 91

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

<210> 92
<211> 23
<212> PRT
<213> Rattus norvegicus

<400> 92

Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu Leu Lys Asp Phe Gly
1 5 10 15

Pro Glu Thr Ala Arg Pro Gln
20

<210> 93

<211> 16
<212> PRT
<213> Rattus norvegicus

<400> 93

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

<210> 94
<211> 24
<212> PRT
<213> Rattus norvegicus

<400> 94

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

Arg Lys Pro Arg Pro Arg Ala Arg
            20
```

<210> 95
<211> 23
<212> PRT
<213> Rattus norvegicus

<400> 95

```
Lys Gly Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln
1               5                   10                  15

Ala Glu Leu Glu Asn Ala Tyr
            20
```

<210> 96
<211> 18
<212> PRT
<213> Rattus norvegicus

<400> 96

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

Phe Arg
```

<210> 97
<211> 22
<212> PRT
<213> Rattus norvegicus

<400> 97

```
Lys Trp Trp Arg Pro Asn Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg
1               5                   10                  15


Tyr Arg Ala Gln Arg Val
            20
```

<210> 98
<211> 213
<212> PRT
<213> Rattus norvegicus

<400> 98

```
Met Gln Leu Ser Leu Ala Pro Cys Leu Ala Cys Leu Leu Val His Ala
1               5                   10                  15

Ala Phe Val Ala Val Glu Ser Gln Gly Trp Gln Ala Phe Lys Asn Asp
            20                  25                  30

Ala Thr Glu Ile Ile Pro Gly Leu Arg Glu Tyr Pro Glu Pro Pro Gln
        35                  40                  45

Glu Leu Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
    50                  55                  60

Pro Pro His His Pro Tyr Asp Thr Lys Asp Val Ser Glu Tyr Ser Cys
65                  70                  75                  80

Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro Cys Arg Ser
                85                  90                  95

Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala
            100                 105                 110

Arg Leu Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn
        115                 120                 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
    130                 135                 140

Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg
145                 150                 155                 160

Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln
                165                 170                 175

Ser Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly
            180                 185                 190

Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu
        195                 200                 205

Leu Glu Asn Ala Tyr
    210
```

<210> 99
<211> 7
<212> PRT
<213> Mus musculus

<400> 99

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

<210> 100
<211> 9
<212> PRT
<213> Mus musculus

<400> 100

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

<210> 101
<211> 11
<212> PRT
<213> Mus musculus

<400> 101

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

<210> 102
<211> 7
<212> PRT
<213> Mus musculus

<400> 102

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

<210> 103
<211> 9
<212> PRT
<213> Mus musculus

<400> 103

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

<210> 104
<211> 11
<212> PRT
<213> Mus musculus

<400> 104

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

<210> 105
<211> 7
<212> PRT
<213> Mus musculus

<400> 105

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

<210> 106
<211> 9
<212> PRT
<213> Mus musculus

<400> 106

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

<210> 107
<211> 11
<212> PRT
<213> Mus musculus

<400> 107

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

<210> 108
<211> 7
<212> PRT
<213> Mus musculus

<400> 108

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

<210> 109
<211> 9
<212> PRT
<213> Mus musculus

<400> 109

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

<210> 110
<211> 11
<212> PRT

<213> Mus musculus

<400> 110

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

<210> 111
<211> 7
<212> PRT
<213> Mus musculus

<400> 111

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

<210> 112
<211> 9
<212> PRT
<213> Mus musculus

<400> 112

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

<210> 113
<211> 11
<212> PRT
<213> Mus musculus

<400> 113

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

<210> 114
<211> 7
<212> PRT
<213> Mus musculus

<400> 114

```
Tyr Thr Ser Thr Leu Gln Ser
1               5
```

<210> 115
<211> 9
<212> PRT
<213> Mus musculus

<400> 115

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 116
<211> 12
<212> PRT
<213> Mus musculus

<400> 116

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

<210> 117
<211> 213
<212> PRT
<213> Mus musculus

<400> 117

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

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

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Thr Arg Val Glu Ala Glu
65                  70                  75                  80

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

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

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

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

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

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

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

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

Asn Arg Asn Glu Cys
    210
```

<210> 118
<211> 642
<212> DNA
<213> Mus musculus

<400> 118

```
caaattgttc tctcccagtc tccagcaatc ctgtctacat ctccagggga gaaggtcaca       60

atgacttgca gggccagctc aagtgtatat tacatgcact ggtaccagca gaagccagga      120

tcctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgttcgc      180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcaccagagt ggaggctgaa      240

gatgctgcca cttattactg ccagcagtgg agtagtgacc cactcacgtt cggtgctggg      300

accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc      360

agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc      420

aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac      480

agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg      540

accaaggacg agtatgaacg acataacagc tatacctgtg aggccactca caagacatca      600

acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag                         642
```

<210> 119
<211> 235
<212> PRT
<213> Mus musculus

<400> 119

```
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1               5                   10                  15


Val Ile Met Ser Arg Gly Gln Ile Val Leu Ser Gln Ser Pro Ala Ile
            20                  25                  30


Leu Ser Thr Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
        35                  40                  45


Ser Ser Val Tyr Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Ser Ser
    50                  55                  60


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


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


Thr Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
            100                 105                 110
```

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

Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
    130                 135                 140

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
                165                 170                 175

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
        195                 200                 205

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
    210                 215                 220

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230                 235
```

<210> 120
<211> 708
<212> DNA
<213> Mus musculus

<400> 120

atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcttcagt cattatgtcc 60
aggggacaaa ttgttctctc ccagtctcca gcaatcctgt ctacatctcc aggggagaag 120
gtcacaatga cttgcagggc cagctcaagt gtatattaca tgcactggta ccagcagaag 180
ccaggatcct cccccaaacc ctggatttat gccacatcca acctggcttc tggagtccct 240
gttcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcac cagagtggag 300
gctgaagatg ctgccactta ttactgccag cagtggagta gtgacccact cacgttcggt 360
gctgggacca agctggagct gaaacgggct gatgctgcac caactgtatc catcttccca 420
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 480
taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 540
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 600
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660
acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 708

<210> 121
<211> 445
<212> PRT
<213> Mus musculus

<400> 121

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

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

Phe Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala Pro Lys Phe
    50                  55                  60

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

Leu Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

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

Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser
        115                 120                 125

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
385                 390                 395                 400

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

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

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

<210> 122
<211> 1338
<212> DNA
<213> Mus musculus

<400> 122

```
gaggttcagg tgcagcagtc tgggccagaa cttgtgaagc caggggcctc agtcaagttg      60
tcctgcacag cttctggctt caacattaaa gactacttta tacactgggt gaagcagagg     120
cctgaacagg gcctggagtg gattggaagg cttgatcctg aggatggtga aagtgattat     180
gccccgaagt tccaggacaa ggccattatg acagcagaca catcatccaa cacagcctat     240

cttcagctca gaagcctgac atctgaggac actgccatct attattgtga gagagaggac     300
tacgatggta cctacacctt ttttccttac tggggccaag ggactctggt cactgtctct     360
gcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact     420
aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg     480
acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct     540
gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc     600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc     660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc     720
ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt     780
gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg     840
gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca     900
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg     960
gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga    1020
ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa    1080
gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag    1140
tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc    1200
tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact    1260
ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc    1320
cactctcctg gtaaatga                                                   1338
```

<210> 123
<211> 464
<212> PRT
<213> Mus musculus

<400> 123

```
Met Lys Cys Ser Trp Val Ile Phe Phe Leu Met Ala Val Val Thr Gly
1               5                   10                  15

Val Asn Ser Glu Val Gln Val Gln Gln Ser Gly Pro Glu 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 Phe Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala
65                  70                  75                  80
```

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

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

Tyr Tyr Cys Glu Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Phe Phe Pro
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr
    130                 135                 140

Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145                 150                 155                 160

Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
        195                 200                 205

Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
    210                 215                 220

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225                 230                 235                 240

Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
                245                 250                 255

Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
            260                 265                 270

Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
        275                 280                 285

Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
    290                 295                 300

Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305                 310                 315                 320

Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
                325                 330                 335
```

```
Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
            340                 345                 350

Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
        355                 360                 365

Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
    370                 375                 380

Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
385                 390                 395                 400

Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
                405                 410                 415

Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
            420                 425                 430

Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
        435                 440                 445

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

<210> 124
<211> 1395
<212> DNA
<213> Mus musculus

<400> 124

atgaaatgca gctgggtcat cttcttcctg atggcagtgg ttacaggggt caattcagag 60

gttcaggtgc agcagtctgg gccagaactt gtgaagccag gggcctcagt caagttgtcc 120

tgcacagctt ctggcttcaa cattaaagac tactttatac actgggtgaa gcagaggcct 180

gaacagggcc tggagtggat tggaaggctt gatcctgagg atggtgaaag tgattatgcc 240

ccgaagttcc aggacaaggc cattatgaca gcagacacat catccaacac agcctatctt 300

cagctcagaa gcctgacatc tgaggacact gccatctatt attgtgagag agaggactac 360

gatggtacct acaccttttt tccttactgg ggccaaggga ctctggtcac tgtctctgca 420

gccaaaacga caccccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac 480

tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 540

tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac 600

ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 660

acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg 720

gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780

cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg 840

gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag 900

gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 960

agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 1020

aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 1080

aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1140

agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 1200

aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1260

tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1320

acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380

tctcctggta aatga 1395

<210> 125
<211> 215
<212> PRT
<213> Mus musculus

<400> 125

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

Glu Lys Val Thr Ile Thr Cys Ser Val Ser Ser Thr Ile Ser Ser Asn
            20                  25                  30

His Leu His Trp Phe Gln Gln Lys Ser Asp Thr Ser Pro Lys Pro Trp
        35                  40                  45

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

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65                  70                  75                  80

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

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

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

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

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

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

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

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

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

<210> 126
<211> 648
<212> DNA
<213> Mus musculus

<400> 126

```
gaaattgtgc tcacccagtc tccagcactc atggctgcat ctccggggga gaaggtcacc        60
atcacctgca gtgtcagttc aactataagt tccaaccact tgcactggtt ccagcagaag       120
tcagacacct cccccaaacc ctggatttat ggcacatcca acctggcttc tggagtccct       180
gttcgcttca gtggcagtgg atctgggacc tcttattctc tcacaatcag cagcatggag       240
gctgaggatg ctgccactta ttactgtcaa cagtggagta gttacccact cacgttcggc       300
gctgggacca agctggagct gagacgggct gatgctgcac caactgtatc catcttccca       360
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc       420
taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc       480
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc       540
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag       600
acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag                    648
```

<210> 127
<211> 237
<212> PRT
<213> Mus musculus

<400> 127

```
Met Asp Phe His Val Gln Ile Phe Ser Phe Met Leu Ile Ser Val Thr
1               5                   10                  15

Val Ile Leu Ser Ser Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Leu
            20                  25                  30
```

```
Met Ala Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Val Ser
        35                  40                  45

Ser Thr Ile Ser Ser Asn His Leu His Trp Phe Gln Gln Lys Ser Asp
    50                  55                  60

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

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

Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
            100                 105                 110

Gln Trp Ser Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu
        115                 120                 125

Leu Arg Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
    130                 135                 140

Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
145                 150                 155                 160

Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
                165                 170                 175

Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
            180                 185                 190

Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
        195                 200                 205

Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser
    210                 215                 220

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

<210> 128
<211> 714
<212> DNA
<213> Mus musculus

<400> 128

atggattttc atgtgcagat tttcagcttc atgctaatca gtgtcacagt cattttgtcc 60

agtggagaaa ttgtgctcac ccagtctcca gcactcatgg ctgcatctcc gggggagaag 120

gtcaccatca cctgcagtgt cagttcaact ataagttcca accacttgca ctggttccag 180

cagaagtcag acacctcccc caaaccctgg atttatggca catccaacct ggcttctgga 240

gtccctgttc gcttcagtgg cagtggatct gggacctctt attctctcac aatcagcagc 300

atggaggctg aggatgctgc cacttattac tgtcaacagt ggagtagtta cccactcacg 360

ttcggcgctg ggaccaagct ggagctgaga cgggctgatg ctgcaccaac tgtatccatc 420

ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac 480

aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat 540

ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc 600

accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact 660

cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg ttag 714

<210> 129
<211> 449
<212> PRT
<213> Mus musculus

<400> 129

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
```

```
            420                 425                 430

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

Lys
```

<210> 130
<211> 1350
<212> DNA
<213> Mus musculus

<400> 130

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

<210> 131
<211> 468
<212> PRT
<213> Mus musculus

<400> 131

```
Met Lys Cys Ser Trp Val Ile Phe Phe Leu Met Ala Val Val Thr Gly
1               5                   10                  15

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

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

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

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

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

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

Tyr Tyr Cys Ser Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr
        115                 120                 125

Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Ile Thr Val Ser Ser
    130                 135                 140

Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
145                 150                 155                 160

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
                165                 170                 175

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
            180                 185                 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
        195                 200                 205

Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
    210                 215                 220

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
225                 230                 235                 240
```

```
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
                245                 250                 255

Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
            260                 265                 270

Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
        275                 280                 285

Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
    290                 295                 300

Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320

Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
        355                 360                 365

Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
    370                 375                 380

Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
385                 390                 395                 400

Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
                405                 410                 415

Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
            420                 425                 430

Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
        435                 440                 445

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

Ser Pro Gly Lys
465
```

<210> 132
<211> 1407

<212> DNA
<213> Mus musculus

<400> 132

atgaaatgca gctgggtcat cttcttcctg atggcagtgg ttacaggggt caattcagag 60

gttcagctgc agcagtctgg ggctgaactt gtgaggccag gggccttagt caagttgtcc 120

tgcacagctt ctgacttcaa cattaaagac ttctatctac actggatgag gcagcggcct 180

gaacagggcc tggactggat tggaaggatt gatcctgaga atggtgatac tttatatgac 240

ccgaagttcc aggacaaggc cactcttaca acagacacat cctccaacac agcctacctg 300

cagctcagcg gcctgacatc tgagaccact gccgtctatt actgttctag agaggcggat 360

tatttccacg atggtacctc ctactggtac ttcgatgtct ggggcgcagg gaccacaatc 420

accgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct 480

gcccaaacta actccatggt gaccctggga tgcctggtca agggctattt ccctgagcca 540

gtgacagtga cctggaactc tggatccctg tccagcggtg tgcacacctt cccagctgtc 600

ctgcagtctg acctctacac tctgagcagc tcagtgactg tcccctccag cacctggccc 660

agcgagaccg tcacctgcaa cgttgcccac ccggccagca gcaccaaggt ggacaagaaa 720

attgtgccca gggattgtgg ttgtaagcct tgcatatgta cagtcccaga agtatcatct 780

gtcttcatct tccccccaaa gcccaaggat gtgctcacca ttactctgac tcctaaggtc 840

acgtgtgttg tggtagacat cagcaaggat gatcccgagg tccagttcag ctggtttgta 900

gatgatgtgg aggtgcacac agctcagacg caaccccggg aggagcagtt caacagcact 960

ttccgctcag tcagtgaact tcccatcatg caccaggact ggctcaatgg caaggagttc 1020

aaatgcaggg tcaacagtgc agctttccct gcccccatcg agaaaaccat ctccaaaacc 1080

aaaggcagac cgaaggctcc acaggtgtac accattccac ctcccaagga gcagatggcc 1140

aaggataaag tcagtctgac ctgcatgata acagacttct tccctgaaga cattactgtg 1200

gagtggcagt ggaatgggca gccagcggag aactacaaga acactcagcc catcatggac 1260

acagatggct cttacttcat ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca 1320

ggaaatactt tcacctgctc tgtgttacat gagggcctgc acaaccacca tactgagaag 1380

agcctctccc actctcctgg taaatga 1407

<210> 133
<211> 214
<212> PRT
<213> Mus musculus

<400> 133

```
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> 134
<211> 645
<212> DNA
<213> Mus musculus

<400> 134

gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60

atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240

gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300

gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 135
<211> 234
<212> PRT
<213> Mus musculus

<400> 135

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

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

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

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

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

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

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

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
        115                 120                 125

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr


            180                 185                 190

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 136
<211> 705
<212> DNA
<213> Mus musculus

<400> 136

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt       60
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc      120
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca      180
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca      240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa      300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg      360
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca      420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac      480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg      540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg      600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca      660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                      705
```

<210> 137
<211> 447
<212> PRT
<213> Mus musculus

<400> 137

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
```

```
305                 310                 315                 320

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

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

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

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

Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385                 390                 395                 400

Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
                405                 410                 415

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

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

<210> 138
<211> 1344
<212> DNA
<213> Mus musculus

<400> 138

gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac 120

caaggaaaga ccctagagtg gataggagaa attaatccta acagtggtgg tgctggctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300

tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360

gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900

cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960

tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320

ctctcccact ctcctggtaa atga 1344

<210> 139
<211> 466
<212> PRT
<213> Mus musculus

<400> 139

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

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30

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

Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu
    50                  55                  60

Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
                85                  90                  95

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

Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115                 120                 125

Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140
```

```
Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145                 150                 155                 160

Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195                 200                 205

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210                 215                 220

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225                 230                 235                 240

Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245                 250                 255

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

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275                 280                 285

Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290                 295                 300

Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
        355                 360                 365

Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
    370                 375                 380

Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385                 390                 395                 400
```

```
Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
                405                 410                 415

Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
            420                 425                 430

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
        435                 440                 445

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

Gly Lys
465
```

<210> 140
<211> 1401
<212> DNA
<213> Mus musculus

<400> 140

```
atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag      60
gtccaactgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc     120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa     180
ggaaagaccc tagagtggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac     240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg     300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac     360
gatgatatct acgacgactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc     420
tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa     480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca     540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag     600
tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag     660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg     720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc     780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt     840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat     900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc     960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc    1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc    1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat    1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg    1200

cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat    1260
ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat    1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc    1380
tcccactctc ctggtaaatg a                                               1401
```

<210> 141
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 141

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

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

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

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

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

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

Thr Phe Gly Gly 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> 142
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 142

```
gacatccaga tgacccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc        60
ataacatgta gagcatctca agatatttcc aactatttga attggtacca acaaaaaccc       120
ggcaaagcac ctaaactcct catttactat acatcaagac tcctctccgg cgttccatca       180
cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca       240
gaagattttg caacctatta ctgtcaacaa ggcgatacac tcccatacac attcggcggc       300
ggcacaaaag ttgaaattaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca       360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat       420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag       480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg       540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc       600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                          642
```

<210> 143
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 143

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

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

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

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

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

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

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

Gly Asp Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

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

<210> 144
<211> 708

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 144

atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc 60

agatgtgaca tccagatgac ccagtctcca tcctccctct ccgcatccgt aggcgaccgc 120

gtaaccataa catgtagagc atctcaagat atttccaact atttgaattg gtaccaacaa 180

aaacccggca aagcacctaa actcctcatt tactatacat caagactcct ctccggcgtt 240

ccatcacgat tctcaggctc cggctccggc acagatttca cactcactat ttcctccctc 300

caaccagaag attttgcaac ctattactgt caacaaggcg atacactccc atacacattc 360

ggcggcggca caaaagttga aattaaacgt acggtggctg caccatctgt cttcatcttc 420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgt 708

<210> 145
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 145

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

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

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

Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
```

```
        50                  55                  60

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

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

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

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

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

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

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

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

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

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
    210                 215                 220

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys
```

<210> 146
<211> 1347
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 146

gaggtgcagc tggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgttaaagtt 60

tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg 120

ccaggacaag gattggaatg gatgggcgaa attaacccta atagtggagg agcaggctac 180

aatcaaaaat tcaaagggag agttacaatg acaacagaca caagcacttc aacagcatat 240

atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg 300

tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc 360

gtctctagtg cctccaccaa gggcccatcg gtcttccccc tggcgccctg ctccaggagc 420

acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 480

acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 540

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag caacttcggc 600

acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 660

gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 720

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 780

gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 840

gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 900

acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 960

tacaagtgca aggtctccaa caaaggcctc ccagccccca tcgagaaaac catctccaaa 1020

accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1080

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1140

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1200

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1260

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1320

aagagcctct ccctgtctcc gggtaaa 1347

<210> 147
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 147

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

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

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

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

```
Glu Trp Met Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80

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

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

Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115                 120                 125

Phe Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
145                 150                 155                 160

Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205

Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
    210                 215                 220

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
225                 230                 235                 240

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
                245                 250                 255

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
```

```
                325                 330                 335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly Lys
465
```

<210> 148
<211> 1404
<212> DNA
<213> Mus musculus

<400> 148

atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60

gtgcagctgg tgcagagcgg cgccgaggta aaaaaaccag gagcaagcgt taaagtttct 120

tgtaaagcaa gcggatatac atttacagat tacaacatgc attgggtaag acaagcgcca 180

ggacaaggat tggaatggat gggcgaaatt aaccctaata gtggaggagc aggctacaat 240

caaaaattca aagggagagt tacaatgaca acagacacaa gcacttcaac agcatatatg 300

gaactgcgat cacttagaag cgacgataca gctgtatact attgcgcacg acttgggtat 360

gatgatatat atgatgactg gtatttcgat gtttggggcc agggaacaac agttaccgtc 420

tctagtgcct ccaccaaggg cccatcggtc ttccccctgg cgccctgctc caggagcacc 480

tccgagagca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540

gtgtcgtgga actcaggcgc tctgaccagc ggcgtgcaca ccttcccagc tgtcctacag 600

tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcaa cttcggcacc 660

cagacctaca cctgcaacgt agatcacaag cccagcaaca ccaaggtgga caagacagtt 720

gagcgcaaat gttgtgtcga gtgcccaccg tgcccagcac cacctgtggc aggaccgtca 780

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc 840

acgtgcgtgg tggtggacgt gagccacgaa gaccccgagg tccagttcaa ctggtacgtg 900

gacggcgtgg aggtgcataa tgccaagaca aagccacggg aggagcagtt caacagcacg 960

ttccgtgtgg tcagcgtcct caccgttgtg caccaggact ggctgaacgg caaggagtac 1020

aagtgcaagg tctccaacaa aggcctccca gcccccatcg agaaaaccat ctccaaaacc 1080

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc 1140

aagaaccagg tcagcctgac ctgcctggtc aaaggcttct accccagcga catcgccgtg 1200

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacacctcc catgctggac 1260

tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag 1320

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag 1380

agcctctccc tgtctccggg taaa 1404

<210> 149
<211> 214
<212> PRT
<213> Mus musculus

<400> 149

```
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> 150
<211> 645
<212> DNA
<213> Mus musculus

<400> 150

```
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc       60
atcagttgca gggcaagtca ggacattagc aattatttaa actggtttca gcagaaacca      120
gatggaactc ttaaactcct gatcttctac acatcaagat tacactcagg agttccatca      180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa      240
gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcgggggg      300
gggaccaagc tggaaataag acgggctgat gctgcaccaa ctgtatccat cttcccacca      360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac      420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg      480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg      540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca      600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                      645
```

<210> 151
<211> 234
<212> PRT
<213> Mus musculus

<400> 151

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

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

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

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

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

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

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

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Arg Arg
        115                 120                 125

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 152
<211> 705
<212> DNA
<213> Mus musculus

<400> 152

atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 120

atcagttgca gggcaagtca ggacattagc aattatttaa actggtttca gcagaaacca 180

gatggaactc ttaaactcct gatcttctac acatcaagat tacactcagg agttccatca 240

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 300

gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcgggggg 360

gggaccaagc tggaaataag acgggctgat gctgcaccaa ctgtatccat cttcccacca 420

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 705

<210> 153
<211> 447
<212> PRT
<213> Mus musculus

<400> 153

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            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> 154
<211> 1344
<212> DNA
<213> Mus musculus

<400> 154

```
gaggtccagc tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg      60
tcctgcaagg cttctggata cacattcact gactacaaca tgcactgggt gaaacagaac     120
caaggaaaga gcctagagtg gataggagaa attaatccta acagtggtgg tagtggctac     180
aaccaaaagt tcaaaggcaa ggccacattg actgtagaca agtcttccag cacagcctac     240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattggtc     300
tacgatggca gctacgagga ctggtacttc gatgtctggg gcgcagggac cacggtcacc     360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc     420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg     480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg     540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc     600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt     660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc     720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg     780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat     840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc     900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa     960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa    1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag    1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag    1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca    1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga    1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc    1320
ctctcccact ctcctggtaa atga                                           1344
```

<210> 155
<211> 466
<212> PRT
<213> Mus musculus

<400> 155

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

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30

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

Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Ser Leu
    50                  55                  60

Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85                  90                  95

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

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

Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140

Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145                 150                 155                 160

Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195                 200                 205

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210                 215                 220

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
```

```
225                 230                 235                 240

Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245                 250                 255

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

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275                 280                 285

Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290                 295                 300

Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
        355                 360                 365

Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
    370                 375                 380

Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385                 390                 395                 400

Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
                405                 410                 415

Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
            420                 425                 430

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
        435                 440                 445

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

Gly Lys
465
```

<210> 156
<211> 1401
<212> DNA
<213> Mus musculus

<400> 156

atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60

gtccagctgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120

tgcaaggctt ctggatacac attcactgac tacaacatgc actgggtgaa acagaaccaa 180

ggaaagagcc tagagtggat aggagaaatt aatcctaaca gtggtggtag tggctacaac 240

caaaagttca aaggcaaggc cacattgact gtagacaagt cttccagcac agcctacatg 300

gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attggtctac 360

gatggcagct acgaggactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420

tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480

actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540

gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600

tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 660

accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720

cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780

atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840

gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900

gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960

tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020

agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080

agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140

aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200

cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260

ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320

actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380

tcccactctc ctggtaaatg a 1401

<210> 157
<211> 214
<212> PRT
<213> Mus musculus

<400> 157

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

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

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

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

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

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            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> 158
<211> 642

<212> DNA
<213> Mus musculus

<400> 158

```
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc      60
atctgttgca gggcaagtca ggtcattacc aattatttat actggtatca gcagaaacca     120
gatggaactt ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca     180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggaacag     240

gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg     300
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca     360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac     420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg     480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg     540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca     600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt                        642
```

<210> 159
<211> 234
<212> PRT
<213> Mus musculus

<400> 159

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

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

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

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

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

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

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

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
        115                 120                 125

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 160
<211> 702

<212> DNA
<213> Mus musculus

<400> 160

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt      60

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc     120

atctgttgca gggcaagtca ggtcattacc aattatttat actggtatca gcagaaacca     180

gatggaactt ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca     240

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggaacag     300

gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg     360

gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca     420

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac     480

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg     540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg     600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca     660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt                        702
```

<210> 161
<211> 447
<212> PRT
<213> Mus musculus

<400> 161

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385                 390                 395                 400

Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
                405                 410                 415

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

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

<210> 162
<211> 1341
<212> DNA
<213> Mus musculus

<400> 162

gaggtccagc tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact gactacaaca tgcactggat gaagcagaac 120
caaggaaaga gcctagaatg gataggagaa attaatccta acagtggtgg tgctggctac 180
aaccagcagt tcaaaggcaa ggccacattg actgtagaca agtcctccag gacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tacgttggta attacgagga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcctggtaa a 1341

<210> 163
<211> 466
<212> PRT
<213> Mus musculus

<400> 163

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

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30

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

Thr Asp Tyr Asn Met His Trp Met Lys Gln Asn Gln Gly Lys Ser Leu
    50                  55                  60

Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80

Gln Gln Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg
                85                  90                  95

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

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

Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
```

```
    130                 135                 140

Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145                 150                 155                 160

Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195                 200                 205

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210                 215                 220

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225                 230                 235                 240

Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245                 250                 255

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

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275                 280                 285

Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290                 295                 300

Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
        355                 360                 365

Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
    370                 375                 380

Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385                 390                 395                 400
```

```
Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
                405                 410                 415

Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
            420                 425                 430

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
    435                 440                 445

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

Gly Lys
465
```

<210> 164
<211> 1398
<212> DNA
<213> Mus musculus

<400> 164

atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccagctgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatacac attcactgac tacaacatgc actggatgaa gcagaaccaa 180
ggaaagagcc tagaatggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
cagcagttca aaggcaaggc cacattgact gtagacaagt cctccaggac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
gttggtaatt acgaggactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140

aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaa 1398

<210> 165
<211> 214
<212> PRT
<213> Mus musculus

<400> 165

```
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> 166
<211> 645
<212> DNA
<213> Mus musculus

<400> 166

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

<210> 167
<211> 234
<212> PRT
<213> Mus musculus

<400> 167

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

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

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

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

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

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

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

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
        115                 120                 125

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 168
<211> 705
<212> DNA
<213> Mus musculus

<400> 168

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt        60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc       120
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca       180
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca       240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa       300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg       360
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca       420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac       480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg       540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg       600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca       660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                        705
```

<210> 169
<211> 447
<212> PRT
<213> Mus musculus

<400> 169

```
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> 170
<211> 1344

<212> DNA
<213> Mus musculus

<400> 170

gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac 120
caaggaaaga ccctagactg gataggagaa attaatccta acagtggtgg tgctggctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcctggtaa atga 1344

<210> 171
<211> 466
<212> PRT
<213> Mus musculus

<400> 171

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

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
```

```
        35                  40                  45

Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu
    50                  55                  60

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

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
                85                  90                  95

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

Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115                 120                 125

Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140

Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145                 150                 155                 160

Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195                 200                 205

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210                 215                 220

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225                 230                 235                 240

Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245                 250                 255

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

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275                 280                 285

Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290                 295                 300
```

```
Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
        355                 360                 365

Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
    370                 375                 380

Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385                 390                 395                 400

Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
                405                 410                 415

Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
            420                 425                 430

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
        435                 440                 445

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

Gly Lys
465
```

<210> 172
<211> 1401
<212> DNA
<213> Mus musculus

<400> 172

atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccaactgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa 180
ggaaagaccc tagactggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
gatgatatct acgacgactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420

tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaatg a 1401

<210> 173
<211> 214
<212> PRT
<213> Mus musculus

<400> 173

```
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> 174
<211> 642
<212> DNA
<213> Mus musculus

<400> 174

gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60

atcagttgca gggcaagtca agacattagc aattatttaa attggtatca gcagaaacca 120

gatggaactt ttaaactcct tatcttctac acatcaagat tattttcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240

gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300

gggaccaagg tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 175
<211> 234
<212> PRT
<213> Mus musculus

<400> 175

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

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

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

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

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

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

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

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
        115                 120                 125

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 176
<211> 702

<212> DNA
<213> Mus musculus

<400> 176

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt       60
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc      120
atcagttgca gggcaagtca agacattagc aattatttaa attggtatca gcagaaacca      180
gatggaactt ttaaactcct tatcttctac acatcaagat tattttcagg agtcccatca      240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa      300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg      360
gggaccaagg tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca      420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac      480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg      540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg      600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca      660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt                         702
```

<210> 177
<211> 450
<212> PRT
<213> Mus musculus

<400> 177

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thr His Lys Pro Cys Pro Pro Cys Pro Ala Pro Asn Leu Leu Gly Gly
225                 230                 235                 240

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

Ser Leu Ser Pro Met Val Thr Cys Val Val Val Asp Val Ser Glu Asp
            260                 265                 270

Asp Pro Asp Val His Val Ser Trp Phe Val Asn Asn Val Glu Val His
        275                 280                 285

Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Ile Arg
    290                 295                 300

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

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

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

Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
        355                 360                 365
```

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

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

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

Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
            420                 425                 430

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

Gly Lys
    450
```

<210> 178
<211> 1350
<212> DNA
<213> Mus musculus

<400> 178

```
gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctgggacttc agtgaagatg      60
tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagacc     120
caaggaaaga ccctagagtg gataggagaa attaatccta acagtggtgg tgctggctac     180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac     240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aaaattgggc     300
tacgatgata tctacgacga ctggtatttc gatgtctggg gcgcagggac cacggtcacc     360
gtctcctcag ccaaaacaac agccccatcg gtctatccac tggcccctgt gtgtggagat     420
acaactggct cctcggtgac tctaggatgc ctggtcaagg gttatttccc tgagccagtg     480
accttgacct ggaactctgg atccctgtcc agtgatgtgc acaccttccc agctctcctg     540
cagtctggcc tctacaccct cagcagctca gtgactgtaa ccacctggcc cagccagacc     600
atcacctgca atgtggccca cccggcaagc agcaccaaag tggacaagaa aattgagccc     660
agagggtccc caacacataa accctgtcct ccatgcccag ctcctaacct cttgggtgga     720
ccatccgtct tcatcttccc tccaaagatc aaggatgtac tcatgatctc cctgagcccc     780
atggtcacgt gtgtggtggt ggatgtgagc gaggatgacc cagatgtcca tgtcagctgg     840
ttcgtgaaca acgtggaagt acacacagct cagacacaaa cccatagaga ggattacaac     900
agtactatcc gggtggtcag tgccctcccc atccagcacc aggactggat gagtggcaag     960
gagttcaaat gcaaggtcaa caacaaagcc ctcccagcgc ccatcgagag aaccatctca    1020
aaacccaaag ggccagtaag agctccacag gtatatgtct tgcctccacc agaagaagag    1080
atgactaaga aacaggtcac tctgacctgc atgatcacag acttcatgcc tgaagacatt    1140
tacgtggagt ggaccaacaa cgggcaaaca gagctaaact acaagaacac tgaaccagtc    1200
ctggactctg atggttctta cttcatgtac agcaagctga gagtggaaaa gaagaactgg    1260
gtggaaagaa atagctactc ctgttcagtg gtccacgagg gtctgcacaa tcaccacacg    1320
actaagagct tctcccggac tccgggtaaa                                     1350
```

<210> 179
<211> 469
<212> PRT
<213> Mus musculus

<400> 179

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

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30

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

Thr Asp Tyr Asn Met His Trp Val Lys Gln Thr Gln Gly Lys Thr Leu
    50                  55                  60

Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
                85                  90                  95

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

Tyr Tyr Cys Ala Lys Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115                 120                 125

Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140

Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr
145                 150                 155                 160

Thr Gly Ser Ser Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser Leu Ser Ser Asp Val
            180                 185                 190
```

```
His Thr Phe Pro Ala Leu Leu Gln Ser Gly Leu Tyr Thr Leu Ser Ser
        195                 200                 205

Ser Val Thr Val Thr Thr Trp Pro Ser Gln Thr Ile Thr Cys Asn Val
    210                 215                 220

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg
225                 230                 235                 240

Gly Ser Pro Thr His Lys Pro Cys Pro Pro Cys Pro Ala Pro Asn Leu
                245                 250                 255

Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val
            260                 265                 270

Leu Met Ile Ser Leu Ser Pro Met Val Thr Cys Val Val Val Asp Val
        275                 280                 285

Ser Glu Asp Asp Pro Asp Val His Val Ser Trp Phe Val Asn Asn Val
    290                 295                 300

Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser
305                 310                 315                 320

Thr Ile Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met
                325                 330                 335

Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Ala Leu Pro Ala
            340                 345                 350

Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Pro Val Arg Ala Pro
        355                 360                 365

Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln
    370                 375                 380

Val Thr Leu Thr Cys Met Ile Thr Asp Phe Met Pro Glu Asp Ile Tyr
385                 390                 395                 400

Val Glu Trp Thr Asn Asn Gly Gln Thr Glu Leu Asn Tyr Lys Asn Thr
                405                 410                 415

Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
            420                 425                 430

Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser
        435                 440                 445
```

```
Val Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser
    450                 455                 460

Arg Thr Pro Gly Lys
465
```

<210> 180
<211> 1407
<212> DNA
<213> Mus musculus

<400> 180

```
atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag      60
gtccaactgc aacagtctgg acctgaacta atgaagcctg ggacttcagt gaagatgtcc     120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagacccaa     180
ggaaagaccc tagagtggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac     240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg     300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaaa attgggctac     360
gatgatatct acgacgactg gtatttcgat gtctggggcg cagggaccac ggtcaccgtc     420
tcctcagcca aaacaacagc cccatcggtc tatccactgg cccctgtgtg tggagataca     480
actggctcct cggtgactct aggatgcctg gtcaagggtt atttccctga gccagtgacc     540
ttgacctgga actctggatc cctgtccagt gatgtgcaca ccttcccagc tctcctgcag     600
tctggcctct acaccctcag cagctcagtg actgtaacca cctggcccag ccagaccatc     660
acctgcaatg tggcccaccc ggcaagcagc accaaagtgg acaagaaaat tgagcccaga     720
gggtccccaa cacataaacc ctgtcctcca tgcccagctc ctaacctctt gggtggacca     780
tccgtcttca tcttccctcc aaagatcaag gatgtactca tgatctccct gagccccatg     840
gtcacgtgtg tggtggtgga tgtgagcgag gatgacccag atgtccatgt cagctggttc     900
gtgaacaacg tggaagtaca cacagctcag acacaaaccc atagagagga ttacaacagt     960
actatccggg tggtcagtgc cctccccatc cagcaccagg actggatgag tggcaaggag    1020
ttcaaatgca aggtcaacaa caaagccctc ccagcgccca tcgagagaac catctcaaaa    1080
cccaaagggc cagtaagagc tccacaggta tatgtcttgc ctccaccaga agaagagatg    1140
actaagaaac aggtcactct gacctgcatg atcacagact tcatgcctga agacatttac    1200
gtggagtgga ccaacaacgg gcaaacagag ctaaactaca agaacactga accagtcctg    1260
gactctgatg gttcttactt catgtacagc aagctgagag tggaaaagaa gaactgggtg    1320
gaaagaaata gctactcctg ttcagtggtc cacgagggtc tgcacaatca ccacacgact    1380
aagagcttct cccggactcc gggtaaa                                        1407
```

<210> 181
<211> 214
<212> PRT
<213> Mus musculus

<400> 181

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Asn Glu Cys
    210
```

<210> 182
<211> 645
<212> DNA
<213> Mus musculus

<400> 182

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60

atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240

gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300

gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacta 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 183
<211> 234
<212> PRT
<213> Mus musculus

<400> 183

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

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

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

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

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

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

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

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
115 120 125

```
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Leu Ser Ser Glu Gln
    130                 135                 140

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 184
<211> 705
<212> DNA
<213> Mus musculus

<400> 184

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt       60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc      120
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca      180
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca      240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa      300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg      360
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacta      420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac      480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg      540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg      600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca      660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                      705
```

<210> 185
<211> 447

<212> PRT
<213> Mus musculus

<400> 185

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

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

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

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

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr
65                  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> 186
<211> 1344
<212> DNA
<213> Mus musculus

<400> 186

gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac 120

caaggaaaga ccctagaatg gataggagaa attaatccta acagtggtgg tgctggctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300

tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360

gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900

cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960

tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320

ctctcccact ctcctggtaa atga 1344

<210> 187
<211> 466
<212> PRT
<213> Mus musculus

<400> 187

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

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30

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

Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu
    50                  55                  60

Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
                85                  90                  95
```

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

Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115                 120                 125

Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140

Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145                 150                 155                 160

Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195                 200                 205

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210                 215                 220

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225                 230                 235                 240

Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245                 250                 255

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

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275                 280                 285

Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290                 295                 300

Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
            340                 345                 350
```

```
Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
        355                 360                 365

Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
    370                 375                 380

Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385                 390                 395                 400

Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
                405                 410                 415

Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
            420                 425                 430

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
        435                 440                 445

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

Gly Lys
465
```

<210> 188
<211> 1401
<212> DNA
<213> Mus musculus

<400> 188

atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60

gtccaactgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120

tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa 180

ggaaagaccc tagaatggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240

cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300

gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360

gatgatatct acgacgactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420

tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480

actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540

gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600

tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 660

accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720

cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780

atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840

gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900

gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960

tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020

agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080

agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140

aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200

cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260

ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320

actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380

tcccactctc ctggtaaatg a 1401

<210> 189
<211> 213
<212> PRT
<213> Mus musculus

<400> 189

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

Asp Lys Val Thr Met Thr Cys Arg Ala Ser Ser 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> 190
<211> 642
<212> DNA
<213> Mus musculus

<400> 190

```
caaattgttc tctcccagtc tccagcattc ctgtctgtat ctccagggga taaggtcaca        60

atgacttgca gggccagctc aagtataagt tacatacact ggtttcagca gaagccagga       120

tcctccccca gatcctggat ttatgccaca tccaacctgg cttctggagt ccctggtcgc       180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgag       240

gatgctgcca cttattactg ccagcagtgg agtagtgacc cactcacgtt cggtgctggg       300

accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc       360

agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc       420

aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac       480

agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg       540

accaaggacg agtatgaacg acataacagc tatacctgtg aggccactca caagacatca       600

acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag                          642
```

<210> 191
<211> 235
<212> PRT
<213> Mus musculus

<400> 191

```
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1               5                   10                  15

Val Ile Met Ser Arg Gly Gln Ile Val Leu Ser Gln Ser Pro Ala Phe
            20                  25                  30
```

```
Leu Ser Val Ser Pro Gly Asp Lys Val Thr Met Thr Cys Arg Ala Ser
        35                  40                  45

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

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

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

Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
            100                 105                 110

Ser Ser Asp Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
        115                 120                 125

Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
    130                 135                 140

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
                165                 170                 175

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
        195                 200                 205

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
    210                 215                 220

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230                 235
```

<210> 192
<211> 708
<212> DNA
<213> Mus musculus

<400> 192

atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcttcagt cataatgtcc 60

agaggacaaa ttgttctctc ccagtctcca gcattcctgt ctgtatctcc aggggataag 120

gtcacaatga cttgcagggc cagctcaagt ataagttaca tacactggtt tcagcagaag 180

ccaggatcct cccccagatc ctggatttat gccacatcca acctggcttc tggagtccct 240

ggtcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagagtggag 300

gctgaggatg ctgccactta ttactgccag cagtggagta gtgacccact cacgttcggt 360

gctgggacca agctggagct gaaacgggct gatgctgcac caactgtatc catcttccca 420

ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 480

taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 540

ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 600

acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660

acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 708

<210> 193
<211> 445
<212> PRT
<213> Mus musculus

<400> 193

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

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

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

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

Pro Gly Lys Ala Thr Phe Thr Thr Asp Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

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

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

Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser
        115                 120                 125

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
385                 390                 395                 400

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

Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
```

420 425 430

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

<210> 194
<211> 1338
<212> DNA
<213> Mus musculus

<400> 194

gaagttcagc tgcaacagtc tggggcagac cttgtgcagc caggggcctc agtcaaggtg 60

tcctgcacag cttctggctt cgacattaag gactactata tacactggat gaaacagagg 120

cctgaccagg gcctggagtg gattggaagg gttgatcctg acaatggtga gactgaattt 180

gccccgaagt tcccgggcaa ggccactttt acaacagaca catcctccaa cacagcctac 240

ctacaactca gaggcctgac atctgaggac actgccatct attactgtgg gagagaagac 300

tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt cactgtctct 360

gcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact 420

aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg 480

acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct 540

gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc 600

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660

agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc 720

ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt 780

gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg 840

gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca 900

gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960

gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga 1020

ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080

gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1140

tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1200

tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1260

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320

cactctcctg gtaaatga 1338

<210> 195

<211> 464
<212> PRT
<213> Mus musculus

<400> 195

```
Met Lys Cys Ser Trp Val Ile Phe Phe Leu Met Ala Val Val Thr Gly
1               5                   10                  15

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

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

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

Glu Trp Ile Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala
65                  70                  75                  80

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

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

Tyr Tyr Cys Gly Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr
    130                 135                 140

Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145                 150                 155                 160

Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
        195                 200                 205

Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
    210                 215                 220

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225                 230                 235                 240

Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
                245                 250                 255
```

```
Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
            260                 265                 270

Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
        275                 280                 285

Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
    290                 295                 300

Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305                 310                 315                 320

Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
                325                 330                 335

Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
            340                 345                 350

Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
        355                 360                 365

Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
    370                 375                 380

Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
385                 390                 395                 400

Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
                405                 410                 415

Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
            420                 425                 430

Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
        435                 440                 445

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

<210> 196
<211> 1395
<212> DNA
<213> Mus musculus

<400> 196

atgaaatgca gctgggtcat cttcttcctg atggcagtgg ttacaggggt caattcagaa 60
gttcagctgc aacagtctgg ggcagacctt gtgcagccag ggcctcagt caaggtgtcc 120
tgcacagctt ctggcttcga cattaaggac tactatatac actggatgaa acagaggcct 180

gaccagggcc tggagtggat tggaagggtt gatcctgaca atggtgagac tgaatttgcc 240
ccgaagttcc cgggcaaggc cacttttaca acagacacat cctccaacac agcctaccta 300
caactcagag gcctgacatc tgaggacact gccatctatt actgtgggag agaagactac 360
gatggtacct acacctggtt tccttattgg ggccaaggga ctctggtcac tgtctctgca 420
gccaaaacga cacccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac 480
tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 540
tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac 600
ctctacactc tgagcagctc agtgactgtc cctccagca cctggcccag cgagaccgtc 660
acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg 720
gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780
cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg 840
gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag 900
gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 960
agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 1020
aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 1080
aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1140
agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 1200
aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1260
tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1320
acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380
tctcctggta aatga 1395

<210> 197
<211> 214
<212> PRT
<213> Mus musculus

<400> 197

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> 198
<211> 645
<212> DNA
<213> Mus musculus

<400> 198

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> 199
<211> 234
<212> PRT
<213> Mus musculus

<400> 199

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

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

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

Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
    50                  55                  60

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

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

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

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
        115                 120                 125

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205

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


            210                 215                 220

        Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
        225                 230
```

<210> 200

<211> 705
<212> DNA
<213> Mus musculus

<400> 200

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg ttccagatgt        60

gatctccaga tgacacagac tacttcctcc ctgtctgcct ctctgggaga cagagtcacc       120

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca       180

gatggaactg ttaagctcct gatcttctac acatcaacat tacagtcagg agtcccatcg       240

aggttcagtg gcagtgggtc tggaacaaat tattctctca ccattaccaa cctggagcaa       300

gatgatgctg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg       360

gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca       420

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac       480

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg       540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg       600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca       660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                      705
```

<210> 201
<211> 447
<212> PRT
<213> Mus musculus

<400> 201

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


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


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


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


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

```
                340                 345                 350

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

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

Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385                 390                 395                 400

Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
                405                 410                 415

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

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

<210> 202
<211> 1344
<212> DNA
<213> Mus musculus

<400> 202

gaggtccagt tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata cacattcact gactacaaca tgcactggat gaagcagaac 120

caaggaaaga gcctagagtg gataggagag attaatccta acagtggtgg ttctggttac 180

aaccagaagt tcaaaggcaa ggccacattg actgtagaca agtcctccag cacagcctac 240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300

tactatggta actacgagga ctggtatttc gatgtctggg gcgcagggac cacggtcacc 360

gtctcctctg ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540

cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600

gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660

gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720

ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780

tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840

gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900

cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960

tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020

ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080

gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140

tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260

aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320

ctctcccact ctcctggtaa atga 1344

<210> 203
<211> 466
<212> PRT
<213> Mus musculus

<400> 203

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

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30

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

Thr Asp Tyr Asn Met His Trp Met Lys Gln Asn Gln Gly Lys Ser Leu
    50                  55                  60

Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85                  90                  95

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

Tyr Tyr Cys Ala Arg Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr
        115                 120                 125

Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140

Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145                 150                 155                 160

Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175
```

```
Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195                 200                 205

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210                 215                 220

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225                 230                 235                 240

Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245                 250                 255

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

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275                 280                 285

Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290                 295                 300

Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
        355                 360                 365

Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
    370                 375                 380

Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385                 390                 395                 400

Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
                405                 410                 415

Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
            420                 425                 430
```

```
Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
        435                 440                 445


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


Gly Lys
465
```

<210> 204
<211> 1401
<212> DNA
<213> Mus musculus

<400> 204

atgggatgga gctggacctt tctcttcctc ctgtcaggaa cttcgggtgt cctctctgag 60

gtccagttgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120

tgcaaggctt ctggatacac attcactgac tacaacatgc actggatgaa gcagaaccaa 180

ggaaagagcc tagagtggat aggagagatt aatcctaaca gtggtggttc tggttacaac 240

cagaagttca aaggcaaggc cacattgact gtagacaagt cctccagcac agcctacatg 300

gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360

tatggtaact acgaggactg gtatttcgat gtctggggcg cagggaccac ggtcaccgtc 420

tcctctgcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480

actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540

gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600

tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 660

accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720

cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780

atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840

gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900

gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960

tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020

agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080

agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140

aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200

cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260

ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320

actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380

tcccactctc ctggtaaatg a 1401

<210> 205
<211> 215
<212> PRT
<213> Mus musculus

<400> 205

```
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
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> 206
<211> 645
<212> DNA
<213> Mus musculus

<400> 206

```
cagattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc       60

atgacctgca gggccagctc aagtgtaact tccagttact tgaactggta ccagcagaag      120

ccaggatctt cccccaaact ctggatttat agcacatcca acctggcttc aggagtccca      180

gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagtgtggag      240

gctgaggatg ctgccactta ttactgccag cagtatgatt ttttcccatc gacgttcggt      300

ggaggcacca agctggaaat caagcgggct gatgctgcac caactgtatc catcttccca      360

ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc      420

taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc      480

ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc      540

acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag      600

acatcaactt cacccatcgt caagagcttc aacaggaatg agtgt                      645
```

<210> 207
<211> 237
<212> PRT
<213> Mus musculus

<400> 207

```
Met Asp Ser Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Leu
1               5                   10                  15

Val Lys Met Ser Arg Gly Gln Ile Val Leu Thr Gln Ser Pro Ala Ile
            20                  25                  30

Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
        35                  40                  45

Ser Ser Val Thr Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

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

Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
                85                  90                  95

Thr Ile Ser Ser Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
            100                 105                 110

Gln Tyr Asp Phe Phe Pro Ser Thr Phe Gly Gly Gly Thr Lys Leu Glu
```

```
                115                 120                 125

        Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
            130                 135                 140

        Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
        145                 150                 155                 160

        Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
                        165                 170                 175

        Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
                    180                 185                 190

        Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
                195                 200                 205

        Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser
            210                 215                 220

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

<210> 208
<211> 711
<212> DNA
<213> Mus musculus

<400> 208

```
atggattctc aagtgcagat tttcagcttc cttctaatca gtgccttagt caaaatgtcc      60

agaggacaga ttgttctcac ccagtctcca gcaatcatgt ctgcatctcc aggggagaag     120

gtcaccatga cctgcagggc cagctcaagt gtaacttcca gttacttgaa ctggtaccag     180

cagaagccag gatcttcccc caaactctgg atttatagca catccaacct ggcttcagga     240

gtcccagctc gcttcagtgg cagtgggtct gggacctctt actctctcac aatcagcagt     300

gtggaggctg aggatgctgc cacttattac tgccagcagt atgatttttt cccatcgacg     360

ttcggtggag gcaccaagct ggaaatcaag cgggctgatg ctgcaccaac tgtatccatc     420

ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac     480

aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat     540

ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc     600

accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact     660

cacaagacat caacttcacc catcgtcaag agcttcaaca ggaatgagtg t              711
```

<210> 209
<211> 445
<212> PRT
<213> Mus musculus

<400> 209

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
```

```
                245                 250                 255

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

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

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

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

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

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

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

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

Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
385                 390                 395                 400

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

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

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

<210> 210
<211> 1335
<212> DNA
<213> Mus musculus

<400> 210

gaggtccagc tgcaacaatc tggacctgag ctggtgaagc ctggggcttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactactaca tgaactgggt gaagcagagc 120
catggagaga gccttgagtg gattggagat attaatcctt acaacgatga tactacctac 180
aaccacaagt tcaagggcaa ggccacattg actgtagaca aatcctccaa cacagcctac 240

atgcagctca acagcctgac atctgaggac tctgcagtct attactgtgc aagagagacg 300
gccgttatta ctacgaatgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360
tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact 420
aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg 480
acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct 540
gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc 600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc 720
ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt 780
gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg 840
gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca 900
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960
gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga 1020
ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080
gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1140
tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1200
tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1260
ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320
cactctcctg gtaaa 1335

<210> 211
<211> 464
<212> PRT
<213> Mus musculus

<400> 211

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

Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys
            20                  25                  30

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

Thr Asp Tyr Tyr Met Asn Trp Val Lys Gln Ser His Gly Glu Ser Leu
    50                  55                  60

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

```
His Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asn
                85                  90                  95

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

Tyr Tyr Cys Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr
    130                 135                 140

Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145                 150                 155                 160

Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
        195                 200                 205

Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
    210                 215                 220

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225                 230                 235                 240

Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
                245                 250                 255

Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
            260                 265                 270

Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
        275                 280                 285

Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
    290                 295                 300

Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305                 310                 315                 320

Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
                325                 330                 335
```

```
Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
            340                 345                 350

Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
        355                 360                 365

Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
    370                 375                 380

Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
385                 390                 395                 400

Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
                405                 410                 415

Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
            420                 425                 430

Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
        435                 440                 445

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

<210> 212
<211> 1392
<212> DNA
<213> Mus musculus

<400> 212

atgggatgga actggatctt tctcttcctc ttgtcaggaa ctgcaggtgt ctactctgag 60

gtccagctgc aacaatctgg acctgagctg gtgaagcctg gggcttcagt gaagatgtcc 120

tgtaaggctt ctggatacac attcactgac tactacatga actgggtgaa gcagagccat 180

ggagagagcc ttgagtggat tggagatatt aatccttaca acgatgatac tacctacaac 240

cacaagttca agggcaaggc cacattgact gtagacaaat cctccaacac agcctacatg 300

cagctcaaca gcctgacatc tgaggactct gcagtctatt actgtgcaag agagacggcc 360

gttattacta cgaatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 420

gccaaaacga cacccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac 480

tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 540

tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac 600

ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 660

acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg 720

gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780

cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg 840

gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag 900

gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 960

agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 1020

aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 1080

aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1140

agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 1200

aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1260

tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1320

acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380

tctcctggta aa 1392

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

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 213

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 214
<211> 645
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 214

gacatccagc tgacccagag ccccagcttc ctttccgcat ccgttggtga ccgagtaaca 60

atcacatgcc gcgcctcatc ttcagttaca tcttcttatc ttaattggta tcaacaaaaa 120

ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatc aggagttccc 180

tctcgatttt caggatctgg atcaggcaca gaatttacac ttactatatc atcactccaa 240

ccagaagact tcgccactta ttactgccaa caatacgatt tttttccaag cacattcgga 300

ggaggtacaa aagtagaaat caagcgtacg gtggctgcac catctgtctt catcttcccg 360

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480

caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540

acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 645

<210> 215
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 215

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

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

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

Ser Ser Val Thr Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

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

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

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

Gln Tyr Asp Phe Phe Pro Ser Thr Phe Gly Gly Gly Thr Lys Val Glu
        115                 120                 125

Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
    130                 135                 140

Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
145                 150                 155                 160

Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
                165                 170                 175

Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys
            180                 185                 190

Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp
        195                 200                 205

Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
    210                 215                 220

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

<210> 216
<211> 711
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 216

```
atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct cccaggtgcc        60

agatgtgaca tccagctgac ccagagcccc agcttccttt ccgcatccgt tggtgaccga       120

gtaacaatca catgccgcgc ctcatcttca gttacatctt cttatcttaa ttggtatcaa       180

caaaaaccag gaaaagcacc taaacttctt atatactcta catctaatct cgcatcagga       240

gttccctctc gattttcagg atctggatca ggcacagaat ttacacttac tatatcatca       300

ctccaaccag aagacttcgc cacttattac tgccaacaat acgatttttt tccaagcaca       360

ttcggaggag gtacaaaagt agaaatcaag cgtacggtgg ctgcaccatc tgtcttcatc       420

ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat       480

aacttctatc ccagagaggc caaagtacag tggaaggtgg ataacgccct ccaatcgggt       540

aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc       600

accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc       660

catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t                711
```

<210> 217
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 217

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
```

```
1               5                   10                  15

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

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

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

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

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

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

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

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

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

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

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

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

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
    210                 215                 220

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 218
<211> 1341
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 218

gaggtgcagc tggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaaggtt 60

agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc 120

cctggacaaa gacttgaatg gatgggagac attaaccctt ataacgacga cactacatac 180

aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat 240

atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact 300

gccgttatta ctactaacgc tatggattac tggggtcaag gaaccactgt taccgtctct 360

agtgcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420

gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480

tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600

acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660

cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780

tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840

ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900

cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960

tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140

tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc 1200

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320

ctctccctgt ctccgggtaa a 1341

<210> 219
<211> 466
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 219

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

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

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


Thr Asp Tyr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu
    50                  55                  60


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


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


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


Tyr Tyr Cys Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp
        115                 120                 125


Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140


Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145                 150                 155                 160


Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175


Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190


Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205


Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220


Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240


Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255


Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270


Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285


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

```
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465
```

<210> 220
<211> 1398
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 220

atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60
gtgcagctgg tgcagagcgg cgccgaggtc aagaaacctg gagcaagcgt aaaggttagt 120
tgcaaagcat ctggatacac atttaccgac tactacatga attgggtacg acaagcccct 180
ggacaaagac ttgaatggat gggagacatt aacccttata acgacgacac tacatacaat 240
cataaattta aaggaagagt tacaattaca agagatacat ccgcatcaac cgcctatatg 300
gaactttcct cattgagatc tgaagacact gctgtttatt actgtgcaag agaaactgcc 360
gttattacta ctaacgctat ggattactgg ggtcaaggaa ccactgttac cgtctctagt 420
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 480
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 540
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 600
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 660
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 720
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 780
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 840
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 900
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 960
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 1020
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1080
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1140
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1200
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1260
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1320
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380
tccctgtctc cgggtaaa 1398

<210> 221
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 221

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

Asp Arg Val Thr Ile Thr Cys Ser Val Ser Ser Thr Ile Ser Ser Asn


            20                  25                  30

His Leu His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu
        35                  40                  45

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

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

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

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

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

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

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

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

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

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

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

<210> 222
<211> 645

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 222

gacatccaga tgacccagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca 60

ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcattggtt ccaacagaaa 120

cccggcaaag cacctaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct 180

tcaagatttt caggctctgg ctcaggcacc gactttactc ttacaatatc ctccctccaa 240

cccgaagact tcgcaaccta ttactgtcaa caatggtcct catatccact cacatttggc 300

ggcggcacaa aagtagaaat taaacgtacg gtggctgcac catctgtctt catcttcccg 360

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480

caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540

acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 645

<210> 223
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 223

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

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

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

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

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

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

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

Gln Trp Ser Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
        115                 120                 125

Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
    130                 135                 140

Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
145                 150                 155                 160

Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
                165                 170                 175

Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys
            180                 185                 190

Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp
        195                 200                 205

Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
    210                 215                 220

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

<210> 224
<211> 711

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 224

atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc 60

agatgtgaca tccagatgac ccagtctcca tcctccctct cagcatccgt aggcgataga 120

gttacaataa catgcagcgt atcatcaact atatcatcaa atcatcttca ttggttccaa 180

cagaaacccg gcaaagcacc taaatcactt atatacggca catcaaatct cgcatcaggc 240

gttccttcaa gattttcagg ctctggctca ggcaccgact ttactcttac aatatcctcc 300

ctccaacccg aagacttcgc aacctattac tgtcaacaat ggtcctcata tccactcaca 360

tttggcggcg gcacaaaagt agaaattaaa cgtacggtgg ctgcaccatc tgtcttcatc 420

ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat 480

aacttctatc ccagagaggc caaagtacag tggaaggtgg ataacgccct ccaatcgggt 540

aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 600

accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc 660

catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t 711

<210> 225
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 225

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

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

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu 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> 226
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 226

gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gattggaagg attgatcctg agaatggtga tactttatat 180

gacccgaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg 300

gattatttcc acgatggtac ctcctactgg tacttcgatg tctggggccg tggcaccctg 360

gtcaccgtct ctagtgcctc caccaagggc ccatcggtct tccccctggc gccctgctcc 420

aggagcacct ccgagagcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 480

ccggtgacgg tgtcgtggaa ctcaggcgct ctgaccagcg gcgtgcacac cttcccagct 540

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcaac 600

ttcggcaccc agacctacac ctgcaacgta gatcacaagc ccagcaacac caaggtggac 660

aagacagttg agcgcaaatg ttgtgtcgag tgcccaccgt gcccagcacc acctgtggca 720

ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 780

cctgaggtca cgtgcgtggt ggtggacgtg agccacgaag accccgaggt ccagttcaac 840

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccacggga ggagcagttc 900

aacagcacgt tccgtgtggt cagcgtcctc accgttgtgc accaggactg gctgaacggc 960

aaggagtaca agtgcaaggt ctccaacaaa ggcctcccag cccccatcga gaaaaccatc 1020

tccaaaacca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 1080

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta ccccagcgac 1140

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacacctccc 1200

atgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1260

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1320

acgcagaaga gcctctccct gtctccgggt aaa 1353

<210> 227
<211> 470
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 227

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

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

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

Lys Asp Phe Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

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

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

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

Tyr Tyr Cys Ala Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr
        115                 120                 125

Trp Tyr Phe Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145                 150                 155                 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                165                 170                 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
            180                 185                 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
        195                 200                 205
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
    210                 215                 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225                 230                 235                 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
                245                 250                 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
            260                 265                 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
        275                 280                 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
    290                 295                 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
305                 310                 315                 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
                325                 330                 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
            340                 345                 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
        355                 360                 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
    370                 375                 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385                 390                 395                 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
                405                 410                 415

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
            420                 425                 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
        435                 440                 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
    450                 455                 460
```

```
Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 228
<211> 1410
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 228

atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60

gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg gggcctcagt gaaggtctcc 120

tgcaaggctt ctgacttcaa cattaaagac ttctatctac actgggtgcg acaggcccct 180

ggacaagggc ttgagtggat tggaaggatt gatcctgaga atggtgatac tttatatgac 240

ccgaagttcc aggacaaggt caccatgacc acagacacgt ccaccagcac agcctacatg 300

gagctgagga gcctgagatc tgacgacacg gccgtgtatt actgtgcgag agaggcggat 360

tatttccacg atggtacctc ctactggtac ttcgatgtct ggggccgtgg caccctggtc 420

accgtctcta gtgcctccac caagggccca tcggtcttcc ccctggcgcc ctgctccagg 480

agcacctccg agagcacagc ggccctgggc tgcctggtca aggactactt ccccgaaccg 540

gtgacggtgt cgtggaactc aggcgctctg accagcggcg tgcacacctt cccagctgtc 600

ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcaacttc 660

ggcacccaga cctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag 720

acagttgagc gcaaatgttg tgtcgagtgc ccaccgtgcc cagcaccacc tgtggcagga 780

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 840

gaggtcacgt gcgtggtggt ggacgtgagc cacgaagacc ccgaggtcca gttcaactgg 900

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cacgggagga gcagttcaac 960

agcacgttcc gtgtggtcag cgtcctcacc gttgtgcacc aggactggct gaacggcaag 1020

gagtacaagt gcaaggtctc caacaaaggc ctcccagccc ccatcgagaa aaccatctcc 1080

aaaaccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 1140

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctaccc cagcgacatc 1200

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac acctcccatg 1260

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1320

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1380

cagaagagcc tctccctgtc tccgggtaaa 1410

<210> 229
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 229

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser 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> 230
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 230

```
gacatccagt tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc     60

atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg    120

aaagccccta agctcctgat ctatgccaca tccaacctgg cttctggggt cccatcaagg    180

ttcagcggca gtggatctgg gacagaattc actctcacaa tcagcagcct gcagcctgaa    240

gattttgcaa cttattactg tcagcagtgg agtagtgacc cactcacgtt cggcggaggg    300

accaaggtgg agatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct    360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc    420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag    480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg    540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg    600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt                           639
```

<210> 231
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 231

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

Leu Pro Gly Ala Arg Cys Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe
```

```
                20                  25                  30

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

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

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

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

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

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

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220

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

<210> 232
<211> 705
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 232

atggacatga gggtccccgc tcagctcctg gggctcctgc tgctctggct cccaggtgcc 60

agatgtgaca tccagttgac ccagtctcca tccttcctgt ctgcatctgt aggagacaga 120

gtcaccatca cttgcagggc cagctcaagt ataagttaca tacactggta tcagcaaaaa 180

ccagggaaag cccctaagct cctgatctat gccacatcca acctggcttc tggggtccca 240

tcaaggttca gcggcagtgg atctgggaca gaattcactc tcacaatcag cagcctgcag 300

cctgaagatt ttgcaactta ttactgtcag cagtggagta gtgacccact cacgttcggc 360

ggagggacca aggtggagat caaacgtacg gtggctgcac catctgtctt catcttcccg 420

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 480

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 540

caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 600

acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 660

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 705

<210> 233
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 233

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

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

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

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

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

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

```
                85                  90                  95

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

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

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

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

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

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

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

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
    210                 215                 220

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> 234
<211> 1341
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 234

gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatcggaagg gttgatcctg acaatggtga gactgaattt 180
gccccgaagt tcccgggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac 300
tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct 360
agtgcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780

tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa a 1341

<210> 235
<211> 466
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 235

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

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

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

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

Glu Trp Ile Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala
65                  70                  75                  80

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

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

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

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145                 150                 155                 160

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

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

```
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465
```

<210> 236
<211> 1398
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 236

```
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag      60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg gggcctcagt gaaggtctcc     120
tgcaaggctt ctggattcga cattaaggac tactatatac actgggtgcg acaggcccct     180
ggacaagggc ttgagtggat cggaagggtt gatcctgaca atggtgagac tgaatttgcc     240
ccgaagttcc cgggcaaggt caccatgacc acagacacgt ccatcagcac agcctacatg     300
gagctgagca ggctgagatc tgacgacacg gccgtgtatt actgtgcgag agaagactac     360
gatggtacct acacctggtt tccttattgg ggccaaggga ctctggtcac cgtctctagt     420
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag     480
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg     540
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca     600
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc     660
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc     720
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc     780
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc     840
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc     900
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt     960
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc    1020
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg    1080
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac    1140
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg    1200
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac    1260
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac    1320
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc    1380
tccctgtctc cgggtaaa                                                  1398
```

<210> 237
<211> 7
<212> PRT
<213> Mus musculus

<400> 237

```
Gly Thr Ser Asn Leu Ala Ser
1               5
```

<210> 238

<211> 8
<212> PRT
<213> Mus musculus

<400> 238

```
Gln Gln Trp Thr Thr Thr Tyr Thr
1               5
```

<210> 239
<211> 11
<212> PRT
<213> Mus musculus

<400> 239

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

<210> 240
<211> 7
<212> PRT
<213> Mus musculus

<400> 240

```
Ser Thr Ser Arg Leu Asn Ser
1               5
```

<210> 241
<211> 8
<212> PRT
<213> Mus musculus

<400> 241

```
Gln Gln Asp Ile Lys His Pro Thr
1               5
```

<210> 242
<211> 11
<212> PRT
<213> Mus musculus

<400> 242

```
Lys Ala Ser Gln Asp Val Phe Thr Ala Val Ala
1               5                   10
```

<210> 243
<211> 7
<212> PRT
<213> Mus musculus

<400> 243

```
Trp Ala Ser Thr Arg His Thr
1               5
```

<210> 244
<211> 9
<212> PRT
<213> Mus musculus

<400> 244

```
Gln Gln Tyr Ser Ser Tyr Pro Leu Thr
1               5
```

<210> 245
<211> 5
<212> PRT
<213> Mus musculus

<400> 245

```
Asp Tyr Asn Met His
1               5
```

<210> 246
<211> 17
<212> PRT
<213> Mus musculus

<400> 246

```
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1               5                   10                  15

Gly
```

<210> 247
<211> 14
<212> PRT
<213> Mus musculus

<400> 247

```
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1               5                   10
```

<210> 248
<211> 5
<212> PRT
<213> Mus musculus

<400> 248

```
Asp Tyr Asn Met His
1               5
```

<210> 249
<211> 17
<212> PRT
<213> Mus musculus

<400> 249

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


Gly
```

<210> 250
<211> 14
<212> PRT
<213> Mus musculus

<400> 250

```
Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr Phe Asp Val
1               5                   10
```

<210> 251
<211> 5
<212> PRT
<213> Mus musculus

<400> 251

```
Asp Tyr Asn Met His


1               5
```

<210> 252
<211> 17
<212> PRT
<213> Mus musculus

<400> 252

```
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Gln Phe Lys
1               5                   10                  15


Gly
```

<210> 253
<211> 14
<212> PRT
<213> Mus musculus

<400> 253

```
Leu Gly Tyr Val Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
1               5                   10
```

<210> 254
<211> 5
<212> PRT
<213> Mus musculus

<400> 254

```
Asp Tyr Asn Met His
1               5
```

<210> 255
<211> 17
<212> PRT
<213> Mus musculus

<400> 255

```
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1               5                   10                  15


Gly
```

<210> 256
<211> 14
<212> PRT
<213> Mus musculus

<400> 256

```
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1               5                   10
```

<210> 257
<211> 5
<212> PRT
<213> Mus musculus

<400> 257

```
Asp Tyr Asn Met His
1               5
```

<210> 258
<211> 17
<212> PRT
<213> Mus musculus

<400> 258

```
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1               5                   10                  15


Gly
```

<210> 259
<211> 14
<212> PRT
<213> Mus musculus

<400> 259

```
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1               5                   10
```

<210> 260
<211> 5
<212> PRT
<213> Mus musculus

<400> 260

```
Asp Tyr Asn Met His
1               5
```

<210> 261
<211> 17
<212> PRT
<213> Mus musculus

<400> 261

```
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
1               5                   10                  15


Gly
```

<210> 262
<211> 14
<212> PRT
<213> Mus musculus

<400> 262

```
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1               5                   10
```

<210> 263
<211> 5
<212> PRT
<213> Mus musculus

<400> 263

```
Asp Tyr Asn Met His
1               5
```

<210> 264
<211> 17
<212> PRT
<213> Mus musculus

<400> 264

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

Gly
```

<210> 265
<211> 14
<212> PRT
<213> Mus musculus

<400> 265

```
Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
1               5                   10
```

<210> 266
<211> 5
<212> PRT
<213> Mus musculus

<400> 266

```
Asp Tyr Tyr Ile His
1               5
```

<210> 267
<211> 17
<212> PRT
<213> Mus musculus

<400> 267

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

Gly

<210> 268
<211> 13
<212> PRT
<213> Mus musculus

<400> 268

Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val Asp Tyr
1   5   10

<210> 269
<211> 5
<212> PRT
<213> Mus musculus

<400> 269

Asp Tyr Ile Met His
1   5

<210> 270
<211> 17
<212> PRT
<213> Mus musculus

<400> 270

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

Gly

<210> 271
<211> 11
<212> PRT
<213> Mus musculus

<400> 271

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

<210> 272
<211> 5
<212> PRT
<213> Mus musculus

<400> 272

```
Asp Tyr Tyr Met His
1               5
```

<210> 273
<211> 17
<212> PRT
<213> Mus musculus

<400> 273

```
Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe Gln
1               5                   10                  15

Gly
```

<210> 274
<211> 10
<212> PRT
<213> Mus musculus

<400> 274

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

<210> 275
<211> 10
<212> PRT
<213> Mus musculus

<400> 275

```
Arg Ala Ser Ser Ser Val Tyr Tyr Met His
1               5                   10
```

<210> 276
<211> 7
<212> PRT
<213> Mus musculus

<400> 276

```
Ala Thr Ser Asn Leu Ala Ser
1               5
```

<210> 277
<211> 9
<212> PRT
<213> Mus musculus

<400> 277

```
Gln Gln Trp Ser Ser Asp Pro Leu Thr
1               5
```

<210> 278
<211> 12
<212> PRT
<213> Mus musculus

<400> 278

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

<210> 279
<211> 7
<212> PRT
<213> Mus musculus

<400> 279

```
Gly Thr Ser Asn Leu Ala Ser
1               5
```

<210> 280
<211> 9
<212> PRT
<213> Mus musculus

<400> 280

```
Gln Gln Trp Ser Ser Tyr Pro Leu Thr
1               5
```

<210> 281
<211> 10
<212> PRT
<213> Mus musculus

<400> 281

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

<210> 282
<211> 7
<212> PRT
<213> Mus musculus

<400> 282

Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 283
<211> 9
<212> PRT
<213> Mus musculus

<400> 283

Gln Gln Trp Ser Ser Asp Pro Leu Thr
1 5

<210> 284
<211> 12
<212> PRT
<213> Mus musculus

<400> 284

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

<210> 285
<211> 7
<212> PRT
<213> Mus musculus

<400> 285

Ser Thr Ser Asn Leu Ala Ser
1 5

<210> 286
<211> 9
<212> PRT
<213> Mus musculus

<400> 286

Gln Gln Tyr Asp Phe Phe Pro Ser Thr
1 5

<210> 287
<211> 5
<212> PRT
<213> Mus musculus

<400> 287

Asp Tyr Phe Ile His
1 5

<210> 288
<211> 17
<212> PRT
<213> Mus musculus

<400> 288

```
Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala Pro Lys Phe Gln
1               5                   10                  15


Asp
```

<210> 289
<211> 12
<212> PRT
<213> Mus musculus

<400> 289

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

<210> 290
<211> 5
<212> PRT
<213> Mus musculus

<400> 290

```
Asp Phe Tyr Leu His
1               5
```

<210> 291
<211> 17
<212> PRT
<213> Mus musculus

<400> 291

```
Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe Gln
1               5                   10                  15


Asp
```

<210> 292
<211> 16
<212> PRT
<213> Mus musculus

<400> 292

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

<210> 293
<211> 5
<212> PRT
<213> Mus musculus

<400> 293

Asp Tyr Tyr Ile His
1   5

<210> 294
<211> 17
<212> PRT
<213> Mus musculus

<400> 294

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

Gly

<210> 295
<211> 12
<212> PRT
<213> Mus musculus

<400> 295

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

<210> 296
<211> 5
<212> PRT
<213> Mus musculus

<400> 296

Asp Tyr Tyr Met Asn
1   5

<210> 297
<211> 17
<212> PRT
<213> Mus musculus

<400> 297

```
Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe Lys
1               5                   10                  15


Gly
```

<210> 298
<211> 11
<212> PRT
<213> Mus musculus

<400> 298

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

<210> 299
<211> 130
<212> PRT
<213> Mus musculus

<400> 299

```
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Met Leu Ile Ser Val Thr
1               5                   10                  15


Val Ile Leu Ser Ser Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Leu
            20                  25                  30


Met Ala Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Val Ser
        35                  40                  45


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


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


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


Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
            100                 105                 110


Gln Trp Thr Thr Thr Tyr Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu
        115                 120                 125


Lys Arg
    130
```

<210> 300
<211> 390
<212> DNA
<213> Mus musculus

<400> 300

```
atggattttc aggtgcagat tttcagcttc atgctaatca gtgtcacagt catattgtcc        60

agtggagaaa ttgtgctcac ccagtctcca gcactcatgg ctgcatctcc aggggagaag       120

gtcaccatca cctgcagtgt cagctcgagt ataagttcca gcaacttaca ctggtcccag       180

cagaagtcag gaacctcccc caaactctgg atttatggca catccaacct tgcttctgga       240

gtccctgttc gcttcagtgg cagtggatct gggacctctt attctctcac aatcagcagc       300

atggaggctg aagatgctgc cacttattac tgtcaacagt ggactactac gtatacgttc       360

ggatcgggga ccaagctgga gctgaaacgt                                        390
```

<210> 301
<211> 141
<212> PRT
<213> Mus musculus

<400> 301

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


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


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

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

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

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

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

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

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

<210> 302
<211> 423
<212> DNA
<213> Mus musculus

<400> 302

```
atgggatgga actggatcat cttcttcctg atggcagtgg ttacaggggt caattcagag       60

gtgcagttgc ggcagtctgg ggcagacctt gtgaagccag gggcctcagt caagttgtcc      120

tgcacagctt ctggcttcaa cattaaagac tactatatac actgggtgaa gcagaggcct      180

gaacagggcc tggagtggat tggaaggatt gatcctgata atggtgaaag tacatatgtc      240

ccgaagttcc agggcaaggc cactataaca gcagacacat catccaacac agcctaccta      300

caactcagaa gcctgacatc tgaggacact gccatctatt attgtgggag agaggggctc      360

gactatggtg actactatgc tgtggactac tggggtcaag gaacctcggt cacagtctcg      420

agc                                                                    423
```

<210> 303
<211> 130
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 303

```
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> 304
<211> 390
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 304

```
atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gccgggcgcg      60

cgctgcgata ttcagctgac ccagagcccg agctttctga gcgcgagcgt gggcgatcgc     120

gtgaccatta cctgcagcgt gagcagcagc attagcagca gcaacctgca ttggtatcag     180

cagaaaccgg gcaaagcgcc gaaactgctg atttatggca ccagcaacct ggcgagcggc     240

gtgccgagcc gctttagcgg cagcggcagc ggcaccgaat ttaccctgac cattagcagc     300

ctgcagccgg aagattttgc gacctattat tgccagcagt ggaccaccac ctataccttt     360

ggccagggca ccaaactgga aattaaacgt                                      390
```

<210> 305
<211> 141
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 305

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

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

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

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

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

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

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

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

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

<210> 306
<211> 423
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 306

```
atggattgga cctggagcat tctgtttctg gtggcggcgc cgaccggcgc gcatagcgaa        60
```

```
gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc      120

tgcaaagcga gcggctttaa cattaaagat tattatattc attgggtgcg ccaggcgccg      180

ggccagggcc tggaatggat gggccgcatt gatccggata acggcgaaag cacctatgtg      240

ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg      300

gaactgcgca gcctgcgcag cgatgatacc gcggtgtatt attgcgcgcg cgaaggcctg      360

gattatggcg attattatgc ggtggattat tggggccagg gcaccctggt gaccgtctcg      420

agc                                                                    423
```

<210> 307
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 307

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


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


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


Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
    50                  55                  60


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


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


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


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

<210> 308
<211> 381
<212> DNA
<213> Mus musculus

<400> 308

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt        60

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcaac       120

atcagctgca gggcaagtca ggacattagc agttatttaa actggtatca gcagaaacca       180

gatggaactg ttaaactcct gatctactcc acatcaagat taaactcagg agtcccatca       240

aggttcagtg gcagtgggtc tgggacagat tattctctca ctattagcaa cctggcacaa       300

gaagatattg ccacttactt ttgccaacag gatattaagc atccgacgtt cggtggaggc       360

accaagttgg agctgaaacg t                                                 381
```

<210> 309
<211> 139
<212> PRT
<213> Mus musculus

<400> 309

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

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

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

Thr Asp Tyr Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu
    50                  55                  60

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

Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser
                85                  90                  95

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

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

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

<210> 310
<211> 417
<212> DNA
<213> Mus musculus

<400> 310

```
atggaatgga tctggatatt tctcttcctc ctgtcaggaa ctgcaggtgt ccactctgag      60

gtccagctgc agcagtctgg acctgagctg gtaaagcctg gggcttcagt gaagatgtcc     120

tgcaaggctt ctgggttcac attcactgac tacattatgc actgggtgaa gcagaagcct     180

gggcagggcc ttgagtggat tggatatatt aatccttaca atgatgatac tgaatacaat     240

gagaagttca aaggcaaggc cacactgact tcagacaaat cctccagcac agcctacatg     300

gatctcagca gtctgacctc tgagggctct gcggtctatt actgtgcaag atcgatttat     360

tactacgatg ccccgtttgc ttactggggc caagggactc tggtcacagt ctcgagc        417
```

<210> 311
<211> 127
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 311

```
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> 312
<211> 381
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 312

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt        60

gatatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc       120

atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca       180

gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca       240

cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct       300

gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc       360

accaaggtgg agatcaaacg t                                                 381
```

<210> 313
<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 313

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


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


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


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


Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn
65                  70                  75                  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> 314
<211> 107
<212> PRT
<213> Mus musculus

<400> 314

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

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

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

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

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

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

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

<210> 315
<211> 128
<212> PRT
<213> Mus musculus

<400> 315

```
Met Lys Ser Gln Thr Gln Val Phe Val Tyr Met Leu Leu Trp Leu Ser
1               5                   10                  15

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

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


        35                  40                  45

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

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

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

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

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

<210> 316
<211> 381
<212> DNA
<213> Mus musculus

<400> 316

```
atgaagtcac agacccaggt ctttgtatac atgttgctgt ggttgtctgg tgttgaagga        60

gacattgtga tgacccagtc tcacaaattc atgtccacgt cagtaggaga cagggtcacc       120

atcacctgca aggccagtca ggatgtcttt actgctgtag cctggtatca acagaaacca       180

ggacaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccctgat       240

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct       300

gaagacttgg cagattattt ctgtcaacaa tatagcagct atcctctcac gttcggtgct       360

gggaccaagt tggagctgaa a                                                 381
```

<210> 317
<211> 138
<212> PRT
<213> Mus musculus

<400> 317

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

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

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

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

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

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

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

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

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

<210> 318
<211> 411
<212> DNA
<213> Mus musculus

<400> 318

```
atgggatgga actggatcat cttcttcctg atggcagtgg ttacaggggt caattcagag      60

gttcagctgc agcagtctgg ggctgagctt gtgaggccag gggccttagt caagttgtcc     120

tgcaaagctt ctggcttcaa tattaaagac tactatatgc actgggtgaa gcagaggcct     180

gaacagggcc tggagtggat tggaaggatt gatcctgaga atggtgatat tatatatgac     240

ccgaagttcc agggcaaggc cagtataaca acagacacat cctccaacac agcctacctg     300

cagctcagca gcctgacgtc tgaggacact gccgtctatt actgtgctta cgatgctggt     360

gacccgcct ggtttactta ctggggccaa gggactctgg tcaccgtctc g               411
```

<210> 319
<211> 130
<212> PRT

<213> Mus musculus

<400> 319

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

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

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

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

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

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

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

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

Lys Arg
    130
```

<210> 320
<211> 390
<212> DNA
<213> Mus musculus

<400> 320

```
atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gcgcggcgcg        60

cgctgcgata tccagatgac ccagagcccg agcagcctga gcgcgagcgt gggcgatcgc       120

gtgaccatta cctgcaaagc gagccaggat gtgtttaccg cggtggcgtg gtatcagcag       180

aaaccgggca aagcgccgaa actgctgatt tattgggcga gcacccgcca taccggcgtg       240

ccgagtcgct ttagcggcag cggcagcggc accgatttta ccctgaccat tagcagcctg       300

cagccggaag attttgcgac ctattattgc cagcagtata gcagctatcc gctgaccttt       360

ggcggcggca ccaaagtgga aattaaacgt                                        390
```

<210> 321
<211> 138
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 321

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

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

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

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

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

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

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

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

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

<210> 322
<211> 414
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<220>
<221> misc_feature
<223> Humanized Antibody Sequence

<400> 322

```
atggattgga cctggagcat tctgtttctg gtggcggcgc cgaccggcgc gcatagcgaa        60
gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc       120
tgcaaagcga gcggctttaa cattaaagat tattatatgc attgggtgcg ccaggcgccg       180
ggccagggcc tggaatggat cggccgcatt gatccggaaa acggcgatat tatttatgat       240
ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg       300
gaactgcgca gcctgcgcag cgatgatacc gcggtgtatt attgcgcgta tgatgcgggc       360
gatccggcgt ggtttaccta ttggggccag ggcaccctgg tgaccgtctc gagc             414
```

<210> 323
<211> 106
<212> PRT
<213> Mus musculus

<400> 323

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

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
            20                  25                  30

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
        35                  40                  45

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
    50                  55                  60

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
65                  70                  75                  80

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
                85                  90                  95

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
            100                 105
```

<210> 324
<211> 320
<212> PRT
<213> Mus musculus

<400> 324

```
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
1               5                   10                  15

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
    50                  55                  60

Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
65                  70                  75                  80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
                85                  90                  95

Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
            100                 105                 110

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

```
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
    130                 135                 140

Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
145                 150                 155                 160

Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
                165                 170                 175

Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
            180                 185                 190

Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
        195                 200                 205

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
    210                 215                 220

Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
225                 230                 235                 240

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

Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
            260                 265                 270

Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
        275                 280                 285

Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
    290                 295                 300

Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
305                 310                 315                 320
```

<210> 325
<211> 106
<212> PRT
<213> Homo sapiens

<400> 325

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

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

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser


        35                  40                  45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
    50                  55                  60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65                  70                  75                  80

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

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
```

<210> 326
<211> 327
<212> PRT
<213> Homo sapiens

<400> 326

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160
```

```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 327
<211> 120
<212> PRT
<213> Mus musculus

<400> 327

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

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

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

Gly Tyr Ile Asn Pro Tyr Asn Asp 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> 328
<211> 120
<212> PRT
<213> Mus musculus

<400> 328

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

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

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

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

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser 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> 329
<211> 120
<212> PRT
<213> Mus musculus

<400> 329

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

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

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

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

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

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

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

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

<210> 330
<211> 226
<212> PRT
<213> Mus musculus

<400> 330

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

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

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

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

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

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

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

Gly Thr Leu Val Thr Val Ser Ser Thr Val Ala Ala Pro Ser Val Phe
        115                 120                 125

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
    130                 135                 140

Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
145                 150                 155                 160

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

Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
            180                 185                 190

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
        195                 200                 205

Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
    210                 215                 220

Glu Cys
225
```

<210> 331
<211> 447

<212> PRT
<213> Mus musculus

<400> 331

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            20                  25                  30

Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
```

```
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385             390                     395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445
```

<210> 332
<211> 107
<212> PRT
<213> Mus musculus

<400> 332

```
Asp Ile Gln Met Thr Gln Ile Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15

Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile
        35                  40                  45

Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 333
<211> 324
<212> PRT
<213> Mus musculus

<400> 333

```
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
1               5                   10                  15

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
    50                  55                  60

Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
65                  70                  75                  80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
                85                  90                  95

Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
            100                 105                 110

Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
        115                 120                 125

Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
    130                 135                 140

Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
145                 150                 155                 160

Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
                165                 170                 175

Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
            180                 185                 190

Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
        195                 200                 205

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
    210                 215                 220

Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
225                 230                 235                 240

Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
                245                 250                 255

Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
```

```
                260                 265                 270

Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
        275                 280                 285

Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
    290                 295                 300

Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
305                 310                 315                 320

Ser Pro Gly Lys
```

<210> 334
<211> 213
<212> PRT
<213> Mus musculus

<400> 334

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15

Asp Arg Val Asn Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Ala Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile Lys His Pro Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Thr Asp Ala Ala Pro
            100                 105                 110

Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
        115                 120                 125

Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
    130                 135                 140

Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145                 150                 155                 160

Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
                165                 170                 175

Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
            180                 185                 190

Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
        195                 200                 205

Asn Arg Asn Glu Cys
    210
```

<210> 335
<211> 444
<212> PRT
<213> Mus musculus

<400> 335

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            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 Ala Lys Thr Thr Pro Pro Ser Val
        115                 120                 125

Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr
    130                 135                 140

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr
145                 150                 155                 160

Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val
```

```
                165                 170                 175

Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser
            180                 185                 190

Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala
        195                 200                 205

Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys
    210                 215                 220

Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe
225                 230                 235                 240

Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val
                245                 250                 255

Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe
            260                 265                 270

Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro
        275                 280                 285

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro
    290                 295                 300

Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val
305                 310                 315                 320

Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
                325                 330                 335

Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys
            340                 345                 350

Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp
        355                 360                 365

Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro
    370                 375                 380

Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser
385                 390                 395                 400

Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala
                405                 410                 415

Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His
            420                 425                 430
```

His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
435 440

<210> 336
<211> 108
<212> PRT
<213> Mus musculus

<400> 336

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Phe Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 337
<211> 324
<212> DNA
<213> Mus musculus

<400> 337

gatatccaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgca aagcgagcca ggatgtgttt accgcggtgg cgtggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttattgg gcgagcaccc gccataccgg cgtgccgagt 180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240

gaagattttg cgacctatta ttgccagcag tatagcagct atccgctgac ctttggcggc 300

ggcaccaaag tggaaattaa acgt 324

<210> 338
<211> 119

<212> PRT
<213> Mus musculus

<400> 338

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

<210> 339
<211> 357
<212> DNA
<213> Mus musculus

<400> 339

```
gaagtgcagc tggtgcagag cggcgcggaa gtgaaaaac cgggcgcgag cgtgaaagtg        60

agctgcaaag cgagcggctt taacattaaa gattattata tgcattgggt gcgccaggcg       120

ccgggccagg gcctggaatg gatcggccgc attgatccgg aaaacggcga tattatttat       180

gatccgaaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat       240

atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gtatgatgcg       300

ggcgatccgg cgtggtttac ctattggggc cagggcaccc tggtgaccgt ctcgagc          357
```

<210> 340
<211> 1395
<212> DNA
<213> Mus musculus

<400> 340

atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60

gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc 120

tgcaaggctt ctggttttac cttcaccgac tatattatgc actgggtgcg tcaggcccct 180

ggtcaagggc ttgagtggat gggctatatc aacccttata atgatgacac cgaatacaac 240

gagaagttca agggccgtgt cacgattacc gcggacaaat ccacgagcac agcctacatg 300

gagctgagca gcctgcgctc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat 360

tactacgatg ccccgtttgc ttactggggc caagggactc tggtcaccgt ctctagtgcc 420

tccaccaagg gcccatcggt cttccccctg gcgccctgct ccaggagcac ctccgagagc 480

acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 540

aactcaggcg ctctgaccag cggcgtgcac accttcccag ctgtcctaca gtcctcagga 600

ctctactccc tcagcagcgt ggtgaccgtg ccctccagca acttcggcac ccagacctac 660

acctgcaacg tagatcacaa gcccagcaac accaaggtgg acaagacagt tgagcgcaaa 720

tgttgtgtcg agtgcccacc gtgcccagca ccacctgtgg caggaccgtc agtcttcctc 780

ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacgtgcgtg 840

gtggtggacg tgagccacga agaccccgag gtccagttca actggtacgt ggacggcgtg 900

gaggtgcata atgccaagac aaagccacgg gaggagcagt tcaacagcac gttccgtgtg 960

gtcagcgtcc tcaccgttgt gcaccaggac tggctgaacg gcaaggagta caagtgcaag 1020

gtctccaaca aaggcctccc agcccccatc gagaaaacca tctccaaaac caaagggcag 1080

ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag 1140

gtcagcctga cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag 1200

agcaatgggc agccggagaa caactacaag accacacctc ccatgctgga ctccgacggc 1260

tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1320

ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1380

ctgtctccgg gtaaa 1395

<210> 341
<211> 213
<212> PRT
<213> Mus musculus

<400> 341

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Ile Lys His Pro Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn Arg Gly Glu Cys
    210
```

<210> 342
<211> 639
<212> DNA
<213> Mus musculus

<400> 342

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc 60
atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca 180
cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc 300
accaaggtgg agatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct 360
gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480
agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600
agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 343
<211> 235
<212> PRT
<213> Mus musculus

<400> 343

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Asp Ile Lys His Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser


            210                 215                 220


        Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
        225                 230                 235
```

<210> 344

<211> 705
<212> DNA
<213> Mus musculus

<400> 344

```
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcc      60

agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt aggtgaccgt     120

gtcaccatca cttgccgcgc aagtcaggat attagcagct atttaaattg gtatcagcag     180

aaaccaggga aagcccctaa gctcctgatc tattctactt cccgtttgaa tagtggggtc     240

ccatcacgct tcagtggcag tggctctggg acagatttca ctctcaccat cagcagtctg     300

caacctgaag attttgcaac ttactactgt caacaggata ttaaacaccc tacgttcggt     360

caaggcacca aggtggagat caaacgtacg gtggctgcac catctgtctt catcttcccg     420

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc     480

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc     540

caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg     600

acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag     660

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt                     705
```

<210> 345
<211> 446
<212> PRT
<213> Mus musculus

<400> 345

```
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

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
    210                 215                 220

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
```

```
            340                 345                 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> 346
<211> 1338
<212> DNA
<213> Mus musculus

<400> 346

gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggttt taccttcacc gactatatta tgcactgggt gcgtcaggcc 120
cctggtcaag ggcttgagtg gatgggctat atcaaccctt ataatgatga caccgaatac 180
aacgagaagt tcaagggccg tgtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgcg ctctgaggac acggccgtgt attactgtgc gcgttcgatt 300
tattactacg atgccccgtt tgcttactgg ggccaaggga ctctggtcac cgtctctagt 360
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 420
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 660
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 720
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 780
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 840
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 900
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 960

aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1020
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1140
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1200
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
tccctgtctc cgggtaaa 1338

<210> 347
<211> 465
<212> PRT
<213> Mus musculus

<400> 347

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly 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 Ala Ser Thr Lys Gly
    130                 135                 140

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
145                 150                 155                 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175
```

```
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
    210                 215                 220

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
225                 230                 235                 240

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
                245                 250                 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260                 265                 270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
        275                 280                 285

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290                 295                 300

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
305                 310                 315                 320

Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
                325                 330                 335

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
            340                 345                 350

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355                 360                 365

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370                 375                 380

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385                 390                 395                 400

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                405                 410                 415

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
            420                 425                 430
```

```
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        435                 440                 445

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    450                 455                 460

Lys
465
```

<210> 348
<211> 1395
<212> DNA
<213> Mus musculus

<400> 348

```
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag      60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc     120
tgcaaggctt ctggttttac cttcaccgac tatattatgc actgggtgcg tcaggcccct     180
ggtcaagggc ttgagtggat gggctatatc aacccttata atgatgacac cgaatacaac     240
gagaagttca agggccgtgt cacgattacc gcggacaaat ccacgagcac agcctacatg     300
gagctgagca gcctgcgctc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat     360
tactacgatg ccccgtttgc ttactggggc caagggactc tggtcaccgt ctctagtgcc     420
tccaccaagg gcccatcggt cttccccctg gcgccctgct ccaggagcac ctccgagagc     480
acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg     540
aactcaggcg ctctgaccag cggcgtgcac accttcccag ctgtcctaca gtcctcagga     600
ctctactccc tcagcagcgt ggtgaccgtg ccctccagca acttcggcac ccagacctac     660
acctgcaacg tagatcacaa gcccagcaac accaaggtgg acaagacagt tgagcgcaaa     720
tgttgtgtcg agtgcccacc gtgcccagca ccacctgtgg caggaccgtc agtcttcctc     780
ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacgtgcgtg     840
gtggtggacg tgagccacga agaccccgag gtccagttca actggtacgt ggacggcgtg     900
gaggtgcata atgccaagac aaagccacgg gaggagcagt tcaacagcac gttccgtgtg     960
gtcagcgtcc tcaccgttgt gcaccaggac tggctgaacg gcaaggagta caagtgcaag    1020
gtctccaaca aaggcctccc agcccccatc gagaaaacca tctccaaaac caaagggcag    1080
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag    1140
gtcagcctga cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag    1200
agcaatgggc agccggagaa caactacaag accacacctc ccatgctgga ctccgacggc    1260
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc    1320
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc    1380
ctgtctccgg gtaaa                                                     1395
```

<210> 349
<211> 417
<212> DNA
<213> Mus musculus

<400> 349

```
atggaatgga tctggatatt tctcttcctc ctgtcaggaa ctgcaggtgt ccactctgag       60

gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc      120

tgcaaggctt ctggttttac cttcaccgac tatattatgc actgggtgcg tcaggcccct      180

ggtcaagggc ttgagtggat gggctatatc aacccttata atgatgacac cgaatacaac      240

gagaagttca agggccgtgt cacgattacc gcggacaaat ccacgagcac agcctacatg      300

gagctgagca gcctgcgctc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat      360

tactacgatg ccccgtttgc ttactggggc caagggactc tggtcacagt ctcgagc         417
```

<210> 350
<211> 218
<212> PRT
<213> Mus musculus

<400> 350

```
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Gln Arg Ala Thr Ile Ala Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20                  25                  30

Gly Thr Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Glu Ile Pro Ala
    50                  55                  60

Arg Phe Ser Gly Thr Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Glu Glu Asp Ile Thr Thr Tyr Tyr Cys Gln Gln Ser Asn
                85                  90                  95

Glu Asp Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
        115                 120                 125

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
    130                 135                 140
```

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145 150 155 160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
180 185 190

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
195 200 205

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
210 215

<210> 351
<211> 15
<212> PRT
<213> Mus musculus

<400> 351

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Thr Ser Tyr Met Asn
1 5 10 15

<210> 352
<211> 7
<212> PRT
<213> Mus musculus

<400> 352

Ala Ala Ser Asn Leu Glu Ser
1 5

<210> 353
<211> 9
<212> PRT
<213> Mus musculus

<400> 353

Gln Gln Ser Asn Glu Asp Pro Phe Thr
1 5

<210> 354
<211> 657
<212> DNA
<213> Mus musculus

<400> 354

```
gacattgtgt tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc        60
atcgcctgca aggccagcca aagtgttgat tatgatggta ctagttatat gaattggtac       120
caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct       180

gagatcccag ccaggtttag tggcactggg tctgggacag acttcaccct caacatccat       240
cctgtggagg aggaggatat cacaacctat tactgtcagc aaagtaatga ggatccgttc       300
acgttcggag gggggaccaa gttggaaata aaacgggctg atgctgcacc aactgtatcc       360
atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg       420
aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa       480
aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc       540
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc       600
actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag          657
```

<210> 355
<211> 238
<212> PRT
<213> Mus musculus

<400> 355

```
Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
            20                  25                  30

Val Ser Leu Gly Gln Arg Ala Thr Ile Ala Cys Lys Ala Ser Gln Ser
        35                  40                  45

Val Asp Tyr Asp Gly Thr Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
    50                  55                  60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
65                  70                  75                  80

Glu Ile Pro Ala Arg Phe Ser Gly Thr Gly Ser Gly Thr Asp Phe Thr
                85                  90                  95

Leu Asn Ile His Pro Val Glu Glu Glu Asp Ile Thr Thr Tyr Tyr Cys
            100                 105                 110

Gln Gln Ser Asn Glu Asp Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu
        115                 120                 125

Glu Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro
    130                 135                 140

Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu
145                 150                 155                 160

Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly
                165                 170                 175

Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser
            180                 185                 190

Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp
        195                 200                 205

Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr
    210                 215                 220

Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230                 235
```

<210> 356
<211> 717

<212> DNA
<213> Mus musculus

<400> 356

```
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt        60

gacattgtgt tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc       120

atcgcctgca aggccagcca aagtgttgat tatgatggta ctagttatat gaattggtac       180

caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct       240

gagatcccag ccaggtttag tggcactggg tctgggacag acttcaccct caacatccat       300

cctgtggagg aggaggatat cacaacctat tactgtcagc aaagtaatga ggatccgttc       360

acgttcggag gggggaccaa gttggaaata aaacgggctg atgctgcacc aactgtatcc       420

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg       480

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa       540

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc       600

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc       660

actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag          717
```

<210> 357
<211> 442
<212> PRT
<213> Mus musculus

<400> 357

```
Gln Val Gln Leu Gln Gln Pro Gly Thr Glu Leu Val Arg Pro Gly Thr
1               5                   10                  15


Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Thr Tyr
            20                  25                  30
```

```
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp Gln Lys Phe
    50                  55                  60

Lys Asp Lys Ala Thr Leu Thr Leu Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met His Leu Ser Gly Pro Thr Ser Val Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Gly Glu Trp Gly Ser Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro
        115                 120                 125

Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly
    130                 135                 140

Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn
145                 150                 155                 160

Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr
            180                 185                 190

Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser
        195                 200                 205

Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro
    210                 215                 220

Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys
                245                 250                 255

Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp
            260                 265                 270

Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu
        275                 280                 285
```

```
Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser
305                 310                 315                 320

Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
                325                 330                 335

Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln
            340                 345                 350

Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe
        355                 360                 365

Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu
    370                 375                 380

Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe
385                 390                 395                 400

Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn
                405                 410                 415

Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr
            420                 425                 430

Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440
```

<210> 358
<211> 5
<212> PRT
<213> Mus musculus

<400> 358

```
Thr Tyr Trp Met Asn
1               5
```

<210> 359
<211> 17
<212> PRT
<213> Mus musculus

<400> 359

Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp Gln Lys Phe Lys
1   5   10   15

Asp

<210> 360
<211> 9
<212> PRT
<213> Mus musculus

<400> 360

Ser Gly Glu Trp Gly Ser Met Asp Tyr
1   5

<210> 361
<211> 1329
<212> DNA
<213> Mus musculus

<400> 361

caggtccaac tacagcagcc tgggactgag ctggtgaggc ctggaacttc agtgaagttg 60

tcctgtaagg cttctggcta catcttcacc acctactgga tgaactgggt gaaacagagg 120

cctggacaag gccttgagtg gattggcatg attcatcctt ccgcaagtga aattaggttg 180

gatcagaaat tcaaggacaa ggccacattg actcttgaca aatcctccag cacagcctat 240

atgcacctca gcggcccgac atctgtggat tctgcggtct attactgtgc aagatcaggg 300

gaatgggggt ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctcagccaaa 360

acgacacccc catctgtcta tccactggcc cctggatctg ctgcccaaac taactccatg 420

gtgaccctgg gatgcctggt caagggctat ttccctgagc cagtgacagt gacctggaac 480

tctggatccc tgtccagcgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac 540

actctgagca gctcagtgac tgtcccctcc agcacctggc ccagcgagac cgtcacctgc 600

aacgttgccc acccggccag cagcaccaag gtggacaaga aaattgtgcc cagggattgt 660

ggttgtaagc cttgcatatg tacagtccca gaagtatcat ctgtcttcat cttcccccca 720

aagcccaagg atgtgctcac cattactctg actcctaagg tcacgtgtgt tgtggtagac 780

atcagcaagg atgatcccga ggtccagttc agctggtttg tagatgatgt ggaggtgcac 840

acagctcaga cgcaaccccg ggaggagcag ttcaacagca ctttccgctc agtcagtgaa 900

cttcccatca tgcaccagga ctggctcaat ggcaaggagt tcaaatgcag ggtcaacagt 960

gcagctttcc ctgcccccat cgagaaaacc atctccaaaa ccaaaggcag accgaaggct 1020

ccacaggtgt acaccattcc acctcccaag gagcagatgg ccaaggataa agtcagtctg 1080

acctgcatga taacagactt cttccctgaa gacattactg tggagtggca gtggaatggg 1140

cagccagcgg agaactacaa gaacactcag cccatcatgg acacagatgg ctcttacttc 1200

atctacagca agctcaatgt gcagaagagc aactgggagg caggaaatac tttcacctgc 1260

tctgtgttac atgagggcct gcacaaccac catactgaga agagcctctc ccactctcct 1320

ggtaaatga 1329

<210> 362
<211> 461
<212> PRT
<213> Mus musculus

<400> 362

```
Met Gly Trp Ser Ser Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Val His Ser Gln Val Gln Leu Gln Gln Pro Gly Thr Glu Leu Val Arg
            20                  25                  30

Pro Gly Thr Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe
        35                  40                  45

Thr Thr Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp
65                  70                  75                  80

Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Leu Asp Lys Ser Ser Ser
                85                  90                  95

Thr Ala Tyr Met His Leu Ser Gly Pro Thr Ser Val Asp Ser Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Ser Gly Glu Trp Gly Ser Met Asp Tyr Trp Gly
        115                 120                 125

Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser
    130                 135                 140

Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
145                 150                 155                 160

Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175

Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190

Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
        195                 200                 205

Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
    210                 215                 220

Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
225                 230                 235                 240
```

```
Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
                245                 250                 255

Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
            260                 265                 270

Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
        275                 280                 285

Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
    290                 295                 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
305                 310                 315                 320

Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
                325                 330                 335

Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            340                 345                 350

Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
        355                 360                 365

Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
    370                 375                 380

Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
385                 390                 395                 400

Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
                405                 410                 415

Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
            420                 425                 430

Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
        435                 440                 445

His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
    450                 455                 460
```

<210> 363
<211> 1386
<212> DNA
<213> Mus musculus

<400> 363

atgggatgga gctctatcat cctcttcttg gtagcaacag ctacaggtgt ccactcccag 60

gtccaactac agcagcctgg gactgagctg gtgaggcctg gaacttcagt gaagttgtcc 120

tgtaaggctt ctggctacat cttcaccacc tactggatga actgggtgaa acagaggcct 180

ggacaaggcc ttgagtggat tggcatgatt catccttccg caagtgaaat taggttggat 240

cagaaattca aggacaaggc cacattgact cttgacaaat cctccagcac agcctatatg 300

cacctcagcg gcccgacatc tgtggattct gcggtctatt actgtgcaag atcaggggaa 360

tgggggtcta tggactactg gggtcaagga acctcagtca ccgtctcctc agccaaaacg 420

acacccccat ctgtctatcc actggcccct ggatctgctg cccaaactaa ctccatggtg 480

accctgggat gcctggtcaa gggctatttc cctgagccag tgacagtgac ctggaactct 540

ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacact 600

ctgagcagct cagtgactgt cccctccagc acctggccca gcgagaccgt cacctgcaac 660

gttgcccacc cggccagcag caccaaggtg gacaagaaaa ttgtgcccag ggattgtggt 720

tgtaagcctt gcatatgtac agtcccagaa gtatcatctg tcttcatctt ccccccaaag 780

cccaaggatg tgctcaccat tactctgact cctaaggtca cgtgtgttgt ggtagacatc 840

agcaaggatg atcccgaggt ccagttcagc tggtttgtag atgatgtgga ggtgcacaca 900

gctcagacgc aaccccggga ggagcagttc aacagcactt tccgctcagt cagtgaactt 960

cccatcatgc accaggactg gctcaatggc aaggagttca aatgcagggt caacagtgca 1020

gctttccctg cccccatcga gaaaaccatc tccaaaacca aaggcagacc gaaggctcca 1080

caggtgtaca ccattccacc tcccaaggag cagatggcca aggataaagt cagtctgacc 1140

tgcatgataa cagacttctt ccctgaagac attactgtgg agtggcagtg gaatgggcag 1200

ccagcggaga actacaagaa cactcagccc atcatggaca cagatggctc ttacttcatc 1260

tacagcaagc tcaatgtgca gaagagcaac tgggaggcag gaaatacttt cacctgctct 1320

gtgttacatg agggcctgca caaccaccat actgagaaga gcctctccca ctctcctggt 1380

aaatga 1386

<210> 364
<211> 106
<212> PRT
<213> Mus musculus

<400> 364

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Ile Lys His Pro Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 365
<211> 318
<212> DNA
<213> Mus musculus

<400> 365

```
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc      60

atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca     120

gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca     180

cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct     240

gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc     300

accaaggtgg agatcaaa                                                   318
```

<210> 366
<211> 120
<212> PRT
<213> Mus musculus

<400> 366

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            20                  25                  30

Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

                85                  90                  95

Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 367
<211> 360
<212> DNA
<213> Mus musculus

<400> 367

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc       60

tcctgcaagg cttctggttt taccttcacc gactatatta tgcactgggt gcgtcaggcc      120

cctggtcaag ggcttgagtg gatgggctat atcaaccctt ataatgatga caccgaatac      180

aacgagaagt tcaagggccg tgtcacgatt accgcggaca aatccacgag cacagcctac      240

atggagctga gcagcctgcg ctctgaggac acggccgtgt attactgtgc gcgttcgatt      300

tattactacg atgccccgtt tgcttactgg ggccaaggga ctctggtcac cgtctctagt      360
```

<210> 368
<211> 108
<212> PRT
<213> Mus musculus

<400> 368

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Phe Thr Ala
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100                 105
```

<210> 369
<211> 324
<212> DNA
<213> Mus musculus

<400> 369

```
gatatccaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc      60

attacctgca aagcgagcca ggatgtgttt accgcggtgg cgtggtatca gcagaaaccg     120

ggcaaagcgc cgaaactgct gatttattgg gcgagcaccc gccataccgg cgtgccgagt     180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg     240

gaagattttg cgacctatta ttgccagcag tatagcagct atccgctgac ctttggcggc     300

ggcaccaaag tggaaattaa acgt                                            324
```

<210> 370
<211> 119
<212> PRT
<213> Mus musculus

<400> 370

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

<210> 371
<211> 357
<212> DNA
<213> Mus musculus

<400> 371

```
gaagtgcagc tggtgcagag cggcgcggaa gtgaaaaac cgggcgcgag cgtgaaagtg       60

agctgcaaag cgagcggctt taacattaaa gattattata tgcattgggt gcgccaggcg      120

ccgggccagg gcctggaatg gatcggccgc attgatccgg aaaacggcga tattatttat      180

gatccgaaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat      240

atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gtatgatgcg      300

ggcgatccgg cgtggtttac ctattggggc cagggcaccc tggtgaccgt ctcgagc         357
```

<210> 372
<211> 108
<212> PRT
<213> Mus musculus

<400> 372

```
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
            20                  25                  30

Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Thr Thr Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105
```

<210> 373
<211> 324
<212> DNA
<213> Mus musculus

<400> 373

```
gatattcagc tgacccagag cccgagcttt ctgagcgcga gcgtgggcga tcgcgtgacc        60

attacctgca gcgtgagcag cagcattagc agcagcaacc tgcattggta tcagcagaaa       120

ccgggcaaag cgccgaaact gctgatttat ggcaccagca acctggcgag cggcgtgccg       180

agccgcttta gcggcagcgg cagcggcacc gaatttaccc tgaccattag cagcctgcag       240

ccggaagatt ttgcgaccta ttattgccag cagtggacca ccacctatac ctttggccag       300

ggcaccaaac tggaaattaa acgt                                              324
```

<210> 374
<211> 122
<212> PRT
<213> Mus musculus

<400> 374

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val Pro Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 375
<211> 366
<212> DNA
<213> Mus musculus

<400> 375

```
gaagtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg        60

agctgcaaag cgagcggctt taacattaaa gattattata ttcattgggt gcgccaggcg       120

ccgggccagg gcctggaatg gatgggccgc attgatccgg ataacggcga aagcacctat       180

gtgccgaaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat       240

atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gcgcgaaggc       300

ctggattatg gcgattatta tgcggtggat tattggggcc agggcaccct ggtgaccgtc       360

tcgagc                                                                  366
```

<210> 376
<211> 107
<212> PRT
<213> Mus musculus

<400> 376

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 377
<211> 321
<212> DNA
<213> Mus musculus

<400> 377

```
gacatccaga 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> 378
<211> 123
<212> PRT
<213> Mus musculus

<400> 378

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
```

```
Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 379
<211> 369
<212> DNA
<213> Mus musculus

<400> 379

```
gaggtgcagc tggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgttaaagtt        60

tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg       120

ccaggacaag gattggaatg gatgggcgaa attaacccta atagtggagg agcaggctac       180

aatcaaaaat tcaaagggag agttacaatg acaacagaca caagcacttc aacagcatat       240

atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg       300

tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc       360

gtctctagt                                                               369
```

<210> 380
<211> 108
<212> PRT
<213> Mus musculus

<400> 380

```
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Thr Ser Ser
            20                  25                  30

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser


    50                  55                  60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Phe Phe Pro
                85                  90                  95

Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 381
<211> 324
<212> DNA
<213> Mus musculus

<400> 381

```
gacatccagc tgacccagag ccccagcttc ctttccgcat ccgttggtga ccgagtaaca        60

atcacatgcc gcgcctcatc ttcagttaca tcttcttatc ttaattggta tcaacaaaaa       120

ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatc aggagttccc       180

tctcgatttt caggatctgg atcaggcaca gaatttacac ttactatatc atcactccaa       240

ccagaagact tcgccactta ttactgccaa caatacgatt tttttccaag cacattcgga       300

ggaggtacaa aagtagaaat caag                                              324
```

<210> 382
<211> 121
<212> PRT
<213> Mus musculus

<400> 382

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 383
<211> 363
<212> DNA
<213> Mus musculus

<400> 383

```
gaggtgcagc tggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaaggtt       60

agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc      120

cctggacaaa gacttgaatg gatgggagac attaaccctt ataacgacga cactacatac      180

aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat      240

atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact      300

gccgttatta ctactaacgc tatggattac tggggtcaag gaaccactgt taccgtctct      360

agt                                                                    363
```

<210> 384
<211> 108
<212> PRT
<213> Mus musculus

<400> 384

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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> 385
<211> 324
<212> DNA
<213> Mus musculus

<400> 385

```
gacatccaga tgacccagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca       60

ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcattggtt ccaacagaaa      120

cccggcaaag cacctaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct      180

tcaagatttt caggctctgg ctcaggcacc gactttactc ttacaatatc ctccctccaa      240

cccgaagact tcgcaaccta ttactgtcaa caatggtcct catatccact cacatttggc      300

ggcggcacaa aagtagaaat taaa                                             324
```

<210> 386
<211> 125
<212> PRT
<213> Mus musculus

<400> 386

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Phe
            20                  25                  30

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
    35                  40                  45

Gly Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe
    50                  55                  60

Gln Asp Lys Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe
            100                 105                 110

Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
```

<210> 387
<211> 375
<212> DNA
<213> Mus musculus

<400> 387

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc      60

tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc     120

cctggacaag ggcttgagtg gattggaagg attgatcctg agaatggtga tactttatat     180

gacccgaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac     240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg     300

gattatttcc acgatggtac ctcctactgg tacttcgatg tctggggccg tggcaccctg     360

gtcaccgtct ctagt                                                      375
```

<210> 388
<211> 106
<212> PRT
<213> Mus musculus

<400> 388

```
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser 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> 389
<211> 318
<212> DNA
<213> Mus musculus

<400> 389

```
gacatccagt tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc        60

atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg       120

aaagccccta agctcctgat ctatgccaca tccaacctgg cttctggggt cccatcaagg       180

ttcagcggca gtggatctgg gacagaattc actctcacaa tcagcagcct gcagcctgaa       240

gattttgcaa cttattactg tcagcagtgg agtagtgacc cactcacgtt cggcggaggg       300

accaaggtgg agatcaaa                                                     318
```

<210> 390
<211> 121
<212> PRT
<213> Mus musculus

<400> 390

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asp Ile Lys Asp Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
    50                  55                  60

Pro Gly Lys Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 391
<211> 363
<212> DNA
<213> Mus musculus

<400> 391

```
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc      60

tcctgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc     120

cctggacaag ggcttgagtg gatcggaagg gttgatcctg acaatggtga gactgaattt     180

gccccgaagt tcccgggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac     240

atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac     300

tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct     360

agt                                                                   363
```

<210> 392
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 392

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
        195                 200                 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
```

```
    210                 215                 220

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445
```

<210> 393
<211> 446
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 393

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
    210                 215                 220
```

```
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445
```

<210> 394
<211> 450
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 394

```
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
    450
```

<210> 395
<211> 446
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE
<223> Humanized Antibody Sequence

<400> 395

```
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
        435                 440                 445
```

<210> 396
<211> 445
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<220>
<221> MISC_FEATURE

<223> Humanized Antibody Sequence

<400> 396

```
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

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
    210                 215                 220

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
```

```
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445
```

Claims

1. An anti-sclerostin antibody or fragment thereof for use in a method for inhibiting bone resorption in a human, the method comprising administering to the human said anti-sclerostin antibody or fragment thereof in an amount from 1 mg/kg to 5 mg/kg, wherein the anti-sclerostin antibody or fragment thereof demonstrates a binding affinity for sclerostin of SEQ ID No: 1 of less than or equal to 1 x 10^{-7} M and cross-blocks the binding to sclerostin of an antibody comprising CDRs of SEQ ID Nos: 245, 246, 247, 78, 79 and 80 or CDRs of SEQ ID Nos. 284, 285, 286, 296, 297 and 298, or is cross-blocked from binding to sclerostin by said antibody, wherein:

- SEQ ID No:245 = Asp Tyr Asn Met His;

- SEQ ID No:246 = Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys Gly;
- SEQ ID No:247 = Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val;
- SEQ ID No: 78 = Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn;
- SEQ ID No: 79 = Tyr Thr Ser Arg Leu Leu Ser; and
- SEQ ID No: 80 = Gln Gln Gly Asp Thr Leu Pro Tyr Thr; and
- SEQ ID NO: 284 = Arg Ala Ser Ser Ser Val Thr Ser Ser Tyr Leu Asn;
- SEQ ID NO: 285 = Ser Thr Ser Asn Leu Ala Ser;
- SEQ ID NO: 286 = Gln Gln Tyr Asp Phe Phe Pro Ser Thr;
- SEQ ID NO: 296 = Asp Tyr Tyr Met Asn;
- SEQ ID NO: 297 = Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe Lys Gly; and
- SEQ ID NO 298 = Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp.

2. The antibody or fragment for use of claim 1, wherein the amount of anti-sclerostin antibody administered is from 1 mg/kg to 3 mg/kg.

3. The antibody or fragment for use of claim 1 or 2, wherein the amount of anti-sclerostin antibody administered is about 2 mg/kg.

4. The antibody or fragment for use of claim 1 or 2, wherein the amount of anti-sclerostin antibody administered is about 3 mg/kg.

5. The antibody or fragment for use of claim 1, wherein the method comprises administering to a human the anti-sclerostin antibody at a dose of from 70 to 450 mg.

6. The antibody or fragment for use of claim 1, where the method comprises administering a dose of about 140 mg.

7. The antibody or fragment for use of claim 1, where the method comprises administering a dose of about 210 mg.

8. The antibody or fragment for use of any one of the preceding claims, wherein the amount of anti-sclerostin antibody is administered to the subject once every two weeks.

9. The antibody or fragment for use of any one of claims 1 to 7, wherein the anti-sclerostin antibody is administered to the subject once a month.

10. The antibody or fragment for use of any one of the preceding claims, wherein the antibody is a human antibody, a humanized antibody, a monoclonal antibody, or a chimeric antibody.

11. The antibody or fragment for use of any one of the preceding claims, where the human is 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 Pisease, Turner Syndrome, Down Syndrome, Klinefelter Syndrome, leprosy, Perthes' Disease, adolescent idiopathic scoliosis, infantile onset multi-system inflammatory disease, Winchester Syndrome, Menkes Disease, Wilson's Disease, ischemic bone disease, Legg-Calve-Perthes disease, regional migratory osteoporosis, anemic states, conditions caused by steroids, glucocorticoid-induced bone loss, heparin-induced bone loss, bone marrow disorders, scurvy, malnutrition, calcium deficiency, 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.

12. The antibody or fragment for use of any one of the preceding claims, wherein the human is a post-menopausal woman.

13. The antibody or fragment for use of any one of the preceding claims, wherein the human is suffering from osteoporosis.

Patentansprüche

1. Anti-Sclerostin-Antikörper oder ein Fragment hiervon zur Verwendung in einer Methode zur Hemmung des Knochenabbaus in einem Menschen, die Methode umfassend die Verabreichung eines solchen Anti-Sclerostin-Antikörpers oder eines Fragments hiervon an einen Menschen in einer Menge zwischen 1 mg/kg und 5 mg/kg, wobei der Anti-Sclerostin-Antikörper oder ein Fragment hiervon eine Bindungsaffinität für Sclerostin der SEQ ID Nr. 1 von weniger als oder gleich 1 x 10^{-7} M zeigt und die Bindung zu Sclerostin eines Antikörpers, der CDR Sequenzen von SEQ ID Nr. 245, 246, 247, 78, 79 und 80 oder CDR Sequenzen von SEQ ID Nr. 284, 285, 286, 296, 297 und 298 umfasst, querblockiert oder selbst von einer Bindung an das Sclerostin durch diesen Antikörper querblockiert ist, wobei

- SEQ ID Nr. 245 = Asp Tyr Asn Met His;
- SEQ ID Nr.246 = Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys Gly;
- SEQ ID Nr.247 = Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val;
- SEQ ID Nr. 78 = Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn;
- SEQ ID Nr. 79 = Tyr Thr Ser Arg Leu Leu Ser; and
- SEQ ID Nr. 80 = Gln Gln Gly Asp Thr Leu Pro Tyr Thr; and
- SEQ ID Nr. 284 = Arg Ala Ser Ser Ser Val Thr Ser Ser Tyr Leu Asn;
- SEQ ID Nr. 285 = Ser Thr Ser Asn Leu Ala Ser;
- SEQ ID Nr. 286 = Gln Gln Tyr Asp Phe Phe Pro Ser Thr;
- SEQ ID Nr. 296 = Asp Tyr Tyr Met Asn;
- SEQ ID Nr. 297 = Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe Lys Gly; und
- SEQ ID Nr. 298 = Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp.

2. Antikörper oder Fragment zur Verwendung nach Anspruch 1, wobei die verabreichte Menge an Anti-Sclerostin-Antikörper zwischen 1 mg/kg und 3 mg/kg liegt.

3. Antikörper oder Fragment zur Verwendung nach Anspruch 1 oder 2, wobei die verabreichte Menge an Anti-Sclerostin-Antikörper bei etwa 2 mg/kg liegt.

4. Antikörper oder Fragment zur Verwendung nach Anspruch 1 oder 2, wobei die verabreichte Menge an Anti-Sclerostin-Antikörper bei etwa 3 mg/kg liegt.

5. Antikörper oder Fragment zur Verwendung nach Anspruch 1, wobei die Methode die Verabreichung eines Anti-Sclerostin-Antikörpers an einen Menschen mit einer Dosis von 70 bis 450 mg umfasst.

6. Antikörper oder Fragment zur Verwendung nach Anspruch 1, wobei die Methode die Verabreichung mit einer Dosis von 140 mg umfasst.

7. Antikörper oder Fragment zur Verwendung nach Anspruch 1, wobei die Methode die Verabreichung mit einer Dosis von 210 mg umfasst.

8. Antikörper oder Fragment zur Verwendung nach einem der vorhergehenden Ansprüche, wobei die Menge des Anti-Sclerostin-Antikörpers der Person einmal alle zwei Wochen verabreicht wird.

9. Antikörper oder Fragment zur Verwendung nach einem der Ansprüche 1 bis 7, wobei der Anti-Sclerostin-Antikörper der Person einmal monatlich verabreicht wird.

10. Antikörper oder Fragment zur Verwendung nach einem der vorhergehenden Ansprüche, wobei der Antikörper ein menschlicher Antikörper, ein humanisierter Antikörper, ein monoklonaler Antikörper oder ein chimärer Antikörper ist.

11. Antikörper oder Fragment zur Verwendung nach einem der vorhergehenden Ansprüche, wobei der Mensch an einer Knochen bezogenen Erkrankung leidet, die ausgewählt ist aus einer Gruppe, die Achondroplasie, kleidokraniale Dysostose, Enchondromatose, fibröse Dysplasie, die Gaucher-Krankheit, hypophosphatämische Knochenerweichung, das Marfan-Syndrom, multiple erbliche Exotosen, Neurofibromatose, Osteogenesis Imperfecta, Osteopetrose, Osteopoikilose, sklerotische Läsionen, Pseudoarthrose, Pyogene Osteomyelitis, Parodontalerkrankung, antiepileptischer Drogeninduzierter Knochenverlust, primären und sekundären Hyperparathyreoidismus, familiäre Hyperparathyreoidismus-Syndrome, durch Schwerelosigkeit induzierter Knochenverlust, Osteoporose bei Männern, postmenopausaler Knochenverlust, Arthrose, renale Osteodystrophie, infiltrative Erkrankungen der Knochen, oralen Knochenverlust, Osteonekrose des Kiefers, die juvenile Paget-Krankheit, Melorheostose, metabolische Knochenkrankheiten, Mastozytose, Sichelzellenanämie, Knochenverlust bedingt durch Organtransplantation, Knochenverlust bedingt durch Nierentransplantation, systemischer Lupus erythematodes, Morbus Bechterew, Epilepsie, juvenile Arthritiden, Thalassämie, Mukopolysaccharidosen, Morbus Fabry, das Turner-Syndrom, das Down-Syndrom, das Klinefelter-Syndrom, Lepra, die Perthes-Krankheit, idiopathische Skoliose bei Heranwachsenden, frühkindliche multisystemische Entzündungen, das Winchester-Syndrom, die Menkes-Krankheit, Morbus Wilson, ischämische Knochenerkrankungen, die Legg-Calve-Perthes-Krankheit, regional wandernde Osteoporose, Blutarmut, durch Steroide hervorgerufene Zustände, Glukokortikoid-induzierten Knochenverlust, Heparin-induzierten Knochenverlust, Knochenmark-Erkrankungen, Skorbut, Mangelernährung, Calciummangel, Osteoporose, Osteopenie, Alkoholismus, chronische Lebererkrankung, postmenopausale Zustände, chronisch entzündliche Erkrankungen, rheumatoide Arthritis, entzündliche Darmerkrankungen, Colitis ulcerosa, entzündliche Kolitis, Morbus Crohn, Oligomenorrhea, Amenorrhoe, Schwangerschaft, Diabetes Mellitus, Hyperthyreose, Erkrankungen der Schilddrüse, Erkrankungen der Nebenschilddrüse, Morbus Cushing, Akromegalie, Hypogonadismus, Immobilisation oder Nichtnutzung, das sympathetische Reflexdystrophie-Syndrom, regionale Osteoporose, Osteomalazie, Knochenverlust im Zusammenhang mit Gelenkersatz, HIV-bedingter Knochenverlust, Knochenverlust bei Verlust von Wachstumshormonen, Knochenverlust bei Mukoviszidose, Knochenverlust im Zusammenhang mit einer Chemotherapie, tumorinduzierter Knochenverlust, krebsbedingter Knochenverlust, hormonell bedingter ablativer Knochenverlust, Multiples Myelom, Arzneimittel-induzierter Knochenverlust, Magersucht, Krankheit bei Verlust von Gesichtsknochen, Krankheit bei Verlust von Schädelknochen, Krankheit bei Verlust von Kieferknochen, Krankheit bei Verlust von Knochen des Schädels mit dem Altern verbundener Knochenverlust, mit dem Altern verbundener Verlust von Gesichtsknochen, mit dem Altern verbundener Verlust von Schädelknochen, mit dem Altern verbundener Verlust von Kieferknochen, mit dem Altern verbundener Verlust von Knochen des Schädels, sowie Knochenabbau im Zusammenhang mit der Raumfahrt umfasst.

12. Antikörper oder Fragment zur Verwendung nach einem der vorhergehenden Ansprüche, wobei der Mensch eine Frau nach den Wechseljahren ist.

13. Antikörper oder Fragment zur Verwendung nach einem der vorhergehenden Ansprüche, wobei der Mensch an Osteoporose leidet.

Revendications

1. Anticorps anti-sclérostine, ou fragment d'un tel anticorps, pour utilisation dans un procédé d'inhibition de la résorption osseuse chez un humain, lequel procédé comporte le fait d'administrer audit humain ledit anticorps anti-sclérostine ou fragment d'un tel anticorps en une quantité de 1 mg/kg à 5 mg/kg, lequel anticorps anti-sclérostine ou fragment d'un tel anticorps montre, vis-à-vis de la sclérostine de Séquence N° 1, une affinité de liaison inférieure ou égale à 1.10^7 M et empêche, en réaction croisée, la liaison à la sclérostine d'un anticorps comprenant les régions CDR de Séquences N° 245, 246, 247, 78, 79 et 80 ou les régions CDR de Séquences N° 284, 285, 286, 296, 297 et 298, ou bien est empêché par un tel anticorps, en réaction croisée, de se lier à la sclérostine, étant entendu que :

    - la Séquence N° 245 est : Asp Tyr Asn Met His ;
    - la Séquence N° 246 est : Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys Gly ;
    - la Séquence N° 247 est : Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val ;
    - la Séquence N° 78 est : Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn ;
    - la Séquence N° 79 est : Tyr Thr Ser Arg Leu Leu Ser ;
    - la Séquence N° 80 est : Gln Gln Gly Asp Thr Leu Pro Tyr Thr ; et que

- la Séquence N° 284 est : Arg Ala Ser Ser Ser Val Thr Ser Ser Tyr Leu Asn ;
- la Séquence N° 285 est : Ser Thr Ser Asn Leu Ala Ser ;
- la Séquence N° 286 est : Gln Gln Tyr Asp Phe Phe Pro Ser Thr ;
- la Séquence N° 296 est : Asp Tyr Tyr Met Asn ;
- la Séquence N° 297 est : Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe Lys Gly ;
- la Séquence N° 298 est : Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp.

2. Anticorps ou fragment pour utilisation conforme à la revendication 1, dans laquelle la quantité d'anticorps anti-sclérostine administrée vaut de 1 mg/kg à 3 mg/kg.

3. Anticorps ou fragment pour utilisation conforme à la revendication 1 ou 2, dans laquelle la quantité d'anticorps anti-sclérostine administrée vaut à peu près 2 mg/kg.

4. Anticorps ou fragment pour utilisation conforme à la revendication 1 ou 2, dans laquelle la quantité d'anticorps anti-sclérostine administrée vaut à peu près 3 mg/kg.

5. Anticorps ou fragment pour utilisation conforme à la revendication 1, dans laquelle le procédé comporte le fait d'administrer à un humain l'anticorps anti-sclérostine en une dose de 70 à 450 mg.

6. Anticorps ou fragment pour utilisation conforme à la revendication 1, dans laquelle le procédé comporte le fait d'administrer une dose d'à peu près 140 mg.

7. Anticorps ou fragment pour utilisation conforme à la revendication 1, dans laquelle le procédé comporte le fait d'administrer une dose d'à peu près 210 mg.

8. Anticorps ou fragment pour utilisation conforme à l'une des revendications précédentes, dans laquelle la quantité d'anticorps anti-sclérostine est administrée au sujet une fois toutes les deux semaines.

9. Anticorps ou fragment pour utilisation conforme à l'une des revendications 1 à 7, dans laquelle la quantité d'anticorps anti-sclérostine est administrée au sujet une fois par mois.

10. Anticorps ou fragment pour utilisation conforme à l'une des revendications précédentes, lequel anticorps est un anticorps humain, un anticorps humanisé, un anticorps monoclonal, ou un anticorps chimérique.

11. Anticorps ou fragment pour utilisation conforme à l'une des revendications précédentes, dans laquelle le sujet humain souffre d'un trouble en rapport avec les os, choisi dans l'ensemble constitué par les suivants : achondroplasie, dysostose cléidocrânienne, enchondromatose, dysplasie fibreuse, maladie de Gaucher, rachitisme hypo-phosphatémique, syndrome de Marfan, exostoses multiples héréditaires, neurofibromatose, ostéogenèse imparfaite, ostéopétrose, ostéopoécilie, lésions sclérotiques, pseudarthrose, ostéomyélite à pyogène, parodontolyse, perte osseuse induite par antiépileptique, hyperparathyroïdisme primitif ou secondaire, syndromes d'hyperparathyroïdisme familial, perte osseuse induite par l'apesanteur, ostéoporose masculine, perte osseuse post-ménopausique, arthrose, ostéodystrophie rénale, maladies infiltrantes des os, perte osseuse orale, ostéonécrose de la mâchoire, maladie de Paget juvénile, mélorhéostose, maladies osseuses métaboliques, mastocytose, anémie falciforme, perte osseuse en relation avec une transplantation d'organe, perte osseuse en relation avec une transplantation de rein, lupus érythémateux aigu disséminé, spondylarthrite ankylosante, épilepsie, arthrite juvénile, thalassémie, mucopolysaccharidoses, maladie de Fabry, syndrome de Turner, syndrome de Down, syndrome de Klinefelter, lèpre, maladie de Perthes, scoliose idiopathique de l'adolescent, maladie inflammatoire multisystémique néonatale, syndrome de Winchester, maladie de Menkès, maladie de Wilson, maladie ischémique des os, maladie de Legg-Calvé-Perthes, ostéoporose migratoire régionale, états d'anémie, états induits par stéroïdes, perte osseuse induite par glucocorticoïdes, perte osseuse induite par héparine, troubles de la moelle osseuse, scorbut, malnutrition, manque de calcium, ostéoporose, ostéopénie, alcoolisme, maladie hépatique chronique, état post-ménopausique, états inflammatoires chroniques, polyarthrite rhumatoïde, affection intestinale inflammatoire, colite ulcéreuse, colite inflammatoire, maladie de Crohn, oligoménorrhée, aménorrhée, grossesse, diabète sucré, hyperthyroïdie, troubles thyroïdiens, troubles parathyroïdiens, maladie ou syndrome de Cushing, acromégalie, hypogonadisme, immobilisation ou inactivité, syndrome de dystrophie sympathique réflexe, ostéoporose régionale, ostéomalacie, perte osseuse associée à la mise en place d'une prothèse d'articulation, perte osseuse associée à une infection par VIH, perte osseuse associée à un déficit d'hormone de croissance, perte osseuse associée à la mucoviscidose, perte osseuse associée à une chimiothérapie, perte osseuse induite par une tumeur, perte osseuse en rapport avec un cancer, perte osseuse en rapport avec une hormonothérapie suppressive, myélome multiple, perte osseuse induite par un médicament, anorexie nerveuse, perte osseuse faciale associée à une maladie, perte osseuse crânienne associée à une maladie, perte osseuse à la mâchoire associée à une maladie, perte osseuse au crâne associée à une maladie, perte osseuse associée au vieillissement, perte osseuse faciale associée au vieillissement, perte osseuse crânienne associée au vieillissement, perte osseuse à la mâchoire associée au vieillissement, perte osseuse au crâne associée au vieillissement, et perte osseuse associée à un voyage spatial.

12. Anticorps ou fragment pour utilisation conforme à l'une des revendications précédentes, dans laquelle le sujet humain est une femme ménopausée.

13. Anticorps ou fragment pour utilisation conforme à l'une des revendications précédentes, dans laquelle le sujet humain souffre d'ostéoporose.

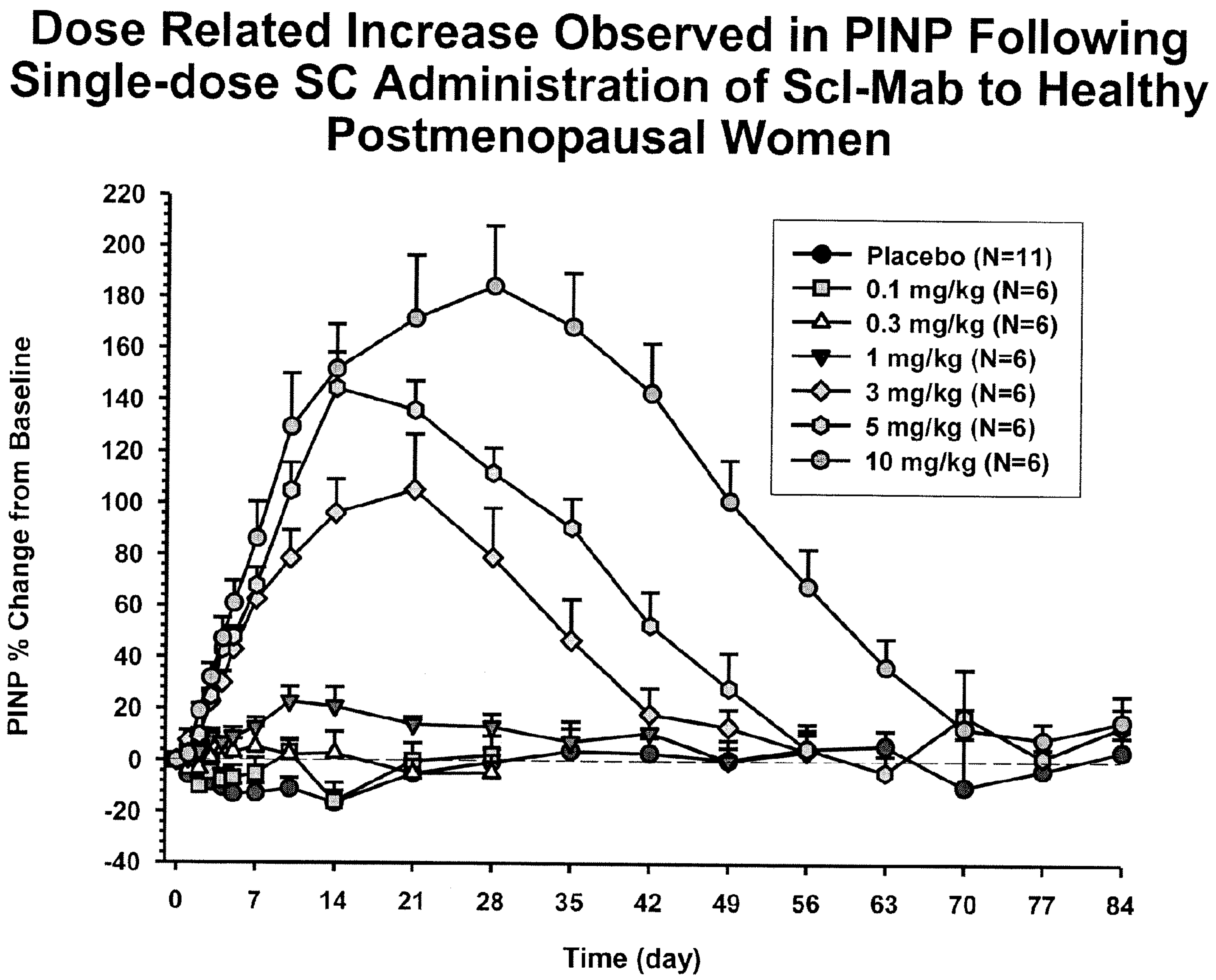

Dose Related Increase Observed in PINP Following Single-dose SC Administration of Scl-Mab to Healthy Postmenopausal Women
PINP % Change from Baseline
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
0
7
14
21
28
35
42
49
56
63
70
77
84
Time (day)
Placebo (N=11)
0.1 mg/kg (N=6)
0.3 mg/kg (N=6)
1 mg/kg (N=6)
3 mg/kg (N=6)
5 mg/kg (N=6)
10 mg/kg (N=6)

FIGURE 1

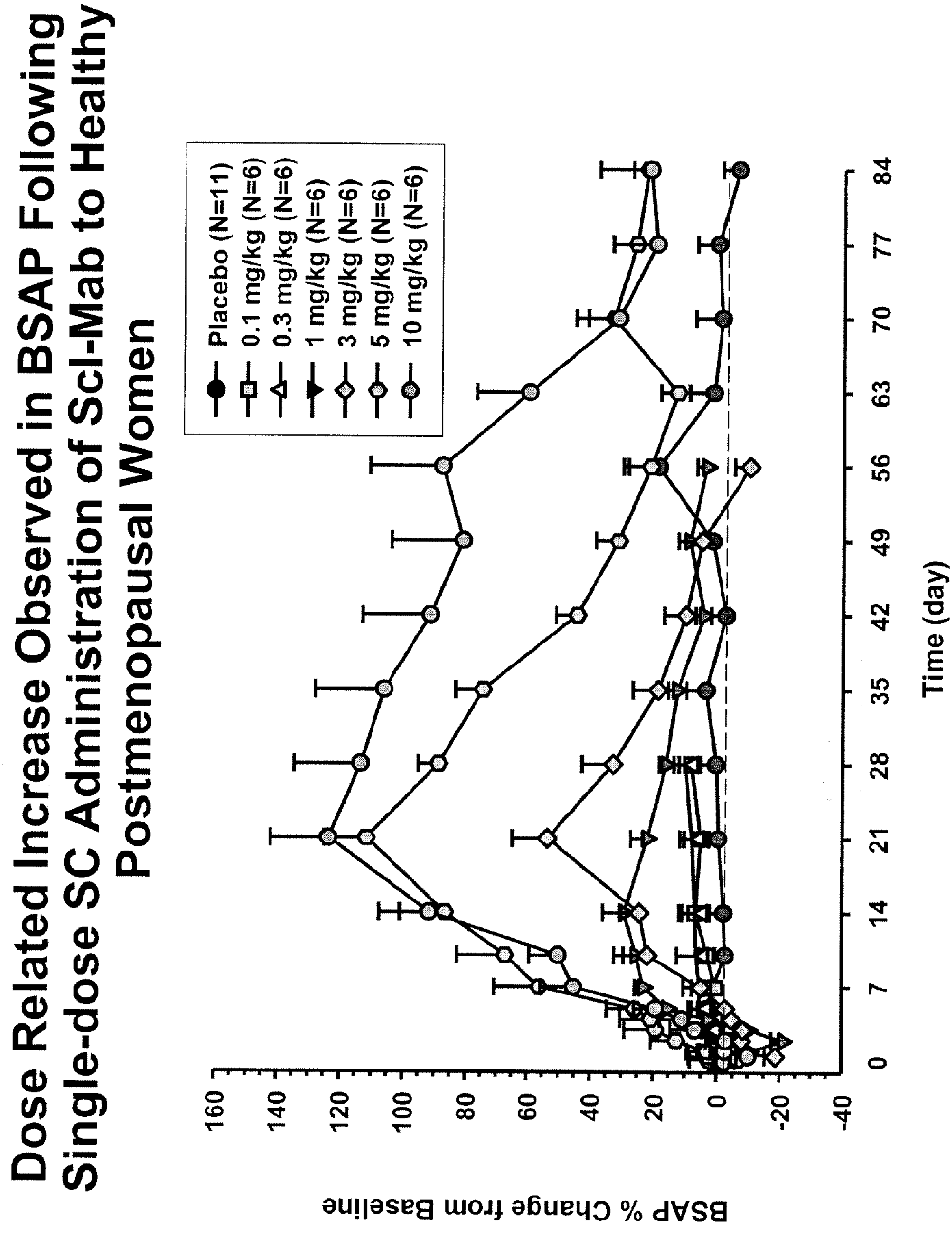

Dose Related Increase Observed in BSAP Following Single-dose SC Administration of Scl-Mab to Healthy Postmenopausal Women
BSAP % Change from Baseline
160
140
120
100
80
60
40
20
0
-20
-40
0
7
14
21
28
35
42
49
56
63
70
77
84
Time (day)
Placebo (N=11)
0.1 mg/kg (N=6)
0.3 mg/kg (N=6)
1 mg/kg (N=6)
3 mg/kg (N=6)
5 mg/kg (N=6)
10 mg/kg (N=6)

FIGURE 2

Dose Related Increase Observed in Osteocalcin Following Single-dose SC Administration of Scl-Mab to Healthy Postmenopausal Women

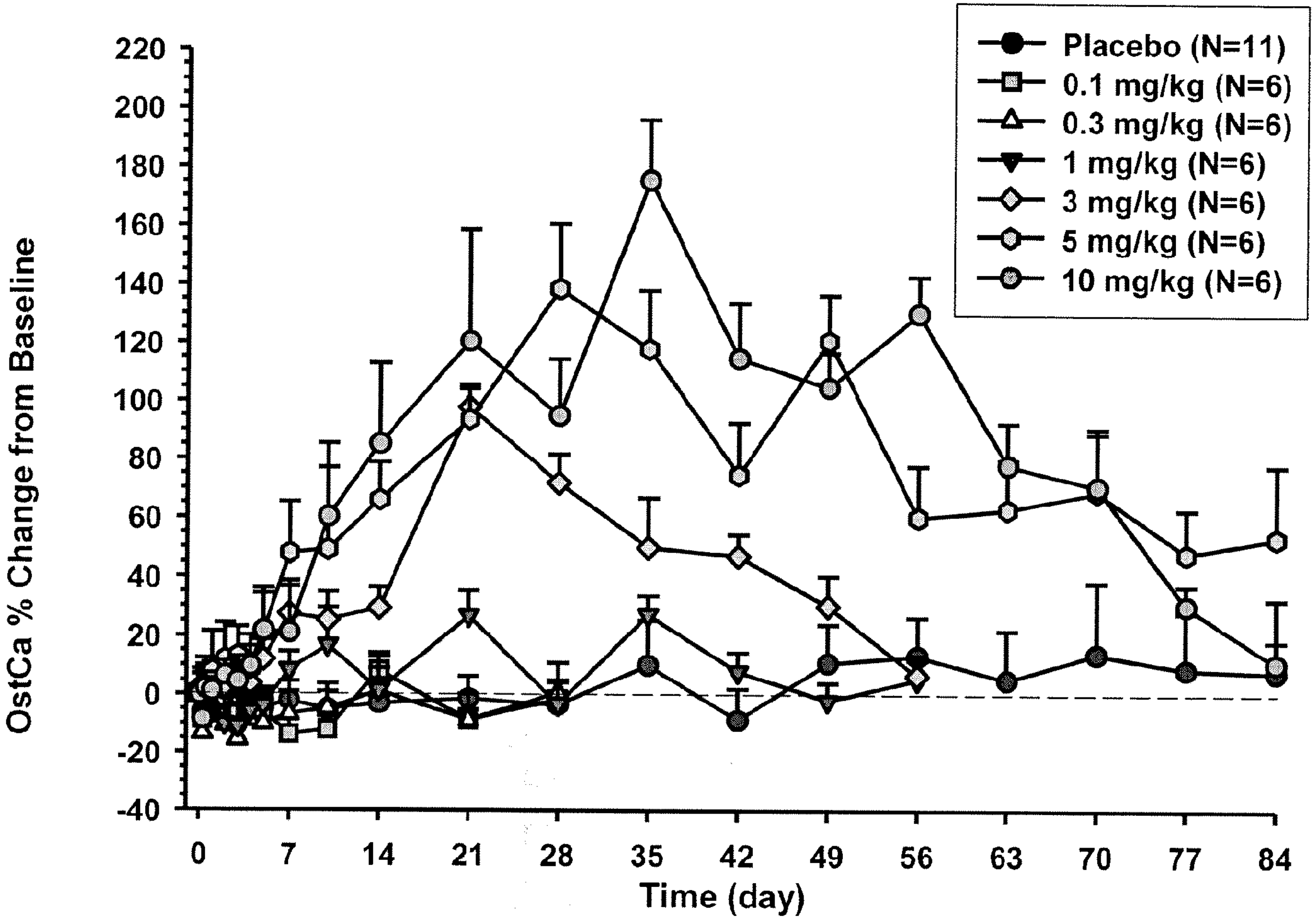


FIGURE 3

Dose Related Decrease in sCTx Following Single-dose SC Administration of Scl-Mab to Healthy Postmenopausal Women

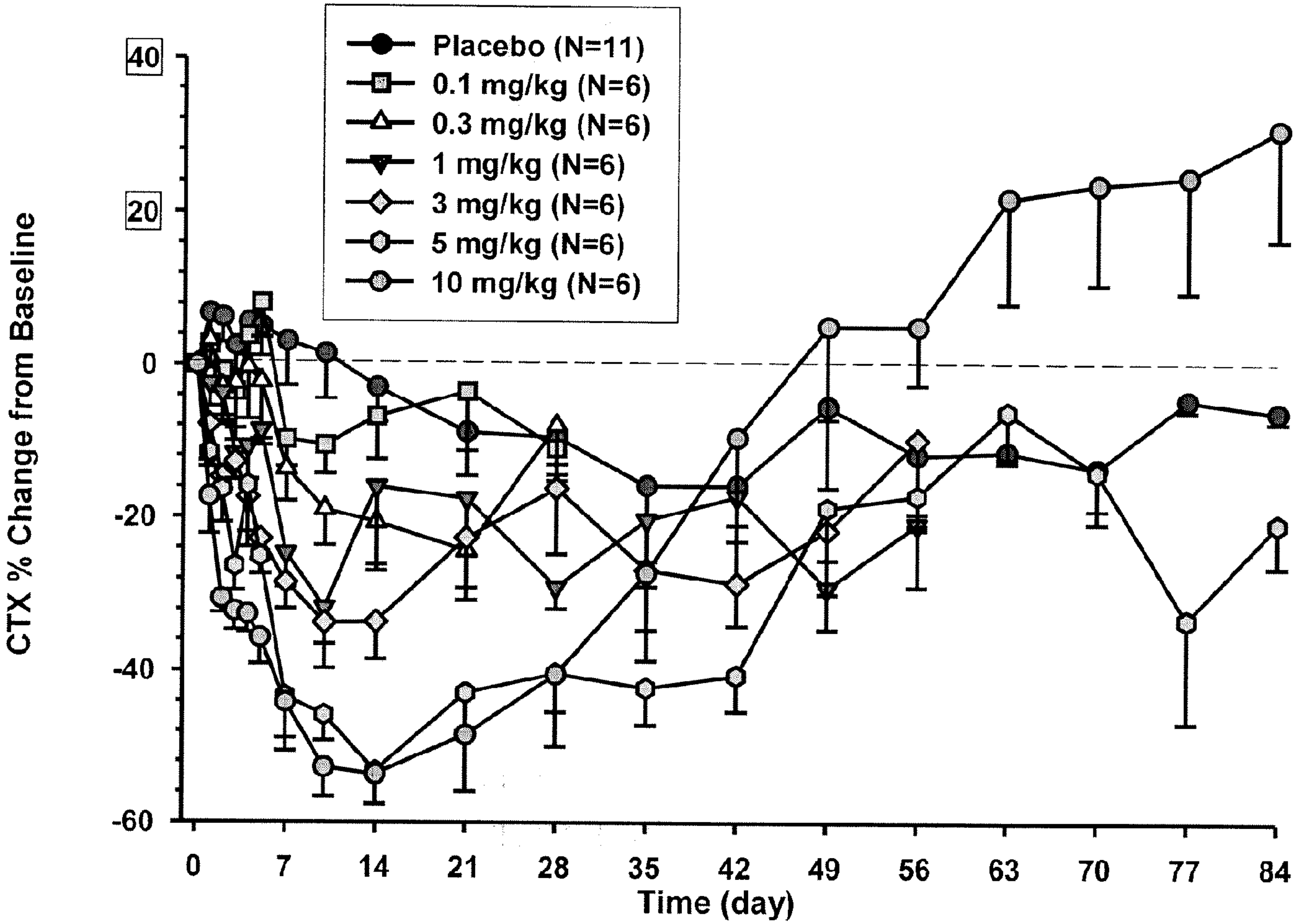


FIGURE 4

Large Anabolic Window Following Single SC Doses of 5 & 10 mg/kg Scl-Mab to Healthy Postmenopausal Women

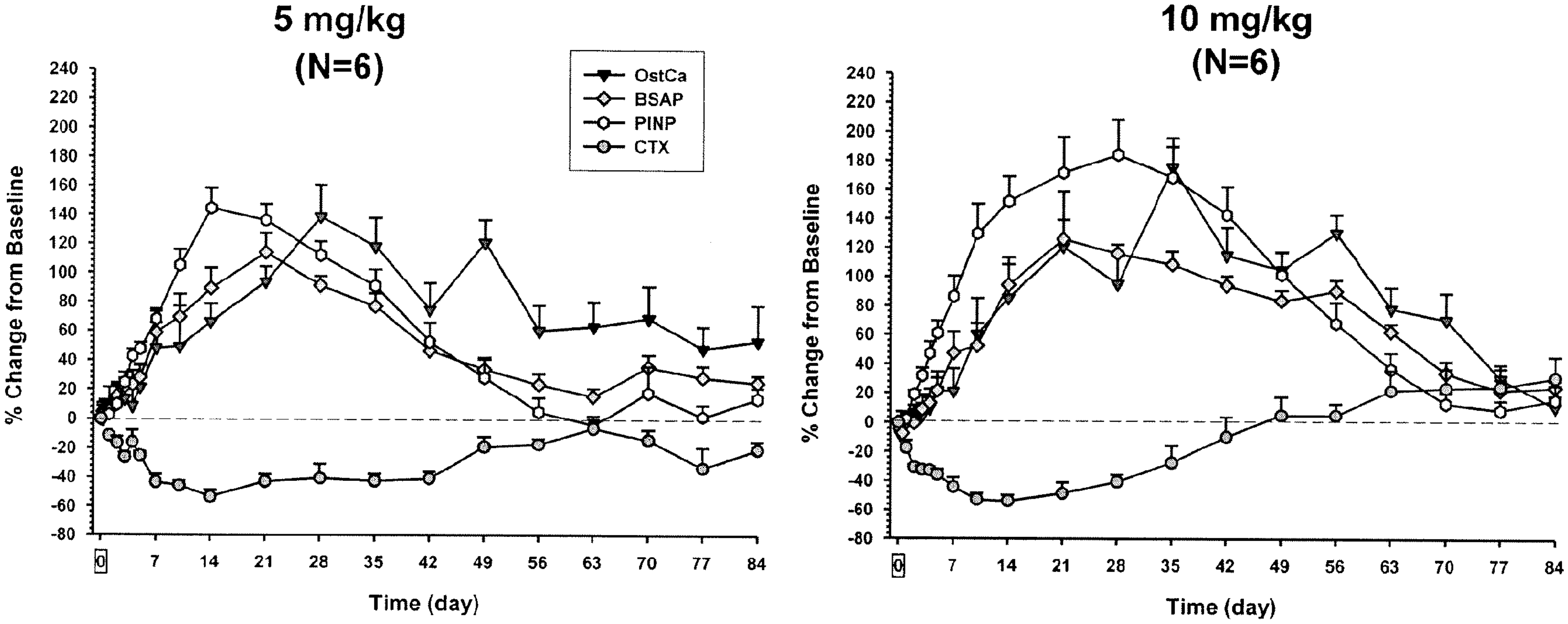
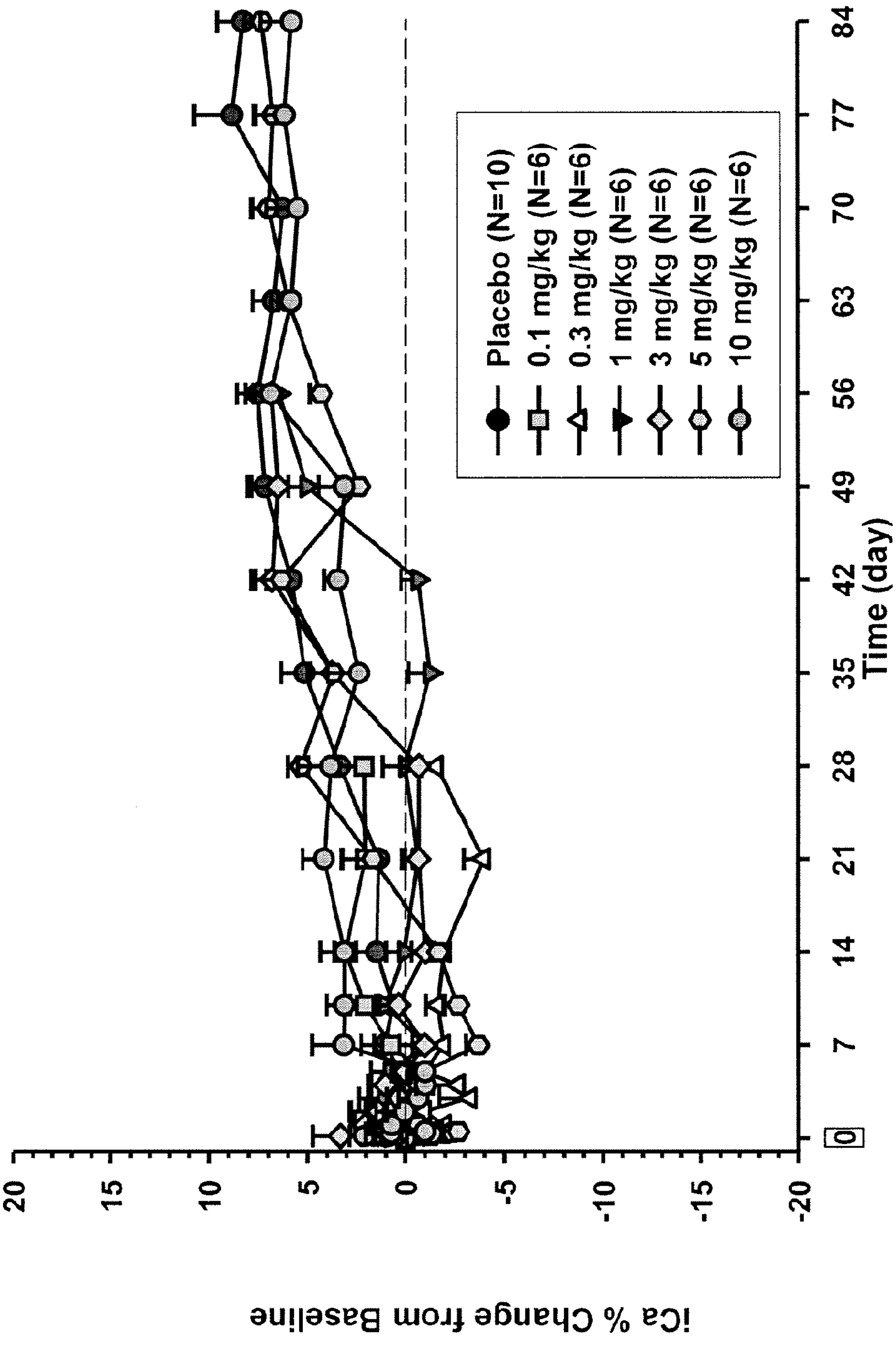


FIGURE 5



No Clinically Significant Changes in Serum Calcium Following Single-dose SC Administration of Scl-Mab to Healthy Postmenopausal Women

FIGURE 6

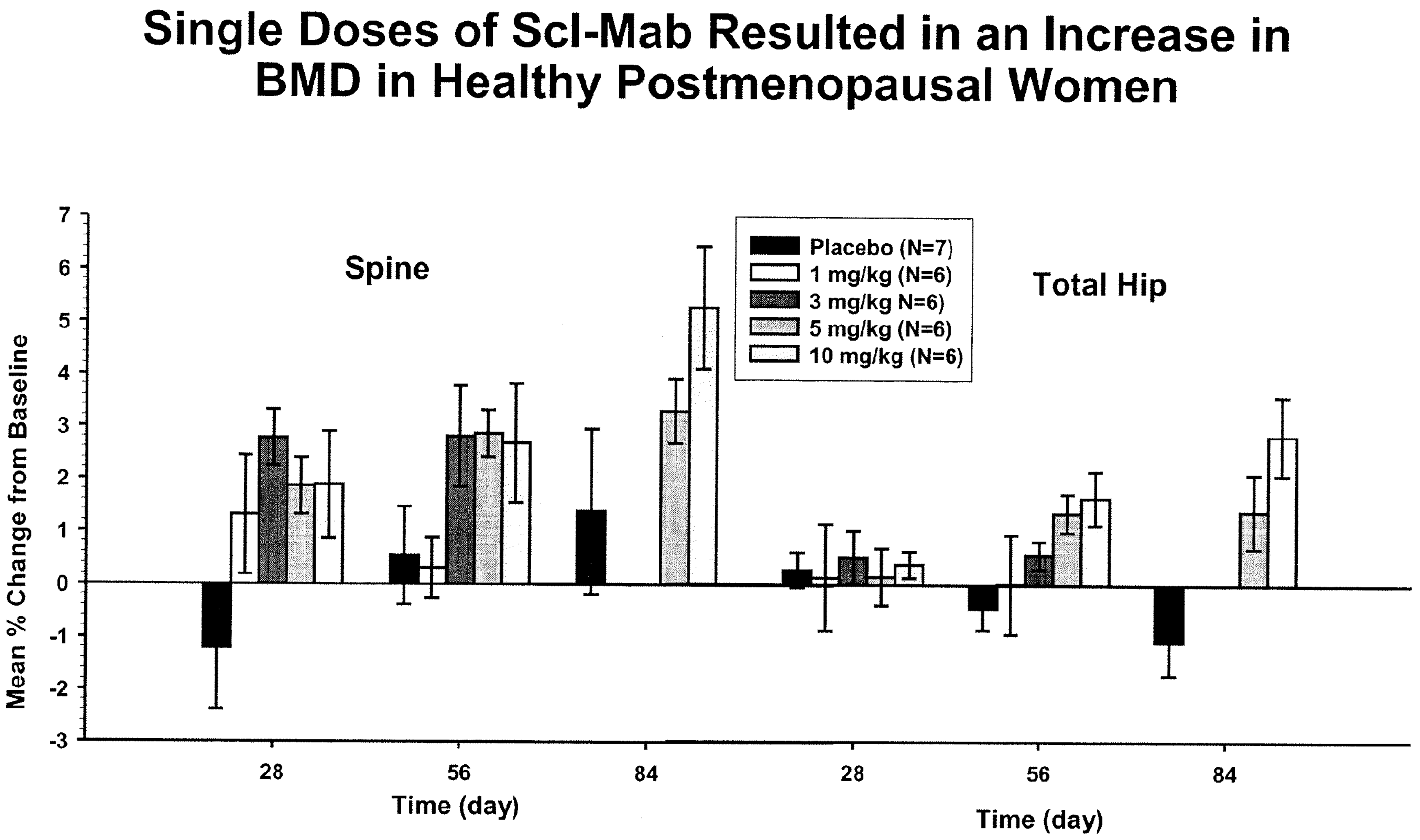

Single Doses of Scl-Mab Resulted in an Increase in BMD in Healthy Postmenopausal Women
Spine
Total Hip
Placebo (N=7)
1 mg/kg (N=6)
3 mg/kg N=6)
5 mg/kg (N=6)
10 mg/kg (N=6)
Mean % Change from Baseline
7
6
5
4
3
2
1
0
-1
-2
-3
28
56
84
Time (day)
28
56
84
Time (day)

FIGURE 7

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- US 20070110747 A **[0011] [0031] [0036] [0040] [0041] [0042] [0043] [0044] [0045] [0046] [0047] [0048] [0049] [0050]**
- US 20050106683 A **[0030] [0036]**
- US 5543158 A **[0031]**
- US 5641515 A **[0031]**
- US 5399363 A **[0031]**
- US 5466468 A **[0031]**
- US 6395511 B **[0036]**
- US 6803453 B **[0036]**
- US 20040009535 A **[0036]**
- US 20070072797 A **[0036]**
- US 20040158045 A **[0036] [0057]**
- US 6703199 B **[0037]**
- US 20050238646 A **[0037]**
- US 20030229041 A **[0051] [0052]**
- US 5738996 A **[0052]**
- US 5807683 A **[0052]**
- US 7261892 B **[0052]**
- US 6251588 B **[0058]**
- US 6278039 B **[0067]**
- US 5723750 A **[0067]**
- US 5244805 A **[0067]**
- US 20050223427 A **[0072]**
- WO 2004090105 A **[0072]**
- WO 2005078094 A **[0072]**
- WO 2004045543 A **[0073]**
- US 20050255487 A **[0073]**
- US 5093246 A **[0074]**
- WO 8905852 A **[0075]**
- WO 8804300 A **[0078]**
- US 6110462 A **[0084] [0086]**
- WO 60973024 A **[0102]**

Non-patent literature cited in the description

- **LI et al.** *J Bone Mineral Research,* 2007, vol. 22 (1), S36 **[0003]**
- **PADHI et al.** *J Bone Mineral Research,* 2007, vol. 22, S37 **[0003]**
- **PADHI et al.** *Oasis Abstract,* 2007 **[0003]**
- **GUINNESS-HEY.** *Metab. Bone Dis. Relat. Res.,* 1984, vol. 5, 177-181 **[0017]**
- **KALU.** *Bone and Mineral,* 1991, vol. 15, 175-192 **[0017]**
- **FROST ; JEE.** *Bone and Mineral,* 1992, vol. 18, 227-236 **[0017]**
- **JEE ; YAO.** *J. Musculoskel. Neuron. Interact.,* 2001, vol. 1, 193-207 **[0017]**
- **DELMAS et al.** *Osteoporos Int.,* 2000, vol. 6, 2-17 **[0019]**
- Prevention and management of osteoporosis: report of a WHO scientific group. World Health Organization Scientific Group on the Prevention and Management of Osteoporosis. WHO Technical Report Series, 2000 **[0022]**
- Remington's Pharmaceutical Sciences. Mack Pub. Co, 1035-1038, 1570-1580 **[0032]**
- **BRUNKOW et al.** *Am. J. Hum. Genet,* 2001, vol. 68, 577-589 **[0036]**
- **BALEMANS et al.** *Hum. Mol. Genet.,* 2001, vol. 10, 537-543 **[0036]**
- **HOLLINGER ; HUDSON.** *Nature Biotechnology,* 2005, vol. 23 (9), 1126-1136 **[0037]**
- **LARRICK et al.** *Methods: A Companion to Methods in Enzymology,* 1991, vol. 2, 106 **[0039]**
- Genetic Manipulation of Monoclonal Antibodies. **COURTENAY-LUCK et al.** Monoclonal Antibodies Production, Engineering and Clinical Application. Cambridge University Press, 1995, 166 **[0039]**
- Genetic Manipulation and Expression of Antibodies. **WARD et al.** Monoclonal Antibodies: Principles and Applications. Wiley-Liss, Inc, 1995, 137 **[0039]**
- **LAM.** *Anticancer Drug Des.,* 1997, vol. 12, 145 **[0052]**
- **ECKSTEIN.** *Antisense Nucleic Acid Drug Dev.,* 2000, vol. 10, 117-121 **[0053]**
- **CROOKE.** *Methods Enzymol.,* 2000, vol. 313, 3-45 **[0053]**
- **GUVALCOVA et al.** *J. Biol. Chem.,* 1995, vol. 270, 2620-2627 **[0053]**
- **MANOHARAN.** *Biochim. Biophys. Acta,* 1999, vol. 1489, 117-130 **[0053]**
- **BAKER et al.** *J. Biol. Chem.,* 1997, vol. 272, 11994-12000 **[0053]**
- **KURRECK.** *Eur. J. Biochem.,* 2003, vol. 270, 1628-1644 **[0053]**
- **SIERALCOWSKA et al.** *Proc. Natl. Acad. Sci. USA,* 1996, vol. 93, 12840-12844 **[0053]**
- **MARWICK.** *J. Am. Med. Assoc.,* 1998, vol. 280, 871 **[0053]**
- **TOMITA ; MORISHITA.** *Curr. Pharm. Des.,* 2004, vol. 10, 797-803 **[0053]**

- **GLEAVE ; MONIA.** *Nat. Rev. Cancer,* 2005, vol. 5, 468-479 **[0053]**
- **PATIL.** *AAPS J.,* 2005, vol. 7, E61-E77 **[0053]**
- **FRANCOIS et al.** *Nucleic Acids Res.,* 1988, vol. 16, 11431-11440 **[0053]**
- **MOSER ; DERVAN.** *Science,* 1987, vol. 238, 645-650 **[0053]**
- **KRUGER et al.** *Tetrahymena. Cell,* 1982, vol. 31, 147-157 **[0053]**
- **UHLENBECK.** *Nature,* 1987, vol. 328, 596-600 **[0053]**
- **SIGURDSSON ; ECKSTEIN.** *Trends Biotechnol.,* 1995, vol. 13, 286-289 **[0053]**
- **KUMAR et al.** *Gene Ther.,* 2005, vol. 12, 1486-1493 **[0053]**
- **BREAKER ; JOYCE.** *Chem. Biol.,* 1994, vol. 1, 223-229 **[0053]**
- **KHACHIGIAN.** *Curr. Pharm. Biotechnol.,* 2004, vol. 5, 337-339 **[0053]**
- **KHACHIGIAN.** *Biochem. Pharmacol,* 2004, vol. 68, 1023-1025 **[0053]**
- **TRULZSCH ; WOOD.** *J. Neurochem.,* 2004, vol. 88, 257-265 **[0053]**
- **FIRE et al.** *Nature,* 1998, vol. 391, 806-811 **[0053]**
- **MONTGOMERY et al.** *Proc. Natl. Acad. Sci. U.S.A.,* 1998, vol. 95, 15502-15507 **[0053]**
- **CULLEN.** *Nat. Immunol.,* 2002, vol. 3, 597-599 **[0053]**
- **HANNON.** *Nature,* 2002, vol. 418, 244-251 **[0053]**
- **BERNSTEIN et al.** *Nature,* 2001, vol. 409, 363-366 **[0053]**
- **NYKANEN et al.** *Cell,* 2001, vol. 107, 309-321 **[0053]**
- **GILMORE et al.** *J. Drug Target.,* 2004, vol. 12, 315-340 **[0053]**
- **REYNOLDS et al.** *Nat. Biotechnol,* 2004, vol. 22, 326-330 **[0053]**
- **SOUTSCHEK et al.** *Nature,* 2004, 432173-178 **[0053]**
- **RALPH et al.** *Nat. Med.,* 2005, vol. 11, 429-433 **[0053]**
- **XIA et al.** *Nat. Med.,* 2004, 10816-820 **[0053]**
- **MILLER et al.** *Nucleic Acids Res.,* 2004, vol. 32, 661-668 **[0053]**
- **ELLINGTON ; SZOSTAK.** *Nature,* 1990, vol. 346, 818-822 **[0053]**
- **DOUDNA et al.** *Proc. Natl. Acad. Sci. U.S.A.,* 1995, vol. 92, 2355-2359 **[0053]**
- **TUERK ; GOLD.** *Science,* 1990, vol. 249, 505-510 **[0053]**
- **WHITE et al.** *Mol. Ther.,* 2001, vol. 4, 567-573 **[0053]**
- **RUSCONI et al.** *Nature,* 2002, vol. 419, 90-94 **[0053]**
- **NIMJEE et al.** *Mol. Ther.,* 2006, vol. 14, 408-415 **[0053]**
- **GRAGOUDAS et al.** *N. Engl. J. Med.,* 2004, vol. 351, 3805-2816 **[0053]**
- **VINORES.** *Curr. Opin. Mol. Ther.,* 2003, 5673-679 **[0053]**
- **KOURLAS ; SCHILLER et al.** *Clin. Ther.,* 2006, vol. 28, 36-44 **[0053]**
- **MORISHITA et al.** *Proc. Natl. Acad. Sci. U.S.A.,* 1995, vol. 92, 5855-5859 **[0053]**
- **ALEXANDER et al.** *J. Am. Med. Assoc.,* 2005, vol. 294, 2446-2454 **[0053]**
- **MANN ; DZAU.** *J. Clin. Invest.,* 2000, vol. 106, 1071-1075 **[0053]**
- **NIMJEE et al.** *Annu. Rev. Med.,* 2005, vol. 56, 555-583 **[0053]**
- **JAEGER et al.** *Proc. Natl. Acad. Sci. USA,* 1989, vol. 86, 7706 **[0060]**
- **TURNER et al.** *Annu. Rev. Biophys. Biophys. Chem.,* 1988, vol. 17, 167 **[0060]**
- **HUNTER et al.** *J. Biol. Chem.,* 1975, vol. 250, 409-17 **[0063]**
- **MANCHE et al.** *Mol. Cell. Biol,* 1992, vol. 12, 5239-48 **[0063]**
- **MINKS et al.** *J. Biol. Chem.,* 1979, vol. 254, 10180-3 **[0063]**
- **ELBASHIR et al.** *Nature,* 2001, vol. 411, 494-8 **[0063] [0064]**
- **BASS.** *Nature,* 2001, vol. 411, 428-9 **[0064]**
- **ELBASHIR et al.** *Genes Dev.,* 2001, vol. 15, 188-200 **[0065]**
- **HANNON et al.** *Nature,* 2004, vol. 431, 371-378 **[0068]**
- **BRUMMELKAMP et al.** *Science,* 2000, vol. 296, 550-553 **[0068]**
- **PADDISON et al.** *Genes Dev.,* 2002, vol. 16, 948-958 **[0068]**
- **BRUMMELKAMP et al.** *Cancer Cell,* 2002, vol. 2, 243-247 **[0068]**
- **DIRAC et al.** *J. Biol. Chem.,* 2003, vol. 278, 11731-11734 **[0068]**
- **MICHIELS et al.** *Nat. Biotechnol.,* 2002, vol. 20, 1154-1157 **[0068]**
- **STEGMEIE et al.** *Proc. Natl. Acad. Sci. USA,* 2005, vol. 102, 13212-13217 **[0068]**
- **KHVOROVA et al.** *Cell,* 2003, vol. 115, 209-216 **[0068]**
- **ROSSI.** *Current Biology,* 1994, vol. 4, 469-471 **[0074]**
- **HASELOFF ; GERLACH.** *Nature,* 1988, vol. 334, 585-591 **[0075]**
- **PERRIMAN et al.** *Proc. Natl. Acad. Sci, USA,* 1995, vol. 92, 6175-79 **[0077]**
- Expressing Ribozymes in Plants. **DE FEYTER ; GAUDRON.** Methods in Molecular Biology. Humana Press Inc, vol. 74 **[0077]**
- **KAWASAKI et al.** *Nature,* 1998, vol. 393, 284-9 **[0077]**
- **KUWABARA et al.** *Nature Biotechnol.,* 1998, vol. 16, 961-5 **[0077]**
- **KUWABARA et al.** *Mol. Cell,* 1998, vol. 2, 617-27 **[0077]**
- **KOSEKI et al.** *J. Virol.,* 1999, vol. 73, 1868-77 **[0077]**
- **KUWABARA et al.** *Proc. Natl. Acad. Sci. USA,* 1999, vol. 96, 1886-91 **[0077]**

- **TANABE et al.** *Nature,* 2000, vol. 406, 473-4 **[0077]**
- **ZAUG et al.** *Science,* 1984, vol. 224, 574-578 **[0078]**
- **ZAUG et al.** *Science,* 1986, vol. 231, 470-475 **[0078]**
- **ZAUG et al.** *Nature,* 1986, vol. 324, 429-433 **[0078]**
- **BEEN et al.** *Cell,* 1986, vol. 47, 207-216 **[0078]**
- **HELENE, C.** *Anticancer Drug Des.,* 1991, vol. 6, 569-84 **[0080]**
- **HELENE et al.** *Ann. N.Y. Acad. Sci.,* 1992, vol. 660, 27-36 **[0080]**
- **MAHER, L. J.** *Bioassays,* 1992, vol. 14, 807-15 **[0080]**
- **PADDISON et al.** *Methods Mol. Biol.,* 2004, vol. 265, 85-100 **[0087]**
- **KEHLENBACK et al.** *J. Cell Biol.,* 1998, vol. 141, 863-74 **[0088]**