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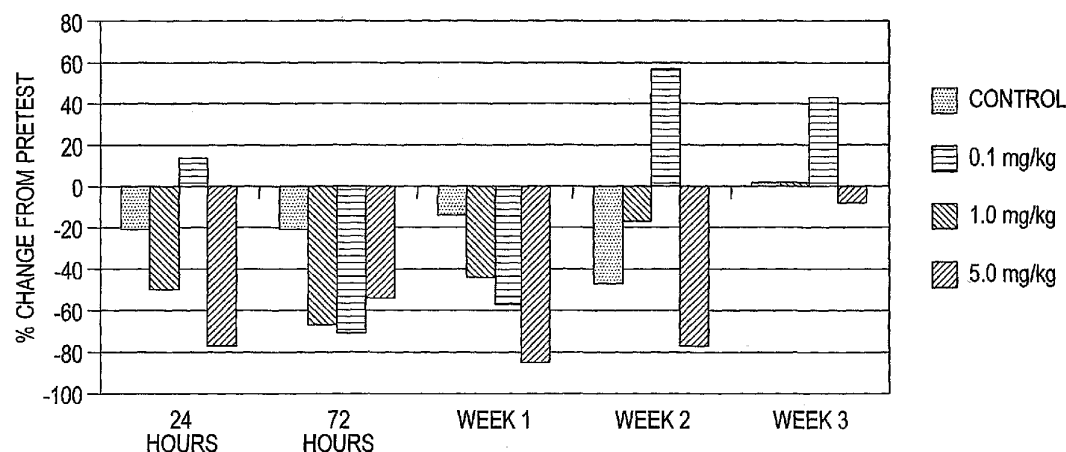
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(54) Title: ANTIBODIES TO M-CSF



(57) Abstract: The present invention relates to antibodies and antigen-binding portions thereof that specifically bind to a M-CSF, preferably human M-CSF, and that function to inhibit a M-CSF. The invention also relates to human anti-M-CSF antibodies and antigen-binding portions thereof. The invention also relates to antibodies that are chimeric, bispecific, derivatized, single chain antibodies or portions of fusion proteins. The invention also relates to isolated heavy and light chain immunoglobulins derived from human anti-M-CSF antibodies and nucleic acid molecules encoding such immunoglobulins. The present invention also relates to methods of making human anti-M-CSF antibodies, compositions comprising these antibodies and methods of using the antibodies and compositions for diagnosis and treatment. The invention also provides gene therapy methods using nucleic acid molecules encoding the heavy and/or light immunoglobulin molecules that comprise the human anti-M-CSF antibodies. The invention also relates to transgenic animals and transgenic plants comprising nucleic acid molecules of the present invention.



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ANTIBODIES TO M-CSF

This application claims the benefit of United States Provisional Application 60/502,163, filed September 10, 2003.

Background of the Invention

5 Macrophage colony stimulating factor (M-CSF) is a member of the family of proteins referred to as colony stimulating factors (CSFs). M-CSF is a secreted or a cell surface glycoprotein comprised of two subunits that are joined by a disulfide bond with a total molecular mass varying from 40 to 90 kD ((Stanley E.R., *et al.*, *Mol. Reprod. Dev.*, 46:4-10 (1997)). Similar to other CSFs, M-CSF is produced by macrophages, monocytes, and human
10 joint tissue cells, such as chondrocytes and synovial fibroblasts, in response to proteins such as interleukin-1 or tumor necrosis factor-alpha. M-CSF stimulates the formation of macrophage colonies from pluripotent hematopoietic progenitor stem cells (Stanley E.R., *et al.*, *Mol. Reprod. Dev.*, 46:4-10 (1997)).

M-CSF typically bind to its receptor, *c-fms*, in order to exert a biological effect. *c-fms*
15 contains five extracellular Ig domains, one transmembrane domain, and an intracellular domain with two kinase domains. Upon M-CSF binding to *c-fms*, the receptor homo-dimerizes and initiates a cascade of signal transduction pathways including the JAK/STAT, PI3K, and ERK pathways.

M-CSF is an important regulator of the function, activation, and survival of
20 monocytes/macrophages. A number of animal models have confirmed the role of M-CSF in various diseases, including rheumatoid arthritis (RA) and cancer. Macrophages comprise key effector cells in RA. The degree of synovial macrophage infiltration in RA has been shown to closely correlate with the extent of underlying joint destruction. M-CSF, endogenously produced in the rheumatoid joint by monocytes/macrophages, fibroblasts, and endothelial cells,
25 acts on cells of the monocyte/macrophage lineage to promote their survival and differentiation into bone destroying osteoclasts, and enhance pro-inflammatory cellular functions such as cytotoxicity, superoxide production, phagocytosis, chemotaxis and secondary cytokine production. For example, treatment with M-CSF in the rat streptococcus agalactiae sonicate-induced experimental arthritis model lead to enhanced pathology (Abd, A.H., *et al.*,
30 *Lymphokine Cytokine Res.* 10:43-50 (1991)). Similarly, subcutaneous injections of M-CSF in a murine model of collagen-induced arthritis (CIA), which is a model for RA, resulted in a significant exacerbation of the RA disease symptoms (Campbell I.K., *et al.*, *J. Leuk. Biol.*

68:144-150 (2000)). Furthermore, MRL/lpr mice that are highly susceptible to RA and other autoimmune diseases have elevated basal M-CSF serum concentrations (Yui M.A., *et al.*, *Am. J. Pathol.* 139:255-261 (1991)). The requirement for endogenous M-CSF in maintaining CIA was demonstrated by a significant reduction in the severity of established disease by M-CSF neutralizing mouse monoclonal antibody (Campbell I.K., *et al.*, *J. Leuk. Biol.* 68:144-150 (2000)).

With respect to cancer, inhibition of colony stimulating factors by antisense oligonucleotides suppresses tumor growth in embryonic and colon tumor xenografts in mice by decelerating macrophage-mediated ECM breakdown (Seyedhossein, A., *et al.*, *Cancer Research*, 62:5317-5324 (2002)).

M-CSF binding to *c-fms* and its subsequent activation of monocyte/macrophages is important in a number of disease states. In addition to RA and cancer, the other examples of M-CSF-related disease states include osteoporosis, destructive arthritis, atherogenesis, glomerulonephritis, Kawasaki disease, and HIV-1 infection, in which monocytes/macrophages and related cell types play a role. For instance, osteoclasts are similar to macrophages and are regulated in part by M-CSF. Growth and differentiation signals induced by M-CSF in the initial stages of osteoclast maturation are essential for their subsequent osteoclastic activity in bone.

Osteoclast mediated bone loss, in the form of both focal bone erosions and more diffuse juxta-articular osteoporosis, is a major unsolved problem in RA. The consequences of this bone loss include joint deformities, functional disability, increased risk of bone fractures and increased mortality. M-CSF is uniquely essential for osteoclastogenesis and experimental blockade of this cytokine in animal models of arthritis successfully abrogates joint destruction. Similar destructive pathways are known to operate in other forms of destructive arthritis such as psoriatic arthritis, and could represent venues for similar intervention.

Postmenopausal bone loss results from defective bone remodeling secondary to an uncoupling of bone formation from exuberant osteoclast mediated bone resorption as a consequence of estrogen deficiency. *In-vivo* neutralization of M-CSF using a blocking antibody has been shown in mice to completely prevent the rise in osteoclast numbers, the increase in bone resorption and the resulting bone loss induced by ovariectomy.

Several lines of evidence point to a central role for M-CSF in atherogenesis, and in proliferative intimal hyperplasia after mechanical trauma to the arterial wall. All the major cell types in atherosclerotic lesions have been shown to express M-CSF, and this is further up-regulated by exposure to oxidized lipoprotein. Blockade of M-CSF signaling with a neutralizing

c-fms antibody reduces the accumulation of macrophage-derived foam cells in the aortic root of apolipoprotein E deficient mice maintained on a high fat diet.

In both experimental and human glomerulonephritis, glomerular M-CSF expression has been found to co-localize with local macrophage accumulation, activation and proliferation and correlate with the extent of glomerular injury and proteinuria. Blockade of M-CSF signaling via an antibody directed against its receptor *c-fms* significantly down-regulates local macrophage accumulation in mice during the renal inflammatory response induced by experimental unilateral ureteric obstruction.

Kawasaki disease (KD) is an acute, febrile, pediatric vasculitis of unknown cause. Its most common and serious complications involve the coronary vasculature in the form of aneurismal dilatation. Serum M-CSF levels are significantly elevated in acute phase Kawasaki's disease, and normalize following treatment with intravenous immunoglobulin. Giant cell arthritis (GCA) is an inflammatory vasculopathy mainly occurring in the elderly in which T cells and macrophages infiltrate the walls of medium and large arteries leading to clinical consequences that include blindness and stroke secondary to arterial occlusion. The active involvement of macrophages in GCA is evidenced by the presence of elevated levels of macrophage derived inflammatory mediators within vascular lesions.

M-CSF has been reported to render human monocyte derived macrophages more susceptible to HIV-1 infection *in vitro*. In a recent study, M-CSF increased the frequency with which monocyte-derived macrophages became infected, the amount of HIV mRNA expressed per infected cell, and the level of proviral DNA expressed per infected culture.

Given the role of M-CSF in various diseases, a method for inhibiting M-CSF activity is desirable.

There is a critical need for therapeutic anti-M-CSF antibodies.

SUMMARY OF THE INVENTION

The present invention provides isolated human antibodies or antigen-binding portions thereof that specifically bind human M-CSF and acts as a M-CSF antagonist and compositions comprising said antibody or portion.

The invention also provides for compositions comprising the heavy and/or light chain, the variable regions thereof, or antigen-binding portions thereof an anti-M-CSF antibody, or nucleic acid molecules encoding an antibody, antibody chain or variable region thereof the invention effective in such treatment and a pharmaceutically acceptable carrier. In certain embodiments, the compositions may further comprise another component, such as a therapeutic

agent or a diagnostic agent. Diagnostic and therapeutic methods are also provided by the invention. In certain embodiments, the compositions are used in a therapeutically effective amount necessary to treat or prevent a particular disease or condition.

The invention also provides methods for treating or preventing a variety of diseases and conditions such as, but not limited to, inflammation, cancer, atherogenesis, neurological disorders and cardiac disorders with an effective amount of an anti-M-CSF antibody of the invention, or antigen binding portion thereof, nucleic acids encoding said antibody, or heavy and/or light chain, the variable regions, or antigen-binding portions thereof.

The invention provides isolated cell lines, such as a hybridomas, that produce anti-M-CSF antibodies or antigen-binding portions thereof.

The invention also provides nucleic acid molecules encoding the heavy and/or light chains of anti-M-CSF antibodies, the variable regions thereof, or the antigen-binding portions thereof.

The invention provides vectors and host cells comprising the nucleic acid molecules, as well as methods of recombinantly producing the polypeptides encoded by the nucleic acid molecules.

Non-human transgenic animals or plants that express the heavy and/or light chains, or antigen-binding portions thereof, of anti-M-CSF antibodies are also provided.

Definitions of the specific embodiments of the invention as claimed herein follow.

According to a first embodiment of the invention, there is provided a human monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion blocks binding to *c-fms* and binds to M-CSF with a K_D of 1.0×10^{-7} M or less.

According to a second embodiment of the invention, there is provided a human monoclonal antibody 8.10.3F or an antigen-binding portion thereof that specifically binds to M-CSF.

According to a third embodiment of the invention, there is provided a human monoclonal antibody 9.14.4I or an antigen-binding portion thereof that specifically binds to M-CSF.

According to a fourth embodiment of the invention, there is provided a human monoclonal antibody or an antigen-binding portion thereof that binds specifically to and inhibits human M-CSF, wherein the antibody or portion has at least one property selected from the group consisting of:

- a) cross-competes for binding to M-CSF with an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2,

9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1;

b) competes for binding to M-CSF with an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1;

c) binds to the same epitope of M-CSF as an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1;

d) binds to M-CSF with substantially the same K_D as an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1; and

e) binds to M-CSF with substantially the same off rate as an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1.

According to a fifth embodiment of the invention, there is provided a monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody is selected from the group consisting of:

a) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 2 and the light chain amino acid sequence set forth in SEQ ID NO: 4 without the signal sequences;

b) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 6 and the light chain amino acid sequence set forth in SEQ ID NO: 8 without the signal sequences;

c) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 10 and the light chain amino acid sequence set forth in SEQ ID NO: 12 without the signal sequences;

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- d) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 14 and the light chain amino acid sequence set forth in SEQ ID NO: 16 without the signal sequences;
- e) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 18 and the light chain amino acid sequence set forth in SEQ ID NO: 20 without the signal sequences;
- f) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 22 and the light chain amino acid sequence set forth in SEQ ID NO: 24 without the signal sequences;
- g) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 26 and the light chain amino acid sequence set forth in SEQ ID NO: 28 without the signal sequences;
- h) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 38 and the light chain amino acid sequence set forth in SEQ ID NO: 28 without the signal sequences;
- i) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 54 and the light chain amino acid sequence set forth in SEQ ID NO: 56 without the signal sequences;
- j) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 74 and the light chain amino acid sequence set forth in SEQ ID NO: 56 without the signal sequences;
- k) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 78 and the light chain amino acid sequence set forth in SEQ ID NO: 56 without the signal sequences;
- l) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 82 and the light chain amino acid sequence set forth in SEQ ID NO: 28 without the signal sequences;
- m) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 102 and the light chain amino acid sequence set forth in SEQ ID NO: 28 without the signal sequences;
- n) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30 and the light chain amino acid sequence set forth in SEQ ID NO: 32 without the signal sequences;

- o) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30 and the light chain amino acid sequence set forth in SEQ ID NO: 44 without the signal sequences;
- p) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 58 and the light chain amino acid sequence set forth in SEQ ID NO: 60 without the signal sequences;
- q) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 62 and the light chain amino acid sequence set forth in SEQ ID NO: 60 without the signal sequences;
- r) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 90 and the light chain amino acid sequence set forth in SEQ ID NO: 44 without the signal sequences;
- s) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 94 and the light chain amino acid sequence set forth in SEQ ID NO: 60 without the signal sequences;
- t) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 98 and the light chain amino acid sequence set forth in SEQ ID NO: 32 without the signal sequences;
- u) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 34 and the light chain amino acid sequence set forth in SEQ ID NO: 36 without the signal sequences;
- v) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 46 and the light chain amino acid sequence set forth in SEQ ID NO: 48 without the signal sequences;
- w) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 50 and the light chain amino acid sequence set forth in SEQ ID NO: 52 without the signal sequences;
- x) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 66 and the light chain amino acid sequence set forth in SEQ ID NO: 52 without the signal sequences;
- y) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 70 and the light chain amino acid sequence set forth in SEQ ID NO: 52 without the signal sequences; and

z) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 86 and the light chain amino acid sequence set forth in SEQ ID NO: 48 without the signal sequences.

According to a sixth embodiment of the invention, there is provided a monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises:

- a) a heavy chain comprising the heavy chain CDR1, CDR2 and CDR3 of an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1; or
- b) the heavy chain of a) and a light chain comprising the light chain CDR1, CDR2 and CDR3 of the selected antibody.

According to a seventh embodiment of the invention, there is provided a monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises:

- a) a heavy chain comprising the amino acid sequence from the beginning of the CDR1 through the end of the CDR3 of the heavy chain of an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1; or
- b) the heavy chain of a) and a light chain comprising the amino acid sequence from the beginning of the CDR1 through the end of the CDR3 of the selected antibody.

According to an eighth embodiment of the invention, there is provided a monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a light chain comprising SEQ ID NO: 32 and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a heavy chain comprising SEQ ID NO: 30.

According to a ninth embodiment of the invention, there is provided a monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the heavy chain variable domain of antibody 8.10.3F and the amino acid

sequences of the CDR1, CDR2 and CDR3 regions found in the light chain variable domain of antibody 8.10.3F.

According to a tenth embodiment of the invention, there is provided a monoclonal antibody that specifically binds to M-CSF, wherein the heavy chain amino acid sequence of said antibody is SEQ ID NO: 30 without the signal sequence, and the light chain amino acid sequence of said antibody is SEQ ID NO: 32 without the signal sequence.

According to an eleventh embodiment of the invention, there is provided a monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a light chain comprising SEQ ID NO: 28 and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a heavy chain comprising SEQ ID NO: 26.

According to a twelfth embodiment of the invention, there is provided a monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the heavy chain variable domain of antibody 9.14.4I and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the light chain variable domain of antibody 9.14.4I.

According to a thirteenth embodiment of the invention, there is provided a monoclonal antibody that specifically binds to M-CSF, wherein the heavy chain amino acid sequence of said antibody is SEQ ID NO: 26 without the signal sequence, and the light chain amino acid sequence of said antibody is SEQ ID NO: 28 without the signal sequence.

According to a fourteenth embodiment of the invention, there is provided an isolated polypeptide selected from the group consisting of:

- a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 without the signal sequence;
- b) a polypeptide comprising the amino acid sequence of SEQ ID NO: 6 without the signal sequence;
- c) a polypeptide comprising the amino acid sequence of SEQ ID NO: 10 without the signal sequence;
- d) a polypeptide comprising the amino acid sequence of SEQ ID NO: 14 without the signal sequence;
- e) a polypeptide comprising the amino acid sequence of SEQ ID NO: 18 without the signal sequence;

- f) a polypeptide comprising the amino acid sequence of SEQ ID NO: 22 without the signal sequence;
- g) a polypeptide comprising the amino acid sequence of SEQ ID NO: 26 without the signal sequence;
- h) a polypeptide comprising the amino acid sequence of SEQ ID NO: 30 without the signal sequence;
- i) a polypeptide comprising the amino acid sequence of SEQ ID NO: 34 without the signal sequence;
- j) a polypeptide comprising the amino acid sequence of SEQ ID NO: 38 without the signal sequence;
- k) a polypeptide comprising the amino acid sequence of SEQ ID NO: 46 without the signal sequence;
- l) a polypeptide comprising the amino acid sequence of SEQ ID NO: 50 without the signal sequence;
- m) a polypeptide comprising the amino acid sequence of SEQ ID NO: 54 without the signal sequence;
- n) a polypeptide comprising the amino acid sequence of SEQ ID NO: 58 without the signal sequence;
- o) a polypeptide comprising the amino acid sequence of SEQ ID NO: 62 without the signal sequence;
- p) a polypeptide comprising the amino acid sequence of SEQ ID NO: 66 without the signal sequence;
- q) a polypeptide comprising the amino acid sequence of SEQ ID NO: 70 without the signal sequence;
- r) a polypeptide comprising the amino acid sequence of SEQ ID NO: 74 without the signal sequence;
- s) a polypeptide comprising the amino acid sequence of SEQ ID NO: 78 without the signal sequence;
- t) a polypeptide comprising the amino acid sequence of SEQ ID NO: 82 without the signal sequence;
- u) a polypeptide comprising the amino acid sequence of SEQ ID NO: 86 without the signal sequence;
- v) a polypeptide comprising the amino acid sequence of SEQ ID NO: 90 without the signal sequence;

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- w) a polypeptide comprising the amino acid sequence of SEQ ID NO: 94 without the signal sequence;
 - x) a polypeptide comprising the amino acid sequence of SEQ ID NO: 98 without the signal sequence; and
 - y) a polypeptide comprising the amino acid sequence of SEQ ID NO: 102 without the signal sequence.

According to a fifteenth embodiment of the invention, there is provided an isolated polypeptide selected from the group consisting of:

- 0
- a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 4 without the signal sequence;
 - b) a polypeptide comprising the amino acid sequence of SEQ ID NO: 8 without the signal sequence;
 - c) a polypeptide comprising the amino acid sequence of SEQ ID NO: 12 without the signal sequence;
 - 5 d) a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 without the signal sequence;
 - e) a polypeptide comprising the amino acid sequence of SEQ ID NO: 20 without the signal sequence;
 - f) a polypeptide comprising the amino acid sequence of SEQ ID NO: 24 without the signal sequence;
 - 0 g) a polypeptide comprising the amino acid sequence of SEQ ID NO: 28 without the signal sequence;
 - h) a polypeptide comprising the amino acid sequence of SEQ ID NO: 36 without the signal sequence;
 - 25 i) a polypeptide comprising the amino acid sequence of SEQ ID NO: 44 without the signal sequence;
 - j) a polypeptide comprising the amino acid sequence of SEQ ID NO: 48 without the signal sequence;
 - k) a polypeptide comprising the amino acid sequence of SEQ ID NO: 52 without the signal sequence;
 - 30 l) a polypeptide comprising the amino acid sequence of SEQ ID NO: 56 without the signal sequence; and
 - m) a polypeptide comprising the amino acid sequence of SEQ ID NO: 60 without the signal sequence.

According to a sixteenth embodiment of the invention, there is provided a pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to any one of the first to thirteenth embodiments, and a pharmaceutically acceptable carrier.

According to a seventeenth embodiment of the invention, there is provided a method for treating a condition selected from the group consisting of arthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn and conjunctivitis shock in a subject, comprising of the step of administering to said subject in need thereof a therapeutically effective amount of the monoclonal antibody or antigen-binding portion according to the first embodiment.

According to an eighteenth embodiment of the invention, there is provided a method for treating a condition selected from the group consisting of arthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn, and conjunctivitis shock in a subject, comprising the step of administering to said subject the monoclonal antibody or antigen-binding portion according to any one of the second to ninth, eleventh and twelfth embodiments, wherein the antibody or portion inhibits M-CSF binding to *c-fms*.

According to a nineteenth embodiment of the invention, there is provided a method for treating a solid tumor such as a sarcoma, a carcinoma or a lymphoma in a subject, comprising the step of administering to said subject the antibody or antigen-binding portion according to the first embodiment.

According to a twentieth embodiment of the invention, there is provided a method for treating a solid tumor such as a sarcoma, a carcinoma or a lymphoma, in a subject, comprising the step of administering to said subject the monoclonal antibody or antigen-binding portion according to any one of the second to ninth, eleventh and twelfth embodiments, wherein the antibody or portion inhibits M-CSF binding to *c-fms*.

According to a twenty-first embodiment of the invention, there is provided use of the monoclonal antibody or antigen-binding portion according to the first embodiments, for the preparation of a pharmaceutical composition.

According to a twenty-second embodiment of the invention, there is provided use of the monoclonal antibody or antigen-binding portion according to any one of the second to ninth, eleventh and twelfth embodiments, for the preparation of a pharmaceutical composition.

According to a twenty-third embodiment of the invention, there is provided an isolated cell line that produces the monoclonal antibody or antigen-binding portion according to any one of the first to thirteenth embodiments, or the heavy chain of the antibody or portion.

According to a twenty-fourth embodiment of the invention, there is provided an isolated nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain, or an antigen-binding portion thereof, or both the heavy chain and light chain, or an antigen-binding portion thereof, of the monoclonal antibody according to any one of the first to thirteenth embodiments.

According to a twenty-fifth embodiment of the invention, there is provided a vector comprising the nucleic acid molecule according to the twenty-fourth embodiment, wherein the vector optionally comprises an expression control sequence operably linked to said nucleic acid molecule.

According to a twenty-sixth embodiment of the invention, there is provided an isolated host cell comprising the vector according to the twenty-fifth embodiment or the nucleic acid molecule according to the twenty-fourth embodiment.

According to a twenty-seventh embodiment of the invention, there is provided a method of making an anti-M-CSF antibody or antigen-binding portion thereof, comprising culturing the host cell according to the twenty-sixth embodiment or the cell line according to the twenty-third embodiment under suitable conditions and recovering the antibody or portion.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are graphs illustrating that the anti-M-CSF antibodies resulted in a dose-related decrease in total monocyte counts in male and female monkeys over time. The

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monocyte counts were determined by light scatter using an Abbott Diagnostics Inc. Cell Dyn system. Monocyte counts were monitored from 24 hours through 3 weeks after administration of vehicle or antibody 8.10.3 at 0, 0.1, 1 or 5 mg/kg in a dose volume of 3.79 mL/kg over an approximately 5 minute period.

Figure 1A male monkeys.

Figure 1B female monkeys.

[Text continues on page 13.]

Figures 2A and 2B are graphs illustrating that anti-M-CSF treatment resulted in a reduction in the percentage of CD14+CD16+ monocytes, in male and female monkeys. 0-21 days after administration of vehicle or antibody 8.10.3 at 0, 0.1, 1 or 5 mg/kg in a dose volume of 3.79 mL/kg over an approximately 5 minute period. For each monkey tested, the percentage of monocytes within the CD14+CD16+ subset was determined after each blood draw, on days 1, 3, 7, 14 and 21 after 8.10.3 injection.

Figure 2A male monkeys.

Figure 2B female monkeys.

Figures 3A and 3B are graphs illustrating that anti-M-CSF treatment resulted in a decrease in the percentage change of total monocytes at all doses of antibody 8.10.3F and antibody 9.14.4I as compared to pre-test levels of monocytes.

Figure 3A shows data collected from experiments using antibody 8.10.3F.

Figure 3B shows data collected from experiments using antibody 9.14.4I.

Figure 4 is a sequence alignment of the predicted amino acid sequences of light and heavy chain variable regions from twenty-six anti-M-CSF antibodies compared with the germline amino acid sequences of the corresponding variable region genes. Differences between the antibody sequences and the germline gene sequences are indicated in bold-faced type. Dashes represent no change from germline. The underlined sequences in each alignment represent, from left to right, the FR1, CDR1, FR2, CDR2, FR3, CDR3 AND FR4 sequences.

Figure 4A shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 252 (residues 21-127 of SEQ ID NO: 4) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4B shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 88 (residues 21-127 of SEQ ID NO: 8) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4C shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 100 (residues 21-127 of SEQ ID NO: 12) to the germline V_κL2, J_κ3 sequence (SEQ ID NO: 107).

Figure 4D shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 3.8.3 (residues 23-130 of SEQ ID NO: 16) to the germline V_κL5, J_κ3 sequence (SEQ ID NO: 109).

Figure 4E shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 2.7.3 (residues 23-130 of SEQ ID NO: 20) to the germline V_κL5, J_κ4 sequence (SEQ ID NO: 117).

Figure 4F shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 1.120.1 (residues 21-134 of SEQ ID NO: 24) to the germline V_κB3, J_κ1 sequence (SEQ ID NO: 112).

Figure 4G shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 252 (residues 20-136 of SEQ ID NO: 2) to the germline V_H3-11, D_H7-27 J_H6 sequence (SEQ ID NO: 106).

Figure 4H shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 88 (residues 20-138 of SEQ ID NO: 6) to the germline V_H3-7, D_H6-13, J_H4 sequence (SEQ ID NO: 105).

Figure 4I shows the alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 100 (residues 20-141 of SEQ ID NO: 10) to the germline V_H3-23, D_H1-26, J_H4 sequence (SEQ ID NO: 104).

Figure 4J shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 3.8.3 (residues 20-135 of SEQ ID NO: 14) to the germline V_H3-11, D_H7-27, J_H4 sequence (SEQ ID NO: 108).

Figure 4K shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 2.7.3 (residues 20-137 of SEQ ID NO: 18) to the germline V_H3-33, D_H1-26, J_H4 sequence (SEQ ID NO: 110).

Figure 4L shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 1.120.1 (residues 20-139 of SEQ ID NO: 22) to the germline V_H1-18, D_H4-23, J_H4 sequence (SEQ ID NO: 111).

Figure 4M shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 8.10.3 (residues 21-129 of SEQ ID NO: 44) to the germline V_κA27, J_κ4 sequence (SEQ ID NO: 114).

Figure 4N shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 8.10.3 (residues 20-141 of SEQ ID NO: 30) to the germline V_H3-48, D_H1-26, J_H4b sequence (SEQ ID NO: 113).

Figure 4O shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.14.4 (residues 23-130 of SEQ ID NO: 28) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4P shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.14.4 (residues 20-135 of SEQ ID NO: 38) to the germline V_H3-11, D_H7-27, J_H4b sequence (SEQ ID NO: 116).

Figure 4Q shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.7.2 (residues 23-130 of SEQ ID NO: 48) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4R shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.7.2 (residues 20-136 of SEQ ID NO: 46) to the germline V_H3-11, D_H6-13, J_H6b sequence (SEQ ID NO: 115).

Figure 4S shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.14.4I (residues 23-130 of SEQ ID NO: 28) to the germline V_κO12 J_κ3 sequence (SEQ ID NO: 103).

Figure 4T shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.14.4I (residues 20-135 of SEQ ID NO: 26) to the germline V_H3-11, D_H7-27, J_H4b sequence (SEQ ID NO: 116).

Figure 4U shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 8.10.3F (residues 21-129 of SEQ ID NO: 32) to the germline V_κA27, J_κ4 sequence (SEQ ID NO: 114).

Figure 4V shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 8.10.3F (residues 20-141 of SEQ ID NO: 30) to the germline V_H3-48, D_H1-26, J_H4b sequence (SEQ ID NO: 113).

Figure 4W shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.7.2IF (residues 23-130 of SEQ ID NO: 36) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4X shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.7.2IF (residues 20-136 of SEQ ID NO: 34) to the germline V_H3-11, D_H6-13, J_H6b sequence (SEQ ID NO: 115).

Figure 4Y shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.7.2C-Ser (residues 23-130 of SEQ ID NO: 52) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4Z shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.7.2C-Ser (residues 20-136 of SEQ ID NO: 50) to the germline V_H3-11, D_H6-13, J_H6b sequence (SEQ ID NO: 115).

Figure 4AA shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.14.4C-Ser (residues 23-130 of SEQ ID NO: 56) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

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Figure 4BB shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.14.4C-Ser (residues 20-135 of SEQ ID NO: 54) to the germline V_H3-11, D_H7-27, J_H4b sequence (SEQ ID NO: 116).

Figure 4CC shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 8.10.3C-Ser (residues 21-129 of SEQ ID NO: 60) to the germline V_κA27, J_κ4 sequence (SEQ ID NO: 114).

Figure 4DD shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 8.10.3C-Ser (residues 20-141 of SEQ ID NO: 58) to the germline V_H3-48, D_H1-26, J_H4b sequence (SEQ ID NO: 113).

Figure 4EE shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 8.10.3-CG2 (residues 21-129 of SEQ ID NO: 60) to the germline V_κA27, J_κ4 sequence (SEQ ID NO: 114).

Figure 4FF shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 8.10.3-CG2 (residues 20-141 of SEQ ID NO: 62) to the germline V_H3-48, D_H1-26, J_H4b sequence (SEQ ID NO: 113).

Figure 4GG shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.7.2-CG2 (residues 23-130 of SEQ ID NO: 52) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4HH shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.7.2-CG2 (residues 20-136 of SEQ ID NO: 66) to the germline V_H3-11, D_H6-13, J_H6b sequence (SEQ ID NO: 115).

Figure 4II shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.7.2-CG4 (residues 23-130 of SEQ ID NO: 52) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4JJ shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.7.2-CG4 (residues 20-135 of SEQ ID NO: 70) to the germline V_H3-11, D_H6-13, J_H6b sequence (SEQ ID NO: 115).

Figure 4KK shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.14.4-CG2 (residues 23-130 of SEQ ID NO: 56) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4LL shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.14.4-CG2 (residues 20-135 of SEQ ID NO: 74) to the germline V_H3-11, D_H7-27, J_H4b sequence (SEQ ID NO: 116).

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Figure 4MM shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.14.4-CG4 (residues 23-130 of SEQ ID NO: 56) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4NN shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.14.4-CG4 (residues 20-135 of SEQ ID NO: 78) to the germline V_H3-11, D_H7-27, J_H4b sequence (SEQ ID NO: 116).

Figure 4OO shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.14.4-Ser (residues 23-130 of SEQ ID NO: 28) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4PP shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.14.4-Ser (residues 20-135 of SEQ ID NO: 82) to the germline V_H3-11, D_H7-27, J_H4b sequence (SEQ ID NO: 116).

Figure 4QQ shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.7.2-Ser (residues 23-130 of SEQ ID NO: 48) to the germline V_κO12, J_κ3 sequence (SEQ ID NO: 103).

Figure 4RR shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.7.2-Ser (residues 20-136 of SEQ ID NO: 86) to the germline V_H3-11, D_H6-13, J_H6b sequence (SEQ ID NO: 115).

Figure 4SS shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 8.10.3-Ser (residues 21-129 of SEQ ID NO: 44) to the germline V_κA27, J_κ4 sequence (SEQ ID NO: 114).

Figure 4TT shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 8.10.3-Ser (residues 20-141 of SEQ ID NO: 90) to the germline V_H3-48, D_H1-26, J_H4b sequence (SEQ ID NO: 113).

Figure 4UU shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 8.10.3-CG4 (residues 21-129 of SEQ ID NO: 60) to the germline V_κA27, J_κ4 sequence (SEQ ID NO: 114).

Figure 4VV shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 8.10.3-CG4 (residues 20-141 of SEQ ID NO: 94) to the germline V_H3-48, D_H1-26, J_H4b sequence (SEQ ID NO: 113).

Figure 4WW shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 9.14.4G1 (residues 23-130 of SEQ ID NO: 28) to the germline V_κO12 J_κ3 sequence (SEQ ID NO: 103).

Figure 4XX shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 9.14.4G1 (residues 20-135 of SEQ ID NO: 102) to the germline V_H3-11, D_H7-27, J_H4b sequence (SEQ ID NO: 116).

Figure 4YY shows an alignment of the predicted amino acid sequence of the light chain variable region for antibody 8.10.3FG1 (residues 21-129 of SEQ ID NO:32) to the germline V_KA27, J_K4 sequence (SEQ ID NO: 114).

Figure 4ZZ shows an alignment of the predicted amino acid sequence of the heavy chain variable region for antibody 8.10.3FG1 (residues 20-141 of SEQ ID NO: 98) to the germline V_H3-48, D_H1-26, J_H4b sequence (SEQ ID NO: 113).

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Techniques

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art.

The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) and Ausubel *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Associates (1992), and Harlow and Lane *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

The term "polypeptide" encompasses native or artificial proteins, protein fragments and polypeptide analogs of a protein sequence. A polypeptide may be monomeric or polymeric.

The term "isolated protein", "isolated polypeptide" or "isolated antibody" is a protein, polypeptide or antibody that by virtue of its origin or source of derivation has one to four of the following: (1) is not associated with naturally associated components that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

Examples of isolated antibodies include an anti-M-CSF antibody that has been affinity purified using M-CSF, an anti-M-CSF antibody that has been synthesized by a hybridoma or other cell line *in vitro*, and a human anti-M-CSF antibody derived from a transgenic mouse.

A protein or polypeptide is "substantially pure," "substantially homogeneous," or "substantially purified" when at least about 60 to 75% of a sample exhibits a single species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A substantially pure polypeptide or protein will typically comprise about 50%, 60%, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be indicated by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel with a stain well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally-occurring sequence. In some embodiments, fragments are at least 5, 6, 8 or 10 amino acids long. In other embodiments, the fragments are at least 14, at least 20, at least 50, or at least 70, 80, 90, 100, 150 or 200 amino acids long.

The term "polypeptide analog" as used herein refers to a polypeptide that comprises a segment that has substantial identity to a portion of an amino acid sequence and that has at least

one of the following properties: (1) specific binding to M-CSF under suitable binding conditions, (2) ability to inhibit M-CSF.

Typically, polypeptide analogs comprise a conservative amino acid substitution (or insertion or deletion) with respect to the normally-occurring sequence. Analogs typically are at least 20 or 25 amino acids long, preferably at least 50, 60, 70, 80, 90, 100, 150 or 200 amino acids long or longer, and can often be as long as a full-length polypeptide.

In certain embodiments, amino acid substitutions of the antibody or antigen-binding portion thereof are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, or (4) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various muteins of a sequence other than the normally-occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the normally-occurring sequence, preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts.

A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence; e.g., a replacement amino acid should not alter the anti-parallel β -sheet that makes up the immunoglobulin binding domain that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence. In general, glycine and proline analogs would not be used in an anti-parallel β -sheet. Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton *et al.*, *Nature* 354:105 (1991), which are each incorporated herein by reference.

Non-peptide analogs are commonly used in the pharmaceutical industry as drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics." Fauchere, *J. Adv. Drug Res.* 15:29 (1986); Veber and Freidinger, *TINS* p.392 (1985); and Evans *et al.*, *J. Med. Chem.* 30:1229 (1987), which are incorporated herein by reference. Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a desired biochemical property or pharmacological

activity), such as a human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH₂NH--, --CH₂S--, --CH₂-CH₂--, --CH=CH--(cis and trans), --COCH₂--, --CH(OH)CH₂--, and --CH₂SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch, *Ann. Rev. Biochem.* 61:387 (1992), incorporated herein by reference); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

An "antibody" refers to an intact antibody or an antigen-binding portion that competes with the intact antibody for specific binding. See generally, Fundamental Immunology, Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. In some embodiments, antigen-binding portions include Fab, Fab', F(ab')₂, Fd, Fv, dAb, and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an antibody that is sufficient to confer specific antigen binding to the polypeptide.

From N-terminus to C-terminus, both the mature light and heavy chain variable domains comprise the regions FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat, *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), Chothia & Lesk, *J. Mol. Biol.* 196:901-917 (1987), or Chothia *et al.*, *Nature* 342:878-883 (1989).

As used herein, an antibody that is referred to by number is the same as a monoclonal antibody that is obtained from the hybridoma of the same number. For example, monoclonal antibody 3.8.3 is the same antibody as one obtained from hybridoma 3.8.3.

As used herein, a Fd fragment means an antibody fragment that consists of the V_H and C_H 1 domains; an Fv fragment consists of the V_L and V_H domains of a single arm of an antibody; and a dAb fragment (Ward *et al.*, *Nature* 341:544-546 (1989)) consists of a V_H domain.

In some embodiments, the antibody is a single-chain antibody (scFv) in which a V_L and V_H domains are paired to form a monovalent molecules via a synthetic linker that enables them to be made as a single protein chain. (Bird *et al.*, *Science* 242:423-426 (1988) and Huston *et*

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5 *al., Proc. Natl. Acad. Sci. USA* 85:5879-5883 (1988).) In some embodiments, the antibodies are diabodies, i.e., are bivalent antibodies in which V_H and V_L domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites. (See e.g., Holliger P. *et al.*, *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993), and Poljak R. J. *et al.*, *Structure* 2:1121-1123 (1994).) In some embodiments, one or more CDRs from an antibody of the invention may be incorporated into a molecule either covalently or noncovalently to make it an immunoadhesin that specifically binds to M-CSF. In such embodiments, the CDR(s) may be incorporated as part of a larger polypeptide chain, may be covalently linked to another polypeptide chain, or may be incorporated noncovalently.

In embodiments having one or more binding sites, the binding sites may be identical to one another or may be different.

15 As used herein, the term "human antibody" means any antibody in which the variable and constant domain sequences are human sequences. The term encompasses antibodies with sequences derived from human genes, but which have been changed, e.g. to decrease possible immunogenicity, increase affinity, eliminate cysteines that might cause undesirable folding, etc. The term encompasses such antibodies produced recombinantly in non-human cells, which might impart glycosylation not typical of human cells. These antibodies may be prepared in a variety of ways, as described below.

20 The term "chimeric antibody" as used herein means an antibody that comprises regions from two or more different antibodies. In one embodiment, one or more of the CDRs are derived from a human anti-M-CSF antibody. In another embodiment, all of the CDRs are derived from a human anti-M-CSF antibody. In another embodiment, the CDRs from more than one human anti-M-CSF antibodies are combined in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human anti-M-CSF antibody, a CDR2 from the light chain of a second human anti-M-CSF antibody and a CDR3 from the light chain of a third human anti-M-CSF antibody, and the CDRs from the heavy chain may be derived from one or more other anti-M-CSF antibodies. Further, the framework regions may be derived from one of the anti-M-CSF antibodies from which one or more of the CDRs are taken or from one or more different human antibodies.

30 Fragments or analogs of antibodies or immunoglobulin molecules can be readily prepared by those of ordinary skill in the art following the teachings of this specification. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of

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functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Preferably, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function.
5 Methods to identify protein sequences that fold into a known three-dimensional structure are known. See Bowie *et al.*, *Science* 253:164 (1991).

The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system
10 (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jonsson U. *et al.*, *Ann. Biol. Clin.* 51:19-26 (1993); Jonsson U. *et al.*, *Biotechniques* 11:620-627 (1991); Jonsson B. *et al.*, *J. Mol. Recognit.* 8:125-131 (1995); and Johnsson B. *et al.*, *Anal. Biochem.* 198:268-277 (1991).

The term " K_D " refers to the equilibrium dissociation constant of a particular
15 antibody-antigen interaction.

The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor or otherwise interacting with a molecule. Epitopic determinants generally consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and generally have specific three dimensional structural
20 characteristics, as well as specific charge characteristics. An epitope may be "linear" or "conformational." In a linear epitope, all of the points of interaction between the protein and the interacting molecule (such as an antibody) occur linearly along the primary amino acid sequence of the protein. In a conformational epitope, the points of interaction occur across amino acid residues on the protein that are separated from one another. An antibody is said to
25 specifically bind an antigen when the dissociation constant is ≤ 1 mM, preferably ≤ 100 nM and most preferably ≤ 10 nM. In certain embodiments, the K_D is 1 pM to 500 pM. In other embodiments, the K_D is between 500 pM to 1 μ M. In other embodiments, the K_D is between 1 μ M to 100 nM. In other embodiments, the K_D is between 100 mM to 10 nM. Once a desired epitope on an antigen is determined, it is possible to generate antibodies to that epitope, e.g.,
30 using the techniques described in the present invention. Alternatively, during the discovery process, the generation and characterization of antibodies may elucidate information about desirable epitopes. From this information, it is then possible to competitively screen antibodies for binding to the same epitope. An approach to achieve this is to conduct cross-competition studies to find antibodies that competitively bind with one another, e.g., the antibodies compete

for binding to the antigen. A high throughput process for "binning" antibodies based upon their cross-competition is described in International Patent Application No. WO 03/48731.

As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See *Immunology - A Synthesis* (2nd Edition, E.S. Golub and D.R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference.

The term "polynucleotide" as referred to herein means a polymeric form of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms.

The term "isolated polynucleotide" as used herein means a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin or source of derivation, the "isolated polynucleotide" has one to three of the following: (1) is not associated with all or a portion of a polynucleotides with which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide to which it is not linked in nature, or (3) does not occur in nature as part of a larger sequence.

The term "oligonucleotide" as used herein includes naturally occurring, and modified nucleotides linked together by naturally occurring and non-naturally occurring oligonucleotide linkages. Oligonucleotides are a polynucleotide subset generally comprising a length of 200 bases or fewer. Preferably oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 bases in length. Oligonucleotides are usually single stranded, e.g. for primers and probes; although oligonucleotides may be double stranded, e.g. for use in the construction of a gene mutant. Oligonucleotides of the invention can be either sense or antisense oligonucleotides.

The term "naturally occurring nucleotides" as used herein includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" as used herein includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" referred to herein includes oligonucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoroamidate, and the like. See e.g., LaPlanche *et al.*, *Nucl. Acids Res.* 14:9081 (1986); Stec *et al.*, *J. Am. Chem. Soc.* 106:6077 (1984); Stein *et al.*, *Nucl. Acids Res.* 16:3209 (1988); Zon *et al.*, *Anti-Cancer Drug Design* 6:539 (1991); Zon *et al.*, *Oligonucleotides and Analogues: A Practical Approach*, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); U.S. Patent No. 5,151,510; Uhlmann and Peyman, *Chemical Reviews* 90:543 (1990), the disclosures of which are hereby incorporated by reference. An oligonucleotide can include a label for detection, if desired.

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“Operably linked” sequences include both expression control sequences that are contiguous with the gene of interest and expression control sequences that act in *trans* or at a distance to control the gene of interest. The term “expression control sequence” as used herein means polynucleotide sequences that are necessary to effect the expression and processing of coding sequences to which they are ligated. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (i.e., Kozak consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence; in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term “control sequences” is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

The term “vector”, as used herein, means a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. In some embodiments, the vector is a plasmid, i.e., a circular double stranded DNA loop into which additional DNA segments may be ligated. In some embodiments, the vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. In some embodiments, the vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). In other embodiments, the vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors” (or simply, “expression vectors”).

The term “recombinant host cell” (or simply “host cell”), as used herein, means a cell into which a recombinant expression vector has been introduced. It should be understood that “recombinant host cell” and “host cell” mean not only the particular subject cell but also the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term “host cell” as used herein.

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The term "selectively hybridize" referred to herein means to detectably and specifically bind. Polynucleotides, oligonucleotides and fragments thereof in accordance with the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. "High stringency" or "highly stringent" conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. One example of "high stringency" or "highly stringent" conditions is the incubation of a polynucleotide with another polynucleotide, wherein one polynucleotide may be affixed to a solid surface such as a membrane, in a hybridization buffer of 6X SSPE or SSC, 50% formamide, 5X Denhardt's reagent, 0.5% SDS, 100 µg/ml denatured, fragmented salmon sperm DNA at a hybridization temperature of 42°C for 12-16 hours, followed by twice washing at 55°C using a wash buffer of 1X SSC, 0.5% SDS. See also Sambrook *et al.*, *supra*, pp. 9.50-9.55.

The term "percent sequence identity" in the context of nucleic acid sequences means the percent of residues when a first contiguous sequence is compared and aligned for maximum correspondence to a second contiguous sequence. The length of sequence identity comparison may be over a stretch of at least about nine nucleotides, usually at least about 18 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36, 48 or more nucleotides. There are a number of different algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using FASTA, Gap or Bestfit, which are programs in Wisconsin Package Version 10.0, Genetics Computer Group (GCG), Madison, Wisconsin. FASTA, which includes, e.g., the programs FASTA2 and FASTA3, provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.* 183:63-98 (1990); Pearson, *Methods Mol. Biol.* 132:185-219 (2000); Pearson, *Methods Enzymol.* 266:227-258 (1996); Pearson, *J. Mol. Biol.* 276:71-84 (1998); herein incorporated by reference). Unless otherwise specified, default parameters for a particular program or algorithm are used. For instance, percent sequence identity between nucleic acid sequences can be determined using FASTA with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) or using Gap with its default parameters as provided in GCG Version 6.1, herein incorporated by reference.

A reference to a nucleotide sequence encompasses its complement unless otherwise specified. Thus, a reference to a nucleic acid having a particular sequence should be understood to encompass its complementary strand, with its complementary sequence.

The term "percent sequence identity" means a ratio, expressed as a percent of the number of identical residues over the number of residues compared.

The term "substantial similarity" or "substantial sequence similarity," when referring to a nucleic acid or fragment thereof, means that when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 85%, preferably at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed above.

As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, as supplied with the programs, share at least 70%, 75% or 80% sequence identity, preferably at least 90% or 95% sequence identity, and more preferably at least 97%, 98% or 99% sequence identity. In certain embodiments, residue positions that are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain R group with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, e.g., Pearson, *Methods Mol. Biol.* 243:307-31 (1994). Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine, and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartic acid and glutamic acid; and 7) sulfur-containing side chains: cysteine and methionine. Conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagines-glutamine.

Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.*, *Science* 256:1443-45 (1992), herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

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Sequence identity for polypeptides, is typically measured using sequence analysis software. Protein analysis software matches sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG contains programs such as "Gap" and "Bestfit" which can be used with default parameters, as specified with the programs, to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, see GCG Version 6.1. (University of Wisconsin WI) FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.* 183:63-98 (1990); Pearson, *Methods Mol. Biol.* 132:185-219 (2000)). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn, using default parameters, as supplied with the programs. See, e.g., Altschul *et al.*, *J. Mol. Biol.* 215:403-410 (1990); Altschul *et al.*, *Nucleic Acids Res.* 25:3389-402 (1997).

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acid residues, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. When searching a database containing sequences from a large number of different organisms, it is preferable to compare amino acid sequences.

As used herein, the terms "label" or "labeled" refers to incorporation of another molecule in the antibody. In one embodiment, the label is a detectable marker, e.g., incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In another embodiment, the label or marker can be therapeutic, e.g., a drug conjugate or toxin. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase), chemiluminescent markers, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper

pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags), magnetic agents, such as gadolinium chelates, toxins such as pertussis toxin, taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Human Anti-M-CSF Antibodies and Characterization Thereof

In one embodiment, the invention provides humanized anti-M-CSF antibodies. In another embodiment, the invention provides human anti-M-CSF antibodies. In some embodiments, human anti-M-CSF antibodies are produced by immunizing a non-human transgenic animal, e.g., a rodent, whose genome comprises human immunoglobulin genes so that the rodent produces human antibodies.

An anti-M-CSF antibody of the invention can comprise a human kappa or a human lamda light chain or an amino acid sequence derived therefrom. In some embodiments comprising a kappa light chain, the light chain variable domain (V_L) is encoded in part by a human $V_{\kappa}O12$, $V_{\kappa}L2$, $V_{\kappa}L5$, $V_{\kappa}A27$ or $V_{\kappa}B3$ gene and a $J_{\kappa}1$, $J_{\kappa}2$, $J_{\kappa}3$, or $J_{\kappa}4$ gene. In particular embodiments of the invention, the light chain variable domain is encoded by $V_{\kappa}O12/J_{\kappa}3$, $V_{\kappa}L2/J_{\kappa}3$, $V_{\kappa}L5/J_{\kappa}3$, $V_{\kappa}L5/J_{\kappa}4$, $V_{\kappa}A27/J_{\kappa}4$ or $V_{\kappa}B3/J_{\kappa}1$ gene.

In some embodiments, the V_L of the M-CSF antibody comprises one or more amino acid substitutions relative to the germline amino acid sequence. In some embodiments, the V_L of the anti-M-CSF antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions relative to the germline amino acid sequence. In some embodiments, one or more of those substitutions from germline is in the CDR regions of the light chain. In some embodiments, the amino acid substitutions relative to germline are at one or more of the same positions as the substitutions relative to germline in any one or more of the V_L of antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. For example, the V_L of the anti-M-CSF

antibody may contain one or more amino acid substitutions compared to germline found in the V_L of antibody 88, and other amino acid substitutions compared to germline found in the V_L of antibody 252 which utilizes the same V_K gene as antibody 88. In some embodiments, the amino acid changes are at one or more of the same positions but involve a different mutation than in the reference antibody.

In some embodiments, amino acid changes relative to germline occur at one or more of the same positions as in any of the V_L of antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1, but the changes may represent conservative amino acid substitutions at such position(s) relative to the amino acid in the reference antibody. For example, if a particular position in one of these antibodies is changed relative to germline and is glutamate, one may substitute aspartate at that position. Similarly, if an amino acid substitution compared to germline is serine, one may substitute threonine for serine at that position. Conservative amino acid substitutions are discussed *supra*.

In some embodiments, the light chain of the human anti-M-CSF antibody comprises the amino acid sequence that is the same as the amino acid sequence of the V_L of antibody 252 (SEQ ID NO: 4), 88 (SEQ ID NO: 8), 100 (SEQ ID NO: 12), 3.8.3 (SEQ ID NO: 16), 2.7.3 (SEQ ID NO: 20), 1.120.1 (SEQ ID NO: 24), 9.14.4I (SEQ ID NO: 28), 8.10.3F (SEQ ID NO: 32), 9.7.2IF (SEQ ID NO: 36), 9.14.4 (SEQ ID NO: 28), 8.10.3 (SEQ ID NO: 44), 9.7.2 (SEQ ID NO: 48), 9.7.2C-Ser (SEQ ID NO: 52), 9.14.4C-Ser (SEQ ID NO: 56), 8.10.3C-Ser (SEQ ID NO: 60), 8.10.3-CG2 (SEQ ID NO: 60), 9.7.2-CG2 (SEQ ID NO: 52), 9.7.2-CG4 (SEQ ID NO: 52), 9.14.4-CG2 (SEQ ID NO: 56), 9.14.4-CG4 (SEQ ID NO: 56), 9.14.4-Ser (SEQ ID NO: 28), 9.7.2-Ser (SEQ ID NO: 48), 8.10.3-Ser (SEQ ID NO: 44), 8.10.3-CG4 (SEQ ID NO: 60) 8.10.3FG1 (SEQ ID NO: 32) or 9.14.4G1 (SEQ ID NO: 28), or said amino acid sequence having up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitutions and/or a total of up to 3 non-conservative amino acid substitutions. In some embodiments, the light chain comprises the amino acid sequence from the beginning of the CDR1 to the end of the CDR3 of any one of the foregoing antibodies.

In some embodiments, the light chain of the anti-M-CSF antibody comprises at least the light chain CDR1, CDR2 or CDR3 of a germline or antibody sequence, as described herein. In another embodiment, the light chain may comprise a CDR1, CDR2 or CDR3 regions of an antibody independently selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2,

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9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1, or CDR regions each having less than 4 or less than 3 conservative amino acid substitutions and/or a total of three or fewer non-conservative amino acid substitutions. In other embodiments, the light chain of the anti-M-CSF antibody comprises the light chain CDR1, CDR2 or CDR3, each of which are independently selected from the CDR1, CDR2 and CDR3 regions of an antibody having a light chain variable region comprising the amino acid sequence of the V_L region selected from SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60, or encoded by a nucleic acid molecule encoding the V_L region selected from SEQ ID NOS: 3, 7, 11, 27, 31, 35, 43 or 47. The light chain of the anti-M-CSF antibody may comprise the CDR1, CDR2 and CDR3 regions of an antibody comprising the amino acid sequence of the V_L region selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1 or SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60.

In some embodiments, the light chain comprises the CDR1, CDR2 and CDR3 regions of antibody 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1, or said CDR regions each having less than 4 or less than 3 conservative amino acid substitutions and/or a total of three or fewer non-conservative amino acid substitutions.

With regard to the heavy chain, in some embodiments, the variable region of the heavy chain amino acid sequence is encoded in part by a human V_H3-11, V_H3-23, V_H3-7, V_H1-18, V_H3-33, V_H3-48 gene and a J_H4, J_H6, J_H4b, or J_H6b gene. In a particular embodiment of the invention, the heavy chain variable region is encoded by V_H3-11/D_H7-27/J_H6, V_H3-7/D_H6-13/J_H4, V_H3-23/D_H1-26/J_H4, V_H3-11/D_H7-27/J_H4, V_H3-33/D_H1-26/J_H4, V_H1-18/D_H4-23/J_H4, V_H3-11/D_H7-27/J_H4b, V_H3-48/D_H1-26/J_H4b, V_H3-11/D_H6-13/J_H6b, V_H3-11/D_H7-27/J_H4b, V_H3-48/D_H1-6/J_H4b, or V_H3-11/D_H6-13/J_H6b gene. In some embodiments, the V_H of the anti-M-CSF antibody contains one or more amino acid substitutions, deletions or insertions (additions) relative to the germline amino acid sequence. In some embodiments, the variable domain of the heavy chain comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 mutations from the germline amino acid sequence. In some embodiments, the mutation(s) are non-conservative substitutions compared to the germline amino acid sequence. In some embodiments, the mutations are in the CDR regions of the heavy chain. In some embodiments, the amino acid changes are made at one or more of the same positions as the mutations from

germline in any one or more of the V_H of antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. In other embodiments, the amino acid changes are at one or more of the same positions but involve a different mutation than in the reference antibody.

In some embodiments, the heavy chain comprises an amino acid sequence of the variable domain (V_H) of antibody 252 (SEQ ID NO: 2), 88 (SEQ ID NO: 6), 100 (SEQ ID NO: 10), 3.8.3 (SEQ ID NO: 14), 2.7.3 (SEQ. ID NO: 18), 1.120.1 (SEQ. ID NO: 22), 9.14.4I (SEQ ID NO: 26), 8.10.3F (SEQ ID NO: 30), 9.7.2IF (SEQ ID NO: 34), 9.14.4 (SEQ ID NO: 38), 8.10.3 (SEQ ID NO: 30), 9.7.2 (SEQ ID NO: 46), 9.7.2C-Ser (SEQ ID NO: 50), 9.14.4C-Ser (SEQ ID NO: 54), 8.10.3C-Ser (SEQ ID NO: 58), 8.10.3-CG2 (SEQ ID NO: 62), 9.7.2-CG2 (SEQ ID NO: 66), 9.7.2-CG4 (SEQ ID NO: 70), 9.14.4-CG2 (SEQ ID NO: 74), 9.14.4-CG4 (SEQ ID NO: 78), 9.14.4-Ser (SEQ ID NO: 82), 9.7.2-Ser (SEQ ID NO: 86), 8.10.3-Ser (SEQ ID NO: 90), 8.10.3-CG4 (SEQ ID NO: 94), 8.10.3FG1 (SEQ ID NO: 98) or 9.14.4G1 (SEQ ID NO: 102), or said amino acid sequence having up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitutions and/or a total of up to 3 non-conservative amino acid substitutions. In some embodiments, the heavy chain comprises the amino acid sequence from the beginning of the CDR1 to the end of the CDR3 of any one of the foregoing antibodies.

In some embodiments, the heavy chain comprises the heavy chain CDR1, CDR2 and CDR3 regions of antibody 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1, or said CDR regions each having less than 8, less than 6, less than 4, or less than 3 conservative amino acid substitutions and/or a total of three or fewer non-conservative amino acid substitutions.

In some embodiments, the heavy chain comprises a germline or antibody CDR3, as described above, of an antibody sequence as described herein, and may also comprise the CDR1 and CDR2 regions of a germline sequence, or may comprise a CDR1 and CDR2 of an antibody sequence, each of which are independently selected from an antibody comprising a heavy chain of an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. In another embodiment, the heavy chain comprises a CDR3 of an antibody sequence as described herein, and may also comprise the CDR1 and CDR2 regions, each of

which are independently selected from a CDR1 and CDR2 region of a heavy chain variable region comprising an amino acid sequence of the V_H region selected from SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102, or encoded by a nucleic acid sequence encoding the V_H region selected from SEQ ID NOS: 1, 5, 9, 25, 29, 33, 37, 45, 97 or 101. In another embodiment, the antibody comprises a light chain as disclosed above and a heavy chain as disclosed above.

One type of amino acid substitution that may be made is to change one or more cysteines in the antibody, which may be chemically reactive, to another residue, such as, without limitation, alanine or serine. In one embodiment, there is a substitution of a non-canonical cysteine. The substitution can be in a framework region of a variable domain or in the constant domain of an antibody. In another embodiment, the cysteine is in a non-canonical region of the antibody.

Another type of amino acid substitution that may be made is to remove any potential proteolytic sites in the antibody, particularly those that are in a CDR or framework region of a variable domain or in the constant domain of an antibody. Substitution of cysteine residues and removal of proteolytic sites may decrease the risk of any heterogeneity in the antibody product and thus increase its homogeneity. Another type of amino acid substitution is elimination of asparagine-glycine pairs, which form potential deamidation sites, by altering one or both of the residues.

In some embodiments, the C-terminal lysine of the heavy chain of the anti-M-CSF antibody of the invention is not present (Lewis D.A., *et al.*, *Anal. Chem.*, 66(5): 585-95 (1994)). In various embodiments of the invention, the heavy and light chains of the anti-M-CSF antibodies may optionally include a signal sequence.

In one aspect, the invention relates to inhibiting human anti-M-CSF monoclonal antibodies and the cell lines engineered to produce them. Table 1 lists the sequence identifiers (SEQ ID NOS) of the nucleic acids that encode the variable region of the heavy and light chains and the corresponding predicted amino acid sequences for the monoclonal antibodies: 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3 and 9.7.2. Additional variant antibodies 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4 8.10.3FG1 or 9.14.4G1 could be made by methods known to one skilled in the art.

Table 1

HUMAN ANTI-M-CSF ANTIBODIES				
MAb	SEQUENCE IDENTIFIER (SEQ ID NOS.)			
	Full Length			
	Heavy		Light	
	DNA	Protein	DNA	Protein
252	1	2	3	4
88	5	6	7	8
100	9	10	11	12
3.8.3		14		16
2.7.3		18		20
1.120.1		22		24
9.14.4I	25	26	27	28
9.14.4	37	38	27	28
9.14.4C-Ser		54		56
9.14.4-CG2		74		56
9.14.4-CG4		78		56
9.14.4-Ser		82	27	28
9.14.4-G1	101	102	27	28
8.10.3F	29	30	31	32
8.10.3	29	30	43	44
8.10.3C-Ser		58		60
8.10.3-CG2		62		60
8.10.3-Ser		90	43	44
8.10.3-CG4		94		60
8.10.3FG1	97	98	31	32
9.7.2IF	33	34	35	36
9.7.2	45	46	47	48
9.7.2C-Ser		50		52
9.7.2-CG2		66		52
9.7.2-CG4		70		52
9.7.2-Ser		86	47	48

Class and Subclass of Anti-M-CSF Antibodies

The class and subclass of anti-M-CSF antibodies may be determined by any method known in the art. In general, the class and subclass of an antibody may be determined using antibodies that are specific for a particular class and subclass of antibody. Such antibodies are commercially available. The class and subclass can be determined by ELISA, or Western Blot as well as other techniques. Alternatively, the class and subclass may be determined by sequencing all or a portion of the constant domains of the heavy and/or light chains of the antibodies, comparing their amino acid sequences to the known amino acid sequences of various class and subclasses of immunoglobulins, and determining the class and subclass of the antibodies.

In some embodiments, the anti-M-CSF antibody is a monoclonal antibody. The anti-M-CSF antibody can be an IgG, an IgM, an IgE, an IgA, or an IgD molecule. In preferred embodiments, the anti-M-CSF antibody is an IgG and is an IgG1, IgG2, IgG3 or IgG4 subclass. In other preferred embodiments, the antibody is subclass IgG2 or IgG4. In another preferred embodiment, the antibody is subclass IgG1.

Species and Molecular Selectivity

In another aspect of the invention, the anti-M-CSF antibodies demonstrate both species and molecule selectivity. In some embodiments, the anti-M-CSF antibody binds to human, cynomolgus monkey and mouse M-CSF. Following the teachings of the specification, one may determine the species selectivity for the anti-M-CSF antibody using methods well known in the art. For instance, one may determine the species selectivity using Western blot, FACS, ELISA, RIA, a cell proliferation assay, or a M-CSF receptor binding assay. In a preferred embodiment, one may determine the species selectivity using a cell proliferation assay or ELISA.

In another embodiment, the anti-M-CSF antibody has a selectivity for M-CSF that is at least 100 times greater than its selectivity for GM-/G-CSF. In some embodiments, the anti-M-CSF antibody does not exhibit any appreciable specific binding to any other protein other than M-CSF. One can determine the selectivity of the anti-M-CSF antibody for M-CSF using methods well known in the art following the teachings of the specification. For instance one can determine the selectivity using Western blot, FACS, ELISA, or RIA.

Identification of M-CSF Epitopes Recognized by Anti- M-CSF Antibodies

The invention provides a human anti-M-CSF monoclonal antibody that binds to M-CSF and competes with, cross-competes with and/or binds the same epitope and/or binds to M-CSF

with the same K_D as (a) an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1; (b) an antibody that comprises a heavy chain variable region having an amino acid sequence of SEQ ID NO: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102; (c) an antibody that comprises a light chain variable region having an amino acid sequence of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60; (d) an antibody that comprises both a heavy chain variable region as defined in (b) and a light chain variable region as defined in (c).

One can determine whether an antibody binds to the same epitope, competes for binding with, cross competes for binding with or has the same K_D an anti-M-CSF antibody by using methods known in the art. In one embodiment, one allows the anti-M-CSF antibody of the invention to bind to M-CSF under saturating conditions and then measures the ability of the test antibody to bind to M-CSF. If the test antibody is able to bind to M-CSF at the same time as the anti-M-CSF antibody, then the test antibody binds to a different epitope as the anti-M-CSF antibody. However, if the test antibody is not able to bind to M-CSF at the same time, then the test antibody binds to the same epitope, an overlapping epitope, or an epitope that is in close proximity to the epitope bound by the human anti-M-CSF antibody. This experiment can be performed using ELISA, RIA, or FACS. In a preferred embodiment, the experiment is performed using BIACORE™.

Binding Affinity of Anti-M-CSF Antibodies to M-CSF

In some embodiments of the invention, the anti-M-CSF antibodies bind to M-CSF with high affinity. In some embodiments, the anti-M-CSF antibody binds to M-CSF with a K_D of 1×10^{-7} M or less. In other preferred embodiments, the antibody binds to M-CSF with a K_D of 1×10^{-8} M, 1×10^{-9} M, 1×10^{-10} M, 1×10^{-11} M, 1×10^{-12} M or less. In certain embodiments, the K_D is 1 pM to 500 pM. In other embodiments, the K_D is between 500 pM to 1 μ M. In other embodiments, the K_D is between 1 μ M to 100 nM. In other embodiments, the K_D is between 100 mM to 10 nM. In an even more preferred embodiment, the antibody binds to M-CSF with substantially the same K_D as an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. In another preferred embodiment, the antibody binds to M-CSF with substantially the same K_D as an antibody that comprises a CDR2 of a light chain,

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and/or a CDR3 of a heavy chain from an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. In still another preferred embodiment, the antibody binds to M-CSF with substantially the same K_D as an antibody that comprises a heavy chain variable region having an amino acid sequence of SEQ ID NO: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102, or that comprises a light chain variable region having an amino acid sequence of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60. In another preferred embodiment, the antibody binds to M-CSF with substantially the same K_D as an antibody that comprises a CDR2, and may optionally comprise a CDR1 and/or CDR3, of a light chain variable region having an amino acid sequence of the V_L region of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60, or that comprises a CDR3, and may optionally comprise a CDR1 and/or CDR2, of a heavy chain variable region having an amino acid sequence of the V_H region of SEQ ID NO: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102.

In some embodiments, the anti-M-CSF antibody has a low dissociation rate. In some embodiments, the anti-M-CSF antibody has an k_{off} of $2.0 \times 10^{-4} \text{ s}^{-1}$ or lower. In other preferred embodiments, the antibody binds to M-CSF with a k_{off} of 2.0×10^{-5} or a k_{off} of $2.0 \times 10^{-6} \text{ s}^{-1}$ or lower. In some embodiments, the k_{off} is substantially the same as an antibody described herein, such as an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. In some embodiments, the antibody binds to M-CSF with substantially the same k_{off} as an antibody that comprises (a) a CDR3, and may optionally comprise a CDR1 and/or CDR2, of a heavy chain of an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1; or (b) a CDR2, and may optionally comprise a CDR1 and/or CDR3, of a light chain from an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. In some embodiments, the antibody binds to M-CSF with substantially the same k_{off} as an antibody that comprises a heavy chain variable region having an amino acid sequence of SEQ ID NO: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78,

82, 86, 90, 94, 98 or 102; or that comprises a light chain variable region having an amino acid sequence of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60; In another preferred embodiment, the antibody binds to M-CSF with substantially the same k_{off} as an antibody that comprises a CDR2, and may optionally comprise a CDR1 and/or CDR3, of a light chain variable region having an amino acid sequence of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60; or a CDR3, and may optionally comprise a CDR1 and/or CDR2, of a heavy chain variable region having an amino acid sequence of SEQ ID NO: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102.

The binding affinity and dissociation rate of an anti-M-CSF antibody to a M-CSF can be determined by methods known in the art. The binding affinity can be measured by competitive ELISAs, RIAs, surface plasmon resonance (e.g., by using BIACORE™ technology). The dissociation rate can be measured by surface plasmon resonance. Preferably, the binding affinity and dissociation rate is measured by surface plasmon resonance. More preferably, the binding affinity and dissociation rate are measured using BIACORE™ technology. Example VI exemplifies a method for determining affinity constants of anti-M-CSF monoclonal antibodies by BIACORE™ technology.

Inhibition of M-CSF Activity by Anti-M-CSF Antibody

Inhibition of M-CSF binding to c-fms

In another embodiment, the invention provides an anti-M-CSF antibody that inhibits the binding of a M-CSF to *c-fms* receptor and blocks or prevents activation of *c-fms*. In an preferred embodiment, the M-CSF is human. In another preferred embodiment, the anti-M-CSF antibody is a human antibody. The IC_{50} can be measured by ELISA, RIA, and cell based assays such as a cell proliferation assay, a whole blood monocyte shape change assay, or a receptor binding inhibition assay. In one embodiment, the antibody or portion thereof inhibits cell proliferation with an IC_{50} of no more than 8.0×10^{-7} M, preferably no more than 3×10^{-7} M, or more preferably no more than 8×10^{-8} M as measured by a cell proliferation assay. In another embodiment, the IC_{50} as measured by a monocyte shape change assay is no more than 2×10^{-6} M, preferably no more than 9.0×10^{-7} M, or more preferably no more than 9×10^{-8} M. In another preferred embodiment, the IC_{50} as measured by a receptor binding assay is no more than 2×10^{-6} M, preferably no more than 8.0×10^{-7} M, or more preferably no more than 7.0×10^{-8} M. Examples III, IV, and V exemplify various types of assays.

In another aspect anti-M-CSF antibodies of the invention inhibit monocyte/macrophage cell proliferation in response to a M-CSF by at least 20%, more preferably 40%, 45%, 50%,

55%, 60%, 65%, 70%, 80%, 85%, 90%, 95% or 100% compared to the proliferation of cell in the absence of antibody.

Methods of Producing Antibodies and Antibody Producing Cell Lines

Immunization

5 In some embodiments, human antibodies are produced by immunizing a non-human animal comprising in its genome some or all of human immunoglobulin heavy chain and light chain loci with a M-CSF antigen. In a preferred embodiment, the non-human animal is a XENOMOUSE™ animal (Abgenix Inc., Fremont, CA). Another non-human animal that may be used is a transgenic mouse produced by Medarex (Medarex, Inc., Princeton, NJ).

10 XENOMOUSE™ mice are engineered mouse strains that comprise large fragments of human immunoglobulin heavy chain and light chain loci and are deficient in mouse antibody production. See, e.g., Green *et al.*, *Nature Genetics* 7:13-21 (1994) and U.S. Patents 5,916,771, 5,939,598, 5,985,615, 5,998,209, 6,075,181, 6,091,001, 6,114,598, 6,130,364, 6,162,963 and 6,150,584. See also WO 91/10741, WO 94/02602, WO 96/34096, WO 96/33735, WO
15 98/16654, WO 98/24893, WO 98/50433, WO 99/45031, WO 99/53049, WO 00/09560, and WO 00/037504.

In another aspect, the invention provides a method for making anti-M-CSF antibodies from non-human, non-mouse animals by immunizing non-human transgenic animals that comprise human immunoglobulin loci with a M-CSF antigen. One can produce such animals
20 using the methods described in the above-cited documents. The methods disclosed in these documents can be modified as described in U.S. Patent 5,994,619. U.S. Patent 5,994,619 describes methods for producing novel cultural inner cell mass (CICM) cells and cell lines, derived from pigs and cows, and transgenic CICM cells into which heterologous DNA has been inserted. CICM transgenic cells can be used to produce cloned transgenic embryos, fetuses, and
25 offspring. The '619 patent also describes the methods of producing the transgenic animals, that are capable of transmitting the heterologous DNA to their progeny. In preferred embodiments, the non-human animals are rats, sheep, pigs, goats, cattle or horses.

XENOMOUSE™ mice produce an adult-like human repertoire of fully human antibodies and generate antigen-specific human antibodies. In some embodiments, the
30 XENOMOUSE™ mice contain approximately 80% of the human antibody V gene repertoire through introduction of megabase sized, germline configuration yeast artificial chromosome (YAC) fragments of the human heavy chain loci and kappa light chain loci. In other embodiments, XENOMOUSE™ mice further contain approximately all of the lambda light

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chain locus. See Mendez *et al.*, *Nature Genetics* 15:146-156 (1997), Green and Jakobovits, *J. Exp. Med.* 188:483-495 (1998), and WO 98/24893, the disclosures of which are hereby incorporated by reference.

In some embodiments, the non-human animal comprising human immunoglobulin genes are animals that have a human immunoglobulin "minilocus". In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of individual genes from the Ig locus. Thus, one or more V_H genes, one or more D_H genes, one or more J_H genes, a mu constant domain, and a second constant domain (preferably a gamma constant domain) are formed into a construct for insertion into an animal. This approach is described, *inter alia*, in U.S. Patent Nos. 5,545,807, 5,545,806, 5,569,825, 5,625,126, 5,633,425, 5,661,016, 5,770,429, 5,789,650, 5,814,318, 5,591,669, 5,612,205, 5,721,367, 5,789,215, and 5,643,763, hereby incorporated by reference.

In another aspect, the invention provides a method for making humanized anti-M-CSF antibodies. In some embodiments, non-human animals are immunized with a M-CSF antigen as described below under conditions that permit antibody production. Antibody-producing cells are isolated from the animals, fused with myelomas to produce hybridomas, and nucleic acids encoding the heavy and light chains of an anti-M-CSF antibody of interest are isolated. These nucleic acids are subsequently engineered using techniques known to those of skill in the art and as described further below to reduce the amount of non-human sequence, i.e., to humanize the antibody to reduce the immune response in humans

In some embodiments, the M-CSF antigen is isolated and/or purified M-CSF. In a preferred embodiment, the M-CSF antigen is human M-CSF. In some embodiments, the M-CSF antigen is a fragment of M-CSF. In some embodiments, the M-CSF fragment is the extracellular domain of M-CSF. In some embodiments, the M-CSF fragment comprises at least one epitope of M-CSF. In other embodiments, the M-CSF antigen is a cell that expresses or overexpresses M-CSF or an immunogenic fragment thereof on its surface. In some embodiments, the M-CSF antigen is a M-CSF fusion protein. M-CSF can be purified from natural sources using known techniques. Recombinant M-CSF is commercially available.

Immunization of animals can be by any method known in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, New York: Cold Spring Harbor Press, 1990. Methods for immunizing non-human animals such as mice, rats, sheep, goats, pigs, cattle and horses are well known in the art. See, e.g., Harlow and Lane, *supra*, and U.S. Patent 5,994,619. In a preferred embodiment, the M-CSF antigen is administered with an adjuvant to stimulate the immune response. Exemplary adjuvants include complete or incomplete Freund's adjuvant,

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RIBI (muramyl dipeptides) or ISCOM (immunostimulating complexes). Such adjuvants may protect the polypeptide from rapid dispersal by sequestering it in a local deposit, or they may contain substances that stimulate the host to secrete factors that are chemotactic for macrophages and other components of the immune system. Preferably, if a polypeptide is being administered, the immunization schedule will involve two or more administrations of the polypeptide, spread out over several weeks. Example I exemplifies a method for producing anti-M-CSF monoclonal antibodies in XENOMOUSE™ mice.

Production of Antibodies and Antibody-Producing Cell Lines

After immunization of an animal with a M-CSF antigen, antibodies and/or antibody-producing cells can be obtained from the animal. In some embodiments, anti-M-CSF antibody-containing serum is obtained from the animal by bleeding or sacrificing the animal. The serum may be used as it is obtained from the animal, an immunoglobulin fraction may be obtained from the serum, or the anti-M-CSF antibodies may be purified from the serum.

In some embodiments, antibody-producing immortalized cell lines are prepared from cells isolated from the immunized animal. After immunization, the animal is sacrificed and lymph node and/or splenic B cells are immortalized. Methods of immortalizing cells include, but are not limited to, transfecting them with oncogenes, infecting them with an oncogenic virus, cultivating them under conditions that select for immortalized cells, subjecting them to carcinogenic or mutating compounds, fusing them with an immortalized cell, e.g., a myeloma cell, and inactivating a tumor suppressor gene. See, e.g., Harlow and Lane, *supra*. If fusion with myeloma cells is used, the myeloma cells preferably do not secrete immunoglobulin polypeptides (a non-secretory cell line). Immortalized cells are screened using M-CSF, a portion thereof, or a cell expressing M-CSF. In a preferred embodiment, the initial screening is performed using an enzyme-linked immunoassay (ELISA) or a radioimmunoassay. An example of ELISA screening is provided in WO 00/37504, incorporated herein by reference.

Anti-M-CSF antibody-producing cells, e.g., hybridomas, are selected, cloned and further screened for desirable characteristics, including robust growth, high antibody production and desirable antibody characteristics, as discussed further below. Hybridomas can be expanded *in vivo* in syngeneic animals, in animals that lack an immune system, e.g., nude mice, or in cell culture *in vitro*. Methods of selecting, cloning and expanding hybridomas are well known to those of ordinary skill in the art.

In a preferred embodiment, the immunized animal is a non-human animal that expresses human immunoglobulin genes and the splenic B cells are fused to a myeloma cell line from the

same species as the non-human animal. In a more preferred embodiment, the immunized animal is a XENOMOUSE™ animal and the myeloma cell line is a non-secretory mouse myeloma. In an even more preferred embodiment, the myeloma cell line is P3-X63-AG8-653. See, e.g., Example I.

Thus, in one embodiment, the invention provides methods of producing a cell line that produces a human monoclonal antibody or a fragment thereof directed to M-CSF comprising (a) immunizing a non-human transgenic animal described herein with M-CSF, a portion of M-CSF or a cell or tissue expressing M-CSF; (b) allowing the transgenic animal to mount an immune response to M-CSF; (c) isolating B lymphocytes from a transgenic animal; (d) immortalizing the B lymphocytes; (e) creating individual monoclonal populations of the immortalized B lymphocytes; and (f) screening the immortalized B lymphocytes to identify an antibody directed to M-CSF.

In another aspect, the invention provides hybridomas that produce an human anti-M-CSF antibody. In a preferred embodiment, the hybridomas are mouse hybridomas, as described above. In other embodiments, the hybridomas are produced in a non-human, non-mouse species such as rats, sheep, pigs, goats, cattle or horses. In another embodiment, the hybridomas are human hybridomas.

In another preferred embodiment, a transgenic animal is immunized with M-CSF, primary cells, e.g., spleen or peripheral blood cells, are isolated from an immunized transgenic animal and individual cells producing antibodies specific for the desired antigen are identified. Polyadenylated mRNA from each individual cell is isolated and reverse transcription polymerase chain reaction (RT-PCR) is performed using sense primers that anneal to variable region sequences, e.g., degenerate primers that recognize most or all of the FR1 regions of human heavy and light chain variable region genes and antisense primers that anneal to constant or joining region sequences. cDNAs of the heavy and light chain variable regions are then cloned and expressed in any suitable host cell, e.g., a myeloma cell, as chimeric antibodies with respective immunoglobulin constant regions, such as the heavy chain and κ or λ constant domains. See Babcook, J.S. *et al.*, *Proc. Natl. Acad. Sci. USA* 93:7843-48, 1996, herein incorporated by reference. Anti M-CSF antibodies may then be identified and isolated as described herein.

In another embodiment, phage display techniques can be used to provide libraries containing a repertoire of antibodies with varying affinities for M-CSF. For production of such repertoires, it is unnecessary to immortalize the B cells from the immunized animal. Rather, the primary B cells can be used directly as a source of DNA. The mixture of cDNAs obtained from

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B cell, e.g., derived from spleens, is used to prepare an expression library, for example, a phage display library transfected into *E.coli*. The resulting cells are tested for immunoreactivity to M-CSF. Techniques for the identification of high affinity human antibodies from such libraries are described by Griffiths *et al.*, *EMBO J.*, 13:3245-3260 (1994); Nissim *et al.*, *ibid*, pp. 692-698 and by Griffiths *et al.*, *ibid*, 12:725-734. Ultimately, clones from the library are identified which produce binding affinities of a desired magnitude for the antigen and the DNA encoding the product responsible for such binding is recovered and manipulated for standard recombinant expression. Phage display libraries may also be constructed using previously manipulated nucleotide sequences and screened in a similar fashion. In general, the cDNAs encoding heavy and light chains are independently supplied or linked to form Fv analogs for production in the phage library.

The phage library is then screened for the antibodies with the highest affinities for M-CSF and the genetic material recovered from the appropriate clone. Further rounds of screening can increase affinity of the original antibody isolated.

In another aspect, the invention provides hybridomas that produce an human anti-M-CSF antibody. In a preferred embodiment, the hybridomas are mouse hybridomas, as described above. In other embodiments, the hybridomas are produced in a non-human, non-mouse species such as rats, sheep, pigs, goats, cattle or horses. In another embodiment, the hybridomas are human hybridomas.

Nucleic Acids, Vectors, Host Cells, and Recombinant Methods of Making Antibodies

Nucleic Acids

The present invention also encompasses nucleic acid molecules encoding anti-M-CSF antibodies. In some embodiments, different nucleic acid molecules encode a heavy chain and a light chain of an anti-M-CSF immunoglobulin. In other embodiments, the same nucleic acid molecule encodes a heavy chain and a light chain of an anti-M-CSF immunoglobulin. In one embodiment, the nucleic acid encodes a M-CSF antibody of the invention.

In some embodiments, the nucleic acid molecule encoding the variable domain of the light chain comprises a human V_κ L5, O12, L2, B3, A27 gene and a J_κ1, J_κ2, J_κ3, or J_κ4 gene.

In some embodiments, the nucleic acid molecule encoding the light chain, encodes an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mutations from the germline amino acid sequence. In some embodiments, the nucleic acid molecule comprises a nucleotide sequence that encodes a V_L amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-conservative amino acid substitutions and/or 1, 2, or 3 non-conservative substitutions compared

to germline sequence. Substitutions may be in the CDR regions, the framework regions, or in the constant domain.

In some embodiments, the nucleic acid molecule encodes a V_L amino acid sequence comprising one or more variants compared to germline sequence that are identical to the variations found in the V_L of one of the antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1.

In some embodiments, the nucleic acid molecule encodes at least three amino acid mutations compared to the germline sequence found in the V_L of one of the antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4, 8.10.3, or 9.7.2.

In some embodiments, the nucleic acid molecule comprises a nucleotide sequence that encodes the V_L amino acid sequence of monoclonal antibody 252 (SEQ ID NO: 4), 88 (SEQ ID NO: 8), 100 (SEQ ID NO: 12), 3.8.3 (SEQ ID NO: 16), 2.7.3 (SEQ ID NO: 20), 1.120.1 (SEQ ID NO: 24), 9.14.4I (SEQ ID NO: 28), 8.10.3F (SEQ ID NO: 32), 9.7.2IF (SEQ ID NO: 36), 9.14.4 (SEQ ID NO: 28), 8.10.3 (SEQ ID NO: 44), 9.7.2 (SEQ ID NO: 48), 9.7.2C-Ser (SEQ ID NO: 52), 9.14.4C-Ser (SEQ ID NO: 56), 8.10.3C-Ser (SEQ ID NO: 60), 8.10.3-CG2 (SEQ ID NO: 60), 9.7.2-CG2 (SEQ ID NO: 52), 9.7.2-CG4 (SEQ ID NO: 52), 9.14.4-CG2 (SEQ ID NO: 56), 9.14.4-CG4 (SEQ ID NO: 56), 9.14.4-Ser (SEQ ID NO: 28), 9.7.2-Ser (SEQ ID NO: 48), 8.10.3-Ser (SEQ ID NO: 44), 8.10.3-CG4 (SEQ ID NO: 60) 8.10.3FG1 (SEQ ID NO: 32) or 9.14.4G1 (SEQ ID NO: 28), or a portion thereof. In some embodiments, said portion comprises at least the CDR2 region. In some embodiments, the nucleic acid encodes the amino acid sequence of the light chain CDRs of said antibody. In some embodiments, said portion is a contiguous portion comprising CDR1-CDR3.

In some embodiments, the nucleic acid molecule comprises a nucleotide sequence that encodes the light chain amino acid sequence of one of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60. In some preferred embodiments, the nucleic acid molecule comprises the light chain nucleotide sequence of SEQ ID NOS: 3, 7, 11, 27, 31, 35, 43 or 47, or a portion thereof.

In some embodiments, the nucleic acid molecule encodes a V_L amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98% or 99% identical to a V_L amino acid sequence shown in Figure 1 or to a V_L amino acid sequences of any one of antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser,

9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1, or an amino acid sequence of any one of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60. Nucleic acid molecules of the invention include nucleic acids that hybridize under highly stringent conditions, such as those described above, to a nucleic acid sequence encoding the light chain amino acid sequence of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60, or that has the light chain nucleic acid sequence of SEQ ID NOS: 3, 7, 11, 27, 31, 35, 43 or 47.

In another embodiment, the nucleic acid encodes a full-length light chain of an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1, or a light chain comprising the amino acid sequence of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60 and a constant region of a light chain, or a light chain comprising a mutation. Further, the nucleic acid may comprise the light chain nucleotide sequence of SEQ ID NOS: 3, 7, 11, 27, 31, 35, 43 or 47 and the nucleotide sequence encoding a constant region of a light chain, or a nucleic acid molecule encoding a light chain comprise a mutation.

In another preferred embodiment, the nucleic acid molecule encodes the variable domain of the heavy chain (V_H) that comprises a human V_H 1-18, 3-33, 3-11, 3-23, 3-48, or 3-7 gene sequence or a sequence derived therefrom. In various embodiments, the nucleic acid molecule comprises a human V_H 1-18 gene, a D_H 4-23 gene and a human J_H 4 gene; a human V_H 3-33 gene, a human D_H 1-26 gene and a human J_H 4 gene; a human V_H 3-11 gene, a human D_H 7-27 gene and a human J_H 4 gene; a human V_H 3-11 gene, a human D_H 7-27 gene and a human J_H 6 gene; a human V_H 3-23 gene, a human D_H 1-26 gene and a human J_H 4 gene; a human V_H 3-7 gene, a human D_H 6-13 gene and a human J_H 4 gene; a human V_H 3-11 gene, a human D_H 7-27 gene, and a human J_H 4b gene; a human V_H 3-48 gene, a human D_H 1-26 gene, and a human J_H 4b gene; a human V_H 3-11 gene, a human D_H 6-13 gene, and a human J_H 6b gene, or a sequence derived from the human genes.

In some embodiments, the nucleic acid molecule encodes an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 mutations compared to the germline amino acid sequence of the human V, D or J genes. In some embodiments, said mutations are in the V_H region. In some embodiments, said mutations are in the CDR regions.

In some embodiments, the nucleic acid molecule encodes one or more amino acid mutations compared to the germline sequence that are identical to amino acid mutations found in the V_H of monoclonal antibody 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4,

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9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. In some embodiments, the nucleic acid encodes at least three amino acid mutations compared to the germline sequences that are identical to at least three amino acid mutations found in one of the above-listed monoclonal antibodies.

In some embodiments, the nucleic acid molecule comprises a nucleotide sequence that encodes at least a portion of the V_H amino acid sequence of antibody 252 (SEQ ID NO: 2), 88 (SEQ ID NO: 6), 100 (SEQ ID NO: 10), 3.8.3 (SEQ ID NO: 14), 2.7.3 (SEQ ID NO: 18), 1.120.1 (SEQ ID NO: 22), 9.14.4I (SEQ ID NO: 26), 8.10.3F (SEQ ID NO: 30), 9.7.2IF (SEQ ID NO: 34), 9.14.4 (SEQ ID NO: 38), 8.10.3 (SEQ ID NO: 30), 9.7.2 (SEQ ID NO: 46), 9.7.2C-Ser (SEQ ID NO: 50), 9.14.4C-Ser (SEQ ID NO: 54), 8.10.3C-Ser (SEQ ID NO: 58), 8.10.3-CG2 (SEQ ID NO: 62), 9.7.2-CG2 (SEQ ID NO: 66), 9.7.2-CG4 (SEQ ID NO: 70), 9.14.4-CG2 (SEQ ID NO: 74), 9.14.4-CG4 (SEQ ID NO: 78), 9.14.4-Ser (SEQ ID NO: 82), 9.7.2-Ser (SEQ ID NO: 86), 8.10.3-Ser (SEQ ID NO: 90), 8.10.3-CG4 (SEQ ID NO: 94) 8.10.3FG1 (SEQ ID NO: 98) or 9.14.4G1 (SEQ ID NO: 102), or said sequence having conservative amino acid mutations and/or a total of three or fewer non-conservative amino acid substitutions. In various embodiments the sequence encodes one or more CDR regions, preferably a CDR3 region, all three CDR regions, a contiguous portion including CDR1-CDR3, or the entire V_H region.

In some embodiments, the nucleic acid molecule comprises a heavy chain nucleotide sequence that encodes the amino acid sequence of one of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102. In some preferred embodiments, the nucleic acid molecule comprises at least a portion of the heavy chain nucleotide sequence of SEQ ID NO: 1, 5, 9, 25, 29, 33, 37, 45, 97 or 101. In some embodiments, said portion encodes the V_H region, a CDR3 region, all three CDR regions, or a contiguous region including CDR1-CDR3.

In some embodiments, the nucleic acid molecule encodes a V_H amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98% or 99% identical to the V_H amino acid sequences shown in Figure 4 or to a V_H amino acid sequence of any one of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102. Nucleic acid molecules of the invention include nucleic acids that hybridize under highly stringent conditions, such as those described above, to a nucleotide sequence encoding the heavy chain amino acid sequence of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102 or that has the nucleotide sequence of SEQ ID NOS: 1, 5, 9, 25, 29, 33, 37, 45, 97 or 101.

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In another embodiment, the nucleic acid encodes a full-length heavy chain of an antibody selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1, or a heavy chain having the amino acid sequence of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102 and a constant region of a heavy chain, or a heavy chain comprising a mutation. Further, the nucleic acid may comprise the heavy chain nucleotide sequence of SEQ ID NOS: 1, 5, 9, 25, 29, 33, 37, 45, 97 or 101 and a nucleotide sequence encoding a constant region of a light chain, or a nucleic acid molecule encoding a heavy chain comprising a mutation.

A nucleic acid molecule encoding the heavy or entire light chain of an anti-M-CSF antibody or portions thereof can be isolated from any source that produces such antibody. In various embodiments, the nucleic acid molecules are isolated from a B cell isolated from an animal immunized with M-CSF or from an immortalized cell derived from such a B cell that expresses an anti-M-CSF antibody. Methods of isolating mRNA encoding an antibody are well-known in the art. See, e.g., Sambrook *et al.* The mRNA may be used to produce cDNA for use in the polymerase chain reaction (PCR) or cDNA cloning of antibody genes. In a preferred embodiment, the nucleic acid molecule is isolated from a hybridoma that has as one of its fusion partners a human immunoglobulin-producing cell from a non-human transgenic animal. In an even more preferred embodiment, the human immunoglobulin producing cell is isolated from a XENOMOUSE™ animal. In another embodiment, the human immunoglobulin-producing cell is from a non-human, non-mouse transgenic animal, as described above. In another embodiment, the nucleic acid is isolated from a non-human, non-transgenic animal. The nucleic acid molecules isolated from a non-human, non-transgenic animal may be used, e.g., for humanized antibodies.

In some embodiments, a nucleic acid encoding a heavy chain of an anti-M-CSF antibody of the invention can comprise a nucleotide sequence encoding a V_H domain of the invention joined in-frame to a nucleotide sequence encoding a heavy chain constant domain from any source. Similarly, a nucleic acid molecule encoding a light chain of an anti-M-CSF antibody of the invention can comprise a nucleotide sequence encoding a V_L domain of the invention joined in-frame to a nucleotide sequence encoding a light chain constant domain from any source.

In a further aspect of the invention, nucleic acid molecules encoding the variable domain of the heavy (V_H) and light (V_L) chains are "converted" to full-length antibody genes.

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In one embodiment, nucleic acid molecules encoding the V_H or V_L domains are converted to full-length antibody genes by insertion into an expression vector already encoding heavy chain constant (C_H) or light chain (C_L) constant domains, respectively, such that the V_H segment is operatively linked to the C_H segment(s) within the vector, and the V_L segment is operatively linked to the C_L segment within the vector. In another embodiment, nucleic acid molecules encoding the V_H and/or V_L domains are converted into full-length antibody genes by linking, e.g., ligating, a nucleic acid molecule encoding a V_H and/or V_L domains to a nucleic acid molecule encoding a C_H and/or C_L domain using standard molecular biological techniques. Nucleic acid sequences of human heavy and light chain immunoglobulin constant domain genes are known in the art. See, e.g., Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th Ed., NIH Publ. No. 91-3242, 1991. Nucleic acid molecules encoding the full-length heavy and/or light chains may then be expressed from a cell into which they have been introduced and the anti-M-CSF antibody isolated.

The nucleic acid molecules may be used to recombinantly express large quantities of anti-M-CSF antibodies. The nucleic acid molecules also may be used to produce chimeric antibodies, bispecific antibodies, single chain antibodies, immunoadhesins, diabodies, mutated antibodies and antibody derivatives, as described further below. If the nucleic acid molecules are derived from a non-human, non-transgenic animal, the nucleic acid molecules may be used for antibody humanization, also as described below.

In another embodiment, a nucleic acid molecule of the invention is used as a probe or PCR primer for a specific antibody sequence. For instance, the nucleic acid can be used as a probe in diagnostic methods or as a PCR primer to amplify regions of DNA that could be used, inter alia, to isolate additional nucleic acid molecules encoding variable domains of anti-M-CSF antibodies. In some embodiments, the nucleic acid molecules are oligonucleotides. In some embodiments, the oligonucleotides are from highly variable regions of the heavy and light chains of the antibody of interest. In some embodiments, the oligonucleotides encode all or a part of one or more of the CDRs of antibody 252, 88, 100, 3.8.3, 2.7.3, or 1.120.1, or variants thereof described herein.

Vectors

The invention provides vectors comprising nucleic acid molecules that encode the heavy chain of an anti-M-CSF antibody of the invention or an antigen-binding portion thereof. The invention also provides vectors comprising nucleic acid molecules that encode the light chain of such antibodies or antigen-binding portion thereof. The invention further provides vectors

comprising nucleic acid molecules encoding fusion proteins, modified antibodies, antibody fragments, and probes thereof.

In some embodiments, the anti-M-CSF antibodies, or antigen-binding portions of the invention are expressed by inserting DNAs encoding partial or full-length light and heavy chains, obtained as described above, into expression vectors such that the genes are operatively linked to necessary expression control sequences such as transcriptional and transnational control sequences. Expression vectors include plasmids, retroviruses, adenoviruses, adeno-associated viruses (AAV), plant viruses such as cauliflower mosaic virus, tobacco mosaic virus, cosmids, YACs, EBV derived episomes, and the like. The antibody gene is ligated into a vector such that transcriptional and transnational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vectors. In a preferred embodiment, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (e.g., ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present).

A convenient vector is one that encodes a functionally complete human C_H or C_L immunoglobulin sequence, with appropriate restriction sites engineered so that any V_H or V_L sequence can easily be inserted and expressed, as described above. In such vectors, splicing usually occurs between the splice donor site in the inserted J region and the splice acceptor site preceding the human C domain, and also at the splice regions that occur within the human C_H exons. Polyadenylation and transcription termination occur at native chromosomal sites downstream of the coding regions. The recombinant expression vector also can encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene may be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the immunoglobulin chain. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (i.e., a signal peptide from a non-immunoglobulin protein).

In addition to the antibody chain genes, the recombinant expression vectors of the invention carry regulatory sequences that control the expression of the antibody chain genes in a host cell. It will be appreciated by those skilled in the art that the design of the expression vector, including the selection of regulatory sequences may depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc.

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Preferred regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from retroviral LTRs, cytomegalovirus (CMV) (such as the CMV promoter/enhancer), Simian Virus 40 (SV40) (such as the SV40 promoter/enhancer), adenovirus, (e.g., the
5 adenovirus major late promoter (AdMLP)), polyoma and strong mammalian promoters such as native immunoglobulin and actin promoters. For further description of viral regulatory elements, and sequences thereof, see e.g., U.S. Patent No. 5,168,062, U.S. Patent No. 4,510,245 and U.S. Patent No. 4,968,615. Methods for expressing antibodies in plants, including a description of promoters and vectors, as well as transformation of plants is known in the art.
10 See, e.g., United States Patents 6,517,529, herein incorporated by reference. Methods of expressing polypeptides in bacterial cells or fungal cells, e.g., yeast cells, are also well known in the art.

In addition to the antibody chain genes and regulatory sequences, the recombinant expression vectors of the invention may carry additional sequences, such as sequences that
15 regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see e.g., U.S. Patent Nos. 4,399,216, 4,634,665 and 5,179,017). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin or methotrexate, on a host cell into which the vector has been introduced. Preferred selectable
20 marker genes include the dihydrofolate reductase (DHFR) gene (for use in dhfr-host cells with methotrexate selection/amplification), the neomycin resistance gene (for G418 selection), and the glutamate synthetase gene.

Non-Hybridoma Host Cells and Methods of Recombinantly Producing Protein

Nucleic acid molecules encoding anti-M-CSF antibodies and vectors comprising these
25 nucleic acid molecules can be used for transfection of a suitable mammalian, plant, bacterial or yeast host cell. Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation
30 of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors. Methods of transforming cells are well known in the art. See, e.g., U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455 (which patents are hereby incorporated herein by

reference). Methods of transforming plant cells are well known in the art, including, e.g., Agrobacterium-mediated transformation, biolistic transformation, direct injection, electroporation and viral transformation. Methods of transforming bacterial and yeast cells are also well known in the art.

5 Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC). These include, *inter alia*, Chinese hamster ovary (CHO) cells, NSO, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), A549 cells, and a number of other cell lines. Cell lines of
10 particular preference are selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells. When recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the
15 antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods. Plant host cells include, e.g., Nicotiana, Arabidopsis, duckweed, corn, wheat, potato, etc. Bacterial host cells include *E. coli* and *Streptomyces* species. Yeast host cells include *Schizosaccharomyces pombe*, *Saccharomyces cerevisiae* and *Pichia pastoris*.

20 Further, expression of antibodies of the invention (or other moieties therefrom) from production cell lines can be enhanced using a number of known techniques. For example, the glutamine synthetase gene expression system (the GS system) is a common approach for enhancing expression under certain conditions. The GS system is discussed in whole or part in connection with European Patent Nos. 0 216 846, 0 256 055, and 0 323 997 and European
25 Patent Application No. 89303964.4.

It is possible that antibodies expressed by different cell lines or in transgenic animals will have different glycosylation from each other. However, all antibodies encoded by the nucleic acid molecules provided herein, or comprising the amino acid sequences provided herein are part of the instant invention, regardless of the glycosylation state or pattern or
30 modification of the antibodies.

Transgenic Animals and Plants

Anti-M-CSF antibodies of the invention also can be produced transgenically through the generation of a mammal or plant that is transgenic for the immunoglobulin heavy and light

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chain sequences of interest and production of the antibody in a recoverable form therefrom. In connection with the transgenic production in mammals, anti-M-CSF antibodies can be produced in, and recovered from, the milk of goats, cows, or other mammals. See, e.g., U.S. Patent Nos. 5,827,690, 5,756,687, 5,750,172, and 5,741,957. In some embodiments, non-human transgenic animals that comprise human immunoglobulin loci are immunized with M-CSF or an immunogenic portion thereof, as described above. Methods for making antibodies in plants, yeast or fungi/algae are described, e.g., in US patents 6,046,037 and US 5,959,177.

In some embodiments, non-human transgenic animals or plants are produced by introducing one or more nucleic acid molecules encoding an anti-M-CSF antibody of the invention into the animal or plant by standard transgenic techniques. See Hogan and United States Patent 6,417,429, *supra*. The transgenic cells used for making the transgenic animal can be embryonic stem cells or somatic cells. The transgenic non-human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes. See, e.g., Hogan *et al.*, *Manipulating the Mouse Embryo: A Laboratory Manual* 2ed., Cold Spring Harbor Press (1999); Jackson *et al.*, *Mouse Genetics and Transgenics: A Practical Approach*, Oxford University Press (2000); and Pinkert, *Transgenic Animal Technology: A Laboratory Handbook*, Academic Press (1999). In some embodiments, the transgenic non-human animals have a targeted disruption and replacement by a targeting construct that encodes a heavy chain and/or a light chain of interest. In a preferred embodiment, the transgenic animals comprise and express nucleic acid molecules encoding heavy and light chains that specifically bind to M-CSF, preferably human M-CSF. In some embodiments, the transgenic animals comprise nucleic acid molecules encoding a modified antibody such as a single-chain antibody, a chimeric antibody or a humanized antibody. The anti-M-CSF antibodies may be made in any transgenic animal. In a preferred embodiment, the non-human animals are mice, rats, sheep, pigs, goats, cattle or horses. The non-human transgenic animal expresses said encoded polypeptides in blood, milk, urine, saliva, tears, mucus and other bodily fluids.

Phage Display Libraries

The invention provides a method for producing an anti-M-CSF antibody or antigen-binding portion thereof comprising the steps of synthesizing a library of human antibodies on phage, screening the library with M-CSF or a portion thereof, isolating phage that bind M-CSF, and obtaining the antibody from the phage. By way of example, one method for preparing the library of antibodies for use in phage display techniques comprises the steps of immunizing a non-human animal comprising human immunoglobulin loci with M-CSF or an antigenic

portion thereof to create an immune response, extracting antibody producing cells from the immunized animal; isolating RNA from the extracted cells, reverse transcribing the RNA to produce cDNA, amplifying the cDNA using a primer, and inserting the cDNA into a phage display vector such that antibodies are expressed on the phage. Recombinant anti-M-CSF antibodies of the invention may be obtained in this way.

Recombinant anti-M-CSF human antibodies of the invention can be isolated by screening a recombinant combinatorial antibody library. Preferably the library is a scFv phage display library, generated using human V_L and V_H cDNAs prepared from mRNA isolated from B cells. Methodologies for preparing and screening such libraries are known in the art. There are commercially available kits for generating phage display libraries (e.g., the Pharmacia Recombinant Phage Antibody System, catalog no. 27-9400-01; and the Stratagene SurfZAP™ phage display kit, catalog no. 240612). There also are other methods and reagents that can be used in generating and screening antibody display libraries (see, e.g., U.S. Patent No. 5,223,409; PCT Publication Nos. WO 92/18619, WO 91/17271, WO 92/20791, WO 92/15679, WO 93/01288, WO 92/01047, WO 92/09690; Fuchs *et al.*, *Bio/Technology* 9:1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas* 3:81-85 (1992); Huse *et al.*, *Science* 246:1275-1281 (1989); McCafferty *et al.*, *Nature* 348:552-554 (1990); Griffiths *et al.*, *EMBO J.* 12:725-734 (1993); Hawkins *et al.*, *J. Mol. Biol.* 226:889-896 (1992); Clackson *et al.*, *Nature* 352:624-628 (1991); Gram *et al.*, *Proc. Natl. Acad. Sci. USA* 89:3576-3580 (1992); Garrad *et al.*, *Bio/Technology* 9:1373-1377 (1991); Hoogenboom *et al.*, *Nuc. Acid Res.* 19:4133-4137 (1991); and Barbas *et al.*, *Proc. Natl. Acad. Sci. USA* 88:7978-7982 (1991).

In one embodiment, to isolate a human anti-M-CSF antibodies with the desired characteristics, a human anti-M-CSF antibody as described herein is first used to select human heavy and light chain sequences having similar binding activity toward M-CSF, using the epitope imprinting methods described in PCT Publication No. WO 93/06213. The antibody libraries used in this method are preferably scFv libraries prepared and screened as described in PCT Publication No. WO 92/01047, McCafferty *et al.*, *Nature* 348:552-554 (1990); and Griffiths *et al.*, *EMBO J.* 12:725-734 (1993). The scFv antibody libraries preferably are screened using human M-CSF as the antigen.

Once initial human V_L and V_H domains are selected, "mix and match" experiments are performed, in which different pairs of the initially selected V_L and V_H segments are screened for M-CSF binding to select preferred V_L/V_H pair combinations. Additionally, to further improve the quality of the antibody, the V_L and V_H segments of the preferred V_L/V_H pair(s) can be randomly mutated, preferably within the CDR3 region of V_H and/or V_L, in a process

analogous to the *in vivo* somatic mutation process responsible for affinity maturation of antibodies during a natural immune response. This *in vitro* affinity maturation can be accomplished by amplifying V_H and V_L domains using PCR primers complimentary to the V_H CDR3 or V_L CDR3, respectively, which primers have been "spiked" with a random mixture of the four nucleotide bases at certain positions such that the resultant PCR products encode V_H and V_L segments into which random mutations have been introduced into the V_H and/or V_L CDR3 regions. These randomly mutated V_H and V_L segments can be re-screened for binding to M-CSF.

Following screening and isolation of an anti-M-CSF antibody of the invention from a recombinant immunoglobulin display library, nucleic acids encoding the selected antibody can be recovered from the display package (e.g., from the phage genome) and subcloned into other expression vectors by standard recombinant DNA techniques. If desired, the nucleic acid can further be manipulated to create other antibody forms of the invention, as described below. To express a recombinant human antibody isolated by screening of a combinatorial library, the DNA encoding the antibody is cloned into a recombinant expression vector and introduced into a mammalian host cells, as described above.

Class switching

Another aspect of the invention provides a method for converting the class or subclass of an anti-M-CSF antibody to another class or subclass. In some embodiments, a nucleic acid molecule encoding a V_L or V_H that does not include any nucleic acid sequences encoding C_L or C_H is isolated using methods well-known in the art. The nucleic acid molecule then is operatively linked to a nucleic acid sequence encoding a C_L or C_H from a desired immunoglobulin class or subclass. This can be achieved using a vector or nucleic acid molecule that comprises a C_L or C_H chain, as described above. For example, an anti-M-CSF antibody that was originally IgM can be class switched to an IgG. Further, the class switching may be used to convert one IgG subclass to another, e.g., from IgG1 to IgG2. Another method for producing an antibody of the invention comprising a desired isotype comprises the steps of isolating a nucleic acid encoding a heavy chain of an anti-M-CSF antibody and a nucleic acid encoding a light chain of an anti-M-CSF antibody, isolating the sequence encoding the V_H region, ligating the V_H sequence to a sequence encoding a heavy chain constant domain of the desired isotype, expressing the light chain gene and the heavy chain construct in a cell, and collecting the anti-M-CSF antibody with the desired isotype.

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In some embodiments, anti-M-CSF antibodies of the invention have the serine at position 228 (according to the EU-numbering convention) of the heavy chain changed to a proline. Accordingly, the CPSC sub-sequence in the F_C region of IgG4 becomes CPPC, which is the sub-sequence in IgG1. (Aalberse, R.C. and Schuurman, J., *Immunology*, 105:9-19 (2002)). For example, the serine at residue 243 SEQ ID NO: 46 (which corresponds to residue 228 in the EU-numbering convention) would become proline. Similarly, the serine at residue 242 of SEQ ID NO: 38 (which corresponds to residue 228 in the EU-numbering convention) would become proline. In some embodiments, the framework region of the IgG4 antibody can be back-mutated to the germline framework sequence. Some embodiments comprise both the back-mutates framework region and the serine to proline change in the F_C region. See, e.g., SEQ ID NO: 54 (antibody 9.14.4C-Ser) and SEQ ID NO: 58 (antibody 8.10.3C-Ser) in Table 1.

Deimmunized Antibodies

Another way of producing antibodies with reduced immunogenicity is the deimmunization of antibodies. In another aspect of the invention, the antibody may be deimmunized using the techniques described in, e.g., PCT Publication Nos. WO98/52976 and WO00/34317 (which incorporated herein by reference in their entirety).

Mutated Antibodies

In another embodiment, the nucleic acid molecules, vectors and host cells may be used to make mutated anti-M-CSF antibodies. The antibodies may be mutated in the variable domains of the heavy and/or light chains, e.g., to alter a binding property of the antibody. For example, a mutation may be made in one or more of the CDR regions to increase or decrease the K_D of the antibody for M-CSF, to increase or decrease k_{off}, or to alter the binding specificity of the antibody. Techniques in site-directed mutagenesis are well-known in the art. See, e.g., Sambrook *et al.* and Ausubel *et al.*, *supra*. In a preferred embodiment, mutations are made at an amino acid residue that is known to be changed compared to germline in a variable domain of an anti-M-CSF antibody. In another embodiment, one or more mutations are made at an amino acid residue that is known to be changed compared to the germline in a CDR region or framework region of a variable domain, or in a constant domain of a monoclonal antibody 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1. In another embodiment, one or more mutations are made at an amino acid residue that is known to be changed compared

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to the germline in a CDR region or framework region of a variable domain of a heavy chain amino acid sequence selected from SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98 or 102, or whose heavy chain nucleotide sequence is presented in SEQ ID NOS: 1, 5, 9, 25, 29, 33, 37, 45, 97 or 101. In another embodiment, one
5 or more mutations are made at an amino acid residue that is known to be changed compared to the germline in a CDR region or framework region of a variable domain of a light chain amino acid sequence selected from SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 48, 52, 56 or 60, or whose light chain nucleotide sequence is presented in SEQ ID NOS: 3, 7, 11, 27, 31, 35, 43 or 47.

10 In one embodiment, the framework region is mutated so that the resulting framework region(s) have the amino acid sequence of the corresponding germline gene. A mutation may be made in a framework region or constant domain to increase the half-life of the anti-M-CSF antibody. See, e.g., PCT Publication No. WO 00/09560, herein incorporated by reference. A mutation in a framework region or constant domain also can be made to alter the immuno-
15 genicity of the antibody, to provide a site for covalent or non-covalent binding to another molecule, or to alter such properties as complement fixation, FcR binding and antibody-dependent cell-mediated cytotoxicity (ADCC). According to the invention, a single antibody may have mutations in any one or more of the CDRs or framework regions of the variable domain or in the constant domain.

20 In some embodiments, there are from 1 to 8 including any number in between, amino acid mutations in either the V_H or V_L domains of the mutated anti-M-CSF antibody compared to the anti-M-CSF antibody prior to mutation. In any of the above, the mutations may occur in one or more CDR regions. Further, any of the mutations can be conservative amino acid substitutions. In some embodiments, there are no more than 5, 4, 3, 2, or 1 amino acid changes
25 in the constant domains.

Modified Antibodies

In another embodiment, a fusion antibody or immunoadhesin may be made that comprises all or a portion of an anti-M-CSF antibody of the invention linked to another polypeptide. In a preferred embodiment, only the variable domains of the anti-M-CSF antibody
30 are linked to the polypeptide. In another preferred embodiment, the V_H domain of an anti-M-CSF antibody is linked to a first polypeptide, while the V_L domain of an anti-M-CSF antibody is linked to a second polypeptide that associates with the first polypeptide in a manner such that the V_H and V_L domains can interact with one another to form an antibody binding site. In

another preferred embodiment, the V_H domain is separated from the V_L domain by a linker such that the V_H and V_L domains can interact with one another (see below under Single Chain Antibodies). The V_H-linker-V_L antibody is then linked to the polypeptide of interest. The fusion antibody is useful for directing a polypeptide to a M-CSF-expressing cell or tissue. The polypeptide may be a therapeutic agent, such as a toxin, growth factor or other regulatory protein, or may be a diagnostic agent, such as an enzyme that may be easily visualized, such as horseradish peroxidase. In addition, fusion antibodies can be created in which two (or more) single-chain antibodies are linked to one another. This is useful if one wants to create a divalent or polyvalent antibody on a single polypeptide chain, or if one wants to create a bispecific antibody.

To create a single chain antibody, (scFv) the V_H- and V_L-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, e.g., encoding the amino acid sequence (Gly₄-Ser)₃, such that the V_H and V_L sequences can be expressed as a contiguous single-chain protein, with the V_L and V_H domains joined by the flexible linker. See, e.g., Bird *et al.*, *Science* 242:423-426 (1988); Huston *et al.*, *Proc. Natl. Acad. Sci. USA* 85:5879-5883 (1988); McCafferty *et al.*, *Nature* 348:552-554 (1990). The single chain antibody may be monovalent, if only a single V_H and V_L are used, bivalent, if two V_H and V_L are used, or polyvalent, if more than two V_H and V_L are used. Bispecific or polyvalent antibodies may be generated that bind specifically to M-CSF and to another molecule.

In other embodiments, other modified antibodies may be prepared using anti-M-CSF antibody-encoding nucleic acid molecules. For instance, "Kappa bodies" (Ill *et al.*, *Protein Eng.* 10: 949-57 (1997)), "Minibodies" (Martin *et al.*, *EMBO J.* 13: 5303-9 (1994)), "Diabodies" (Holliger *et al.*, *Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993)), or "Janusins" (Traunecker *et al.*, *EMBO J.* 10:3655-3659 (1991) and Traunecker *et al.*, *Int. J. Cancer* (Suppl.) 7:51-52 (1992)) may be prepared using standard molecular biological techniques following the teachings of the specification.

Bispecific antibodies or antigen-binding fragments can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79: 315-321 (1990), Kostelny *et al.*, *J. Immunol.* 148:1547-1553 (1992). In addition, bispecific antibodies may be formed as "diabodies" or "Janusins." In some embodiments, the bispecific antibody binds to two different epitopes of M-CSF. In some embodiments, the bispecific antibody has a first heavy chain and a first light chain from monoclonal antibody 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, or 9.7.2 and an additional antibody heavy chain and light chain. In some embodiments,

the additional light chain and heavy chain also are from one of the above-identified monoclonal antibodies, but are different from the first heavy and light chains.

In some embodiments, the modified antibodies described above are prepared using one or more of the variable domains or CDR regions from a human anti-M-CSF monoclonal antibody provided herein, from an amino acid sequence of said monoclonal antibody, or from a heavy chain or light chain encoded by a nucleic acid sequence encoding said monoclonal antibody.

Derivatized and Labeled Antibodies

An anti-M-CSF antibody or antigen-binding portion of the invention can be derivatized or linked to another molecule (e.g., another peptide or protein). In general, the antibodies or portion thereof is derivatized such that the M-CSF binding is not affected adversely by the derivatization or labeling. Accordingly, the antibodies and antibody portions of the invention are intended to include both intact and modified forms of the human anti-M-CSF antibodies described herein. For example, an antibody or antibody portion of the invention can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (e.g., a bispecific antibody or a diabody), a detection agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

One type of derivatized antibody is produced by crosslinking two or more antibodies (of the same type or of different types, e.g., to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (e.g., m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (e.g., disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

Another type of derivatized antibody is a labeled antibody. Useful detection agents with which an antibody or antigen-binding portion of the invention may be derivatized include fluorescent compounds, including fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-naphthalenesulfonyl chloride, phycoerythrin, lanthanide phosphors and the like. An antibody can also be labeled with enzymes that are useful for detection, such as horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase, glucose oxidase and the like. When an antibody is labeled with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a reaction product that can be discerned.

For example, when the agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody can also be labeled with biotin, and detected through indirect measurement of avidin or streptavidin binding. An antibody can also be labeled with a predetermined polypeptide epitope recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

An anti-M-CSF antibody can also be labeled with a radiolabeled amino acid. The radiolabeled anti-M-CSF antibody can be used for both diagnostic and therapeutic purposes. For instance, the radiolabeled anti-M-CSF antibody can be used to detect M-CSF-expressing tumors by x-ray or other diagnostic techniques. Further, the radiolabeled anti-M-CSF antibody can be used therapeutically as a toxin for cancerous cells or tumors. Examples of labels for polypeptides include, but are not limited to, the following radioisotopes or radionuclides – ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , and ^{131}I .

An anti-M-CSF antibody can also be derivatized with a chemical group such as polyethylene glycol (PEG), a methyl or ethyl group, or a carbohydrate group. These groups are useful to improve the biological characteristics of the antibody, e.g., to increase serum half-life or to increase tissue binding.

Pharmaceutical Compositions and Kits

The invention also relates to compositions comprising a human anti-M-CSF antagonist antibody for the treatment of subjects in need of treatment for rheumatoid arthritis, osteoporosis, or atherosclerosis. In some embodiments, the subject of treatment is a human. In other embodiments, the subject is a veterinary subject. Hyperproliferative disorders where monocytes play a role that may be treated by an antagonist anti-M-CSF antibody of the invention can involve any tissue or organ and include but are not limited to brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, liver, renal, ovarian, prostate, colorectal, esophageal, gynecological, nasopharynx, or thyroid cancers, melanomas, lymphomas, leukemias or multiple myelomas. In particular, human antagonist anti-M-CSF antibodies of the invention are useful to treat or prevent carcinomas of the breast, prostate, colon and lung.

This invention also encompasses compositions for the treatment of a condition selected from the group consisting of arthritis, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis,

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ankylosing spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis shock in a mammal, including a human, comprising an amount of a human anti-M-CSF monoclonal antibody of the invention effective in such treatment and a pharmaceutically acceptable carrier.

Treatment may involve administration of one or more antagonist anti-M-CSF monoclonal antibodies of the invention, or antigen-binding fragments thereof, alone or with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Some examples of pharmaceutically acceptable carriers are water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Additional examples of pharmaceutically acceptable substances are wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody.

Anti-M-CSF antibodies of the invention and compositions comprising them, can be administered in combination with one or more other therapeutic, diagnostic or prophylactic agents. Additional therapeutic agents include other anti-neoplastic, anti-tumor, anti-angiogenic or chemotherapeutic agents. Such additional agents may be included in the same composition or administered separately. In some embodiments, one or more inhibitory anti-M-CSF antibodies of the invention can be used as a vaccine or as adjuvants to a vaccine.

The compositions of this invention may be in a variety of forms, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans. The preferred mode of

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administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection. In another embodiment, the invention includes a method of treating a subject in need thereof with an antibody or an antigen-binding portion thereof that specifically binds to M-CSF comprising the steps of : (a) administering an effective amount of an isolated nucleic acid molecule encoding the heavy chain or the antigen-binding portion thereof, an isolated nucleic acid molecule encoding the light chain or the antigen-binding portion thereof, or both the nucleic acid molecules encoding the light chain and the heavy chain or antigen-binding portions thereof; and (b) expressing the nucleic acid molecule.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the anti-M-CSF antibody in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

The antibodies of the present invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is subcutaneous, intramuscular, or intravenous infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results.

In certain embodiments, the antibody compositions active compound may be prepared with a carrier that will protect the antibody against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate,

polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., *Sustained and Controlled Release Drug Delivery Systems* (J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978).

5 In certain embodiments, an anti-M-CSF antibody of the invention can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) can also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the anti-M-CSF antibodies can be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

15 Additional active compounds also can be incorporated into the compositions. In certain embodiments, an anti-M-CSF antibody of the invention is co-formulated with and/or co-administered with one or more additional therapeutic agents. These agents include antibodies that bind other targets, antineoplastic agents, antitumor agents, chemotherapeutic agents, peptide analogues that inhibit M-CSF, soluble *c-fms* that can bind M-CSF, one or more chemical agents that inhibit M-CSF, anti-inflammatory agents, anti-coagulants, agents that lower blood pressure (i.e., angiotensin-converting enzyme (ACE) inhibitors). Such combination therapies may require lower dosages of the anti-M-CSF antibody as well as the co-administered agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

25 Inhibitory anti-M-CSF antibodies of the invention and compositions comprising them also may be administered in combination with other therapeutic regimens, in particular in combination with radiation treatment for cancer. The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, farnesyl transferase inhibitors, VEGF inhibitors, and anti-metabolites such as methotrexate.

30 The compounds of the invention may also be used in combination with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antisepsis compounds such as Valant.

The compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antigen-binding portion of the invention.

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5 A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody or antibody portion may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a
10 desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

15 Dosage regimens can be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response). For example, a single bolus can be administered, several divided doses can be administered over time or the dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect
20 in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the anti-M-CSF antibody or portion and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an antibody for the treatment of sensitivity in individuals.

25 An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is 0.025 to 50 mg/kg, more preferably 0.1 to 50 mg/kg, more preferably 0.1-25, 0.1 to 10 or 0.1 to 3 mg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be
30 adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

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Another aspect of the present invention provides kits comprising an anti-M-CSF antibody or antigen-binding portion of the invention or a composition comprising such an antibody or portion. A kit may include, in addition to the antibody or composition, diagnostic or therapeutic agents. A kit also can include instructions for use in a diagnostic or therapeutic method. In a preferred embodiment, the kit includes the antibody or a composition comprising it and a diagnostic agent that can be used in a method described below. In another preferred embodiment, the kit includes the antibody or a composition comprising it and one or more therapeutic agents that can be used in a method described below. One embodiment of the invention is a kit comprising a container, instructions on the administration of an anti-M-CSF antibody to a human suffering from an inflammatory disease, or instructions for measuring the number of CD14+CD16+ monocytes in a biological sample and an anti-M-CSF antibody.

This invention also relates to compositions for inhibiting abnormal cell growth in a mammal comprising an amount of an antibody of the invention in combination with an amount of a chemotherapeutic agent, wherein the amounts of the compound, salt, solvate, or prodrug, and of the chemotherapeutic agent are together effective in inhibiting abnormal cell growth. Many chemotherapeutic agents are known in the art. In some embodiments, the chemotherapeutic agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, e.g. anti-androgens, and anti-angiogenesis agents.

Anti-angiogenic agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with an anti-M-CSF antibody of the invention. Examples of useful COX-II inhibitors include CELEBREXTM (celecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European

Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), U.S. Provisional Application No. 60/148,464 (filed August 12, 1999), U.S. Patent 5,863,949 (issued January 26, 1999), U.S. Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP inhibitors are those that do not demonstrate arthralgia. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e. MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list: 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid; 4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; (R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid; 3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and (R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide; and pharmaceutically acceptable salts and solvates of said compounds.

A compound comprising a human anti-M-CSF monoclonal antibody of the invention can also be used with signal transduction inhibitors, such as agents that can inhibit EGF-R (epidermal growth factor receptor) responses, such as EGF-R antibodies, EGF antibodies, and molecules that are EGF-R inhibitors; VEGF (vascular endothelial growth factor) inhibitors, such as VEGF receptors and molecules that can inhibit VEGF; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTINTM (Genentech, Inc.). EGF-R inhibitors are described in, for example in WO

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95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein. EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated), ABX-EGF (Abgenix/Cell Genesys), EMD-7200 (Merck KgaA), EMD-5590 (Merck KgaA), MDX-447/H-477 (Medarex Inc. and Merck KgaA), and the compounds ZD-1834, ZD-1838 and ZD-1839 (AstraZeneca), PKI-166 (Novartis), PKI-166/CGP-75166 (Novartis), PTK 787 (Novartis), CP 701 (Cephalon), leflunomide (Pharmacia/Sugen), CI-1033 (Warner Lambert Parke Davis), CI-1033/PD 183,805 (Warner Lambert Parke Davis), CL-387,785 (Wyeth-Ayerst), BBR-1611 (Boehringer Mannheim GmbH/Roche), Naamidine A (Bristol Myers Squibb), RC-3940-II (Pharmacia), BIBX-1382 (Boehringer Ingelheim), OLX-103 (Merck & Co.), VRCTC-310 (Ventech Research), EGF fusion toxin (Seragen Inc.), DAB-389 (Seragen/Lilgand), ZM-252808 (Imperial Cancer Research Fund), RG-50864 (INSERM), LFM-A12 (Parker Hughes Cancer Center), WHI-P97 (Parker Hughes Cancer Center), GW-282974 (Glaxo), KT-8391 (Kyowa Hakko) and EGF-R Vaccine (York Medical/Centro de Immunologia Molecular (CIM)). These and other EGF-R-inhibiting agents can be used in the present invention.

VEGF inhibitors, for example SU-5416 and SU-6668 (Sugen Inc.), AVASTIN™ (Genentech), SH-268 (Schering), and NX-1838 (NeXstar) can also be combined with the compound of the present invention. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc.); anti-VEGF monoclonal antibody of Genentech, Inc.; and angiozyme, a synthetic ribozyme from Ribozyme and Chiron. These and other VEGF inhibitors can be used in the present invention as described herein. ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209

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(Aronex Pharmaceuticals Inc.) and 2B-1 (Chiron), can furthermore be combined with the compound of the invention, for example those indicated in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in United States Patent 6,465,449 (issued October 15, 2002), and in United States Patent 6,284,764 (issued September 4, 2001), both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with the compound of the present invention in accordance with the present invention.

Anti-survival agents include anti-IGF-IR antibodies and anti-integrin agents, such as anti-integrin antibodies.

Anti-inflammatory agents can be used in conjunction with an anti-M-CSF antibody of the invention. For the treatment of rheumatoid arthritis, the human anti-M-CSF antibodies of the invention may be combined with agents such as TNF- α inhibitors such as TNF drugs (such as REMICADETM, CDP-870 and HUMIRATM) and TNF receptor immunoglobulin molecules (such as ENBRELTM), IL-1 inhibitors, receptor antagonists or soluble IL-1ra (e.g. Kineret or ICE inhibitors), COX-2 inhibitors (such as celecoxib, rofecoxib, valdecoxib and etoricoxib), metalloprotease inhibitors (preferably MMP-13 selective inhibitors), p2X7 inhibitors, α 2 δ ligands (such as NEUROTINTM AND PREGABALINTM), low dose methotrexate, leflunomide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold. The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

Anti-coagulant agents can be used in conjunction with an anti-M-CSF antibody of the invention. Examples of anti-coagulant agents include, but are not limited to, warfarin (COUMADINTM), heparin, and enoxaparin (LOVENOXTM).

The human anti-M-CSF antibodies of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors. The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, REQUIPTM, MIRAPEXTM, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, V28 LIGANDS (such as NEUROTINTM and PREGABALINTM) inhibitors, COX-2 inhibitors, propentofylline or metryfonate.

The human anti-M-CSF antibodies of the present invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

Diagnostic Methods of Use

In another aspect, the invention provides diagnostic methods. The anti-M-CSF antibodies can be used to detect M-CSF in a biological sample *in vitro* or *in vivo*. In one embodiment, the invention provides a method for diagnosing the presence or location of a M-CSF-expressing tumor in a subject in need thereof, comprising the steps of injecting the antibody into the subject, determining the expression of M-CSF in the subject by localizing where the antibody has bound, comparing the expression in the subject with that of a normal reference subject or standard, and diagnosing the presence or location of the tumor.

The anti-M-CSF antibodies can be used in a conventional immunoassay, including, without limitation, an ELISA, an RIA, FACS, tissue immunohistochemistry, Western blot or immunoprecipitation. The anti-M-CSF antibodies of the invention can be used to detect M-CSF from humans. In another embodiment, the anti-M-CSF antibodies can be used to detect M-CSF from primates such as cynomologus monkey, rhesus monkeys, chimpanzees or apes. The invention provides a method for detecting M-CSF in a biological sample comprising contacting a biological sample with an anti-M-CSF antibody of the invention and detecting the bound antibody. In one embodiment, the anti-M-CSF antibody is directly labeled with a

detectable label. In another embodiment, the anti-M-CSF antibody (the first antibody) is unlabeled and a second antibody or other molecule that can bind the anti-M-CSF antibody is labeled. As is well known to one of skill in the art, a second antibody is chosen that is able to specifically bind the particular species and class of the first antibody. For example, if the anti-M-CSF antibody is a human IgG, then the secondary antibody could be an anti-human-IgG. Other molecules that can bind to antibodies include, without limitation, Protein A and Protein G, both of which are available commercially, e.g., from Pierce Chemical Co.

Suitable labels for the antibody or secondary antibody have been disclosed *supra*, and include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

In other embodiments, M-CSF can be assayed in a biological sample by a competition immunoassay utilizing M-CSF standards labeled with a detectable substance and an unlabeled anti-M-CSF antibody. In this assay, the biological sample, the labeled M-CSF standards and the anti-M-CSF antibody are combined and the amount of labeled M-CSF standard bound to the unlabeled antibody is determined. The amount of M-CSF in the biological sample is inversely proportional to the amount of labeled M-CSF standard bound to the anti-M-CSF antibody.

One can use the immunoassays disclosed above for a number of purposes. For example, the anti-M-CSF antibodies can be used to detect M-CSF in cells or on the surface of cells in cell culture, or secreted into the tissue culture medium. The anti-M-CSF antibodies can be used to determine the amount of M-CSF on the surface of cells or secreted into the tissue culture medium that have been treated with various compounds. This method can be used to identify compounds that are useful to inhibit or activate M-CSF expression or secretion. According to this method, one sample of cells is treated with a test compound for a period of time while another sample is left untreated. If the total level of M-CSF is to be measured, the cells are lysed and the total M-CSF level is measured using one of the immunoassays described above. The total level of M-CSF in the treated versus the untreated cells is compared to determine the effect of the test compound.

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An immunoassay for measuring total M-CSF levels is an ELISA or Western blot. If the cell surface level of M-CSF is to be measured, the cells are not lysed, and the M-CSF cell surface levels can be measured using one of the immunoassays described above. An immunoassay for determining cell surface levels of M-CSF can include the steps of labeling the cell surface proteins with a detectable label, such as biotin or ^{125}I , immunoprecipitating the M-CSF with an anti-M-CSF antibody and then detecting the labeled M-CSF. Another immunoassay for determining the localization of M-CSF, e.g., cell surface levels, can be immunohistochemistry. Methods such as ELISA, RIA, Western blot, immunohistochemistry, cell surface labeling of integral membrane proteins and immunoprecipitation are well known in the art. See, e.g., Harlow and Lane, *supra*. In addition, the immunoassays can be scaled up for high throughput screening in order to test a large number of compounds for inhibition or activation of M-CSF.

Another example of an immunoassay for measuring secreted M-CSF levels can be an antigen capture assay, ELISA, immunohistochemistry assay, Western blot and the like using antibodies of the invention. If secreted M-CSF is to be measured, cell culture media or body fluid, such as blood serum, urine, or synovial fluid, can be assayed for secreted M-CSF and/or cells can be lysed to release produced, but not yet secreted M-CSF. An immunoassay for determining secreted levels of M-CSF includes the steps of labeling the secreted proteins with a detectable label, such as biotin or ^{125}I , immunoprecipitating the M-CSF with an anti-M-CSF antibody and then detecting the labeled M-CSF. Another immunoassay for determining secreted levels of M-CSF can include the steps of (a) pre-binding anti-M-CSF antibodies to the surface of a microtiter plate; (b) adding tissue culture cell media or body fluid containing the secreted M-CSF to the wells of the microtiter plate to bind to the anti-M-CSF antibodies; (c) adding an antibody that will detect the anti-M-CSF antibody, e.g., anti-M-CSF labeled with digoxigenin that binds to an epitope of M-CSF different from the anti-M-CSF antibody of step (a); (d) adding an antibody to digoxigenin conjugated to peroxidase; and (e) adding a peroxidase substrate that will yield a colored reaction product that can be quantitated to determine the level of secreted M-CSF in tissue culture cell media or a body fluid sample. Methods such as ELISA, RIA, Western blot, immunohistochemistry, and antigen capture assay are well known in the art. See, e.g., Harlow and Lane, *supra*. In addition, the immunoassays can be scaled up for high throughput screening in order to test a large number of compounds for inhibition or activation of M-CSF.

The anti-M-CSF antibodies of the invention can also be used to determine the levels of cell surface M-CSF in a tissue or in cells derived from the tissue. In some embodiments, the

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tissue is from a diseased tissue. In some embodiments, the tissue can be a tumor or a biopsy thereof. In some embodiments of the method, a tissue or a biopsy thereof can be excised from a patient. The tissue or biopsy can then be used in an immunoassay to determine, e.g., total M-CSF levels, cell surface levels of M-CSF, or localization of M-CSF by the methods discussed
5 above.

The method can comprise the steps of administering a detectably labeled anti-M-CSF antibody or a composition comprising them to a patient in need of such a diagnostic test and subjecting the patient to imaging analysis to determine the location of the M-CSF-expressing tissues. Imaging analysis is well known in the medical art, and includes, without limitation, x-ray analysis, magnetic resonance imaging (MRI) or computed tomography (CE). The antibody
10 can be labeled with any agent suitable for *in vivo* imaging, for example a contrast agent, such as barium, which can be used for x-ray analysis, or a magnetic contrast agent, such as a gadolinium chelate, which can be used for MRI or CE. Other labeling agents include, without limitation, radioisotopes, such as ⁹⁹Tc. In another embodiment, the anti-M-CSF antibody will
15 be unlabeled and will be imaged by administering a second antibody or other molecule that is detectable and that can bind the anti-M-CSF antibody. In an embodiment, a biopsy is obtained from the patient to determine whether the tissue of interest expresses M-CSF.

The anti-M-CSF antibodies of the invention can also be used to determine the secreted levels of M-CSF in a body fluid such as blood serum, urine, or synovial fluid derived from a
20 tissue. In some embodiments, the body fluid is from a diseased tissue. In some embodiments, the body fluid is from a tumor or a biopsy thereof. In some embodiments of the method, body fluid is removed from a patient. The body fluid is then used in an immunoassay to determine secreted M-CSF levels by the methods discussed above. One embodiment of the invention is a method of assaying for the activity of a M-CSF antagonist comprising: administering a M-CSF
25 antagonist to a primate or human subject and measuring the number of CD14+CD16+ monocytes in a biological sample.

Therapeutic Methods of Use

In another embodiment, the invention provides a method for inhibiting M-CSF activity by administering an anti-M-CSF antibody to a patient in need thereof. Any of the types of
30 antibodies described herein may be used therapeutically. In a preferred embodiment, the anti-M-CSF antibody is a human, chimeric or humanized antibody. In another preferred embodiment, the M-CSF is human and the patient is a human patient. Alternatively, the patient may be a mammal that expresses a M-CSF that the anti-M-CSF antibody cross-reacts with. The

antibody may be administered to a non-human mammal expressing a M-CSF with which the antibody cross-reacts (i.e. a primate) for veterinary purposes or as an animal model of human disease. Such animal models may be useful for evaluating the therapeutic efficacy of antibodies of this invention.

As used herein, the term "a disorder in which M-CSF activity is detrimental" is intended to include diseases and other disorders in which the presence of high levels of M-CSF in a subject suffering from the disorder has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Such disorders may be evidenced, for example, by an increase in the levels of M-CSF secreted and/or on the cell surface or increased tyrosine autophosphorylation of *c-fms* in the affected cells or tissues of a subject suffering from the disorder. The increase in M-CSF levels may be detected, for example, using an anti-M-CSF antibody as described above.

In one embodiment, an anti-M-CSF antibody may be administered to a patient who has a *c-fms*-expressing tumor or a tumor that secretes M-CSF and/or that expresses M-CSF on its cell surface. Preferably, the tumor expresses a level of *c-fms* or M-CSF that is higher than a normal tissue. The tumor may be a solid tumor or may be a non-solid tumor, such as a lymphoma. In a more preferred embodiment, an anti-M-CSF antibody may be administered to a patient who has a *c-fms*-expressing tumor, a M-CSF-expressing tumor, or a tumor that secretes M-CSF that is cancerous. Further, the tumor may be cancerous. In an even more preferred embodiment, the tumor is a cancer of lung, breast, prostate or colon. In another preferred embodiment, the anti-M-CSF antibody administered to a patient results in M-CSF no longer bound to the *c-fms* receptor. In a highly preferred embodiment, the method causes the tumor not to increase in weight or volume or to decrease in weight or volume. In another embodiment, the method causes *c-fms* on tumor cells to not be bound by M-CSF. In another embodiment, the method causes M-CSF on tumor cells to not be bound to *c-fms*. In another embodiment, the method causes secreted M-CSF of the tumor cells to not be bound to *c-fms*. In a preferred embodiment, the antibody is selected from 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1 or 9.14.4G1, or comprises a heavy chain, light chain or antigen binding region thereof.

In another preferred embodiment, an anti-M-CSF antibody may be administered to a patient who expresses inappropriately high levels of M-CSF. It is known in the art that high-level expression of M-CSF can lead to a variety of common cancers. In one embodiment, said

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method relates to the treatment of cancer such as brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer. Patients that can be treated with a compounds of the invention according to the methods of this invention include, for example, patients that have been

5 diagnosed as having lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's

10 disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors (e.g., sarcomas, carcinomas or lymphomas that are cancers of body tissues other than blood, bone marrow or the lymphatic system), solid tumors of childhood, lymphocytic lymphomas, cancer

15 of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas). In a more preferred embodiment, the anti-M-CSF antibody is administered to a patient with breast cancer, prostate cancer, lung cancer or colon cancer. In an even more preferred embodiment, the method causes the cancer to stop

20 proliferating abnormally, or not to increase in weight or volume or to decrease in weight or volume.

The antibody may be administered once, but more preferably is administered multiple times. For example, the antibody may be administered from three times daily to once every six months or longer. The administering may be on a schedule such as three times daily, twice

25 daily, once daily, once every two days, once every three days, once weekly, once every two weeks, once every month, once every two months, once every three months and once every six months. The antibody may also be administered continuously via a minipump. The antibody may be administered via an oral, mucosal, buccal, intranasal, inhalable, intravenous, subcutaneous, intramuscular, parenteral, intratumor or topical route. The antibody may be

30 administered at the site of the tumor or inflamed body part, into the tumor or inflamed body part, or at a site distant from the site of the tumor or inflamed body part. The antibody may be administered once, at least twice or for at least the period of time until the condition is treated, palliated or cured. The antibody generally will be administered for as long as the tumor is present provided that the antibody causes the tumor or cancer to stop growing or to decrease in

weight or volume or until the inflamed body part is healed. The antibody will generally be administered as part of a pharmaceutical composition as described *supra*. The dosage of antibody will generally be in the range of 0.1-100 mg/kg, more preferably 0.5-50 mg/kg, more preferably 1-20 mg/kg, and even more preferably 1-10 mg/kg. The serum concentration of the antibody may be measured by any method known in the art.

In another aspect, the anti-M-CSF antibody may be co-administered with other therapeutic agents, such as anti-inflammatory agents, anti-coagulant agents, agents that will lower or reduce blood pressure, anti-neoplastic drugs or molecules, to a patient who has a hyperproliferative disorder, such as cancer or a tumor. In one aspect, the invention relates to a method for the treatment of the hyperproliferative disorder in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the invention in combination with an anti-tumor agent selected from the group consisting of, but not limited to, mitotic inhibitors, alkylating agents, anti-metabolites, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, kinase inhibitors, matrix metalloprotease inhibitors, genetic therapeutics and anti-androgens. In a more preferred embodiment, the antibody may be administered with an antineoplastic agent, such as adriamycin or taxol. In another preferred embodiment, the antibody or combination therapy is administered along with radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy. In yet another preferred embodiment, the antibody will be administered with another antibody. For example, the anti-M-CSF antibody may be administered with an antibody or other agent that is known to inhibit tumor or cancer cell proliferation, e.g., an antibody or agent that inhibits erbB2 receptor, EGF-R, CD20 or VEGF.

Co-administration of the antibody with an additional therapeutic agent (combination therapy) encompasses administering a pharmaceutical composition comprising the anti-M-CSF antibody and the additional therapeutic agent and administering two or more separate pharmaceutical compositions, one comprising the anti-M-CSF antibody and the other(s) comprising the additional therapeutic agent(s). Further, although co-administration or combination therapy generally means that the antibody and additional therapeutic agents are administered at the same time as one another, it also encompasses instances in which the antibody and additional therapeutic agents are administered at different times. For instance, the antibody may be administered once every three days, while the additional therapeutic agent is administered once daily. Alternatively, the antibody may be administered prior to or subsequent to treatment of the disorder with the additional therapeutic agent. Similarly, administration of the anti-M-CSF

antibody may be administered prior to or subsequent to other therapy, such as radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy

The antibody and one or more additional therapeutic agents (the combination therapy) may be administered once, twice or at least the period of time until the condition is treated, palliated or cured. Preferably, the combination therapy is administered multiple times. The combination therapy may be administered from three times daily to once every six months. The administering may be on a schedule such as three times daily, twice daily, once daily, once every two days, once every three days, once weekly, once every two weeks, once every month, once every two months, once every three months and once every six months, or may be administered continuously via a minipump. The combination therapy may be administered via an oral, mucosal, buccal, intranasal, inhalable, intravenous, subcutaneous, intramuscular, parenteral, intratumor or topical route. The combination therapy may be administered at a site distant from the site of the tumor. The combination therapy generally will be administered for as long as the tumor is present provided that the antibody causes the tumor or cancer to stop growing or to decrease in weight or volume.

In a still further embodiment, the anti-M-CSF antibody is labeled with a radiolabel, an immunotoxin or a toxin, or is a fusion protein comprising a toxic peptide. The anti-M-CSF antibody or anti-M-CSF antibody fusion protein directs the radiolabel, immunotoxin, toxin or toxic peptide to the M-CSF-expressing cell. In a preferred embodiment, the radiolabel, immunotoxin, toxin or toxic peptide is internalized after the anti-M-CSF antibody binds to the M-CSF on the surface of the target cell.

In another aspect, the anti-M-CSF antibody may be used to treat noncancerous states in which high levels of M-CSF and/or M-CSF have been associated with the noncancerous state or disease. In one embodiment, the method comprises the step of administering an anti-M-CSF antibody to a patient who has a noncancerous pathological state caused or exacerbated by high levels of M-CSF and/or M-CSF levels or activity. In a more preferred embodiment, the anti-M-CSF antibody slows the progress of the noncancerous pathological state. In a more preferred embodiment, the anti-M-CSF antibody stops or reverses, at least in part, the noncancerous pathological state.

Gene Therapy

The nucleic acid molecules of the instant invention can be administered to a patient in need thereof via gene therapy. The therapy may be either *in vivo* or *ex vivo*. In a preferred embodiment, nucleic acid molecules encoding both a heavy chain and a light chain are

administered to a patient. In a more preferred embodiment, the nucleic acid molecules are administered such that they are stably integrated into chromosomes of B cells because these cells are specialized for producing antibodies. In a preferred embodiment, precursor B cells are transfected or infected *ex vivo* and re-transplanted into a patient in need thereof. In another embodiment, precursor B cells or other cells are infected *in vivo* using a virus known to infect the cell type of interest. Typical vectors used for gene therapy include liposomes, plasmids and viral vectors. Exemplary viral vectors are retroviruses, adenoviruses and adeno-associated viruses. After infection either *in vivo* or *ex vivo*, levels of antibody expression can be monitored by taking a sample from the treated patient and using any immunoassay known in the art or discussed herein.

In a preferred embodiment, the gene therapy method comprises the steps of administering an isolated nucleic acid molecule encoding the heavy chain or an antigen-binding portion thereof of an anti-M-CSF antibody and expressing the nucleic acid molecule. In another embodiment, the gene therapy method comprises the steps of administering an isolated nucleic acid molecule encoding the light chain or an antigen-binding portion thereof of an anti-M-CSF antibody and expressing the nucleic acid molecule. In a more preferred method, the gene therapy method comprises the steps of administering of an isolated nucleic acid molecule encoding the heavy chain or an antigen-binding portion thereof and an isolated nucleic acid molecule encoding the light chain or the antigen-binding portion thereof of an anti-M-CSF antibody of the invention and expressing the nucleic acid molecules. The gene therapy method may also comprise the step of administering another anti-cancer agent, such as taxol or adriamycin.

In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the invention in any manner.

EXAMPLE I

Generation of Cell Lines Producing Anti-M-CSF Antibody

Antibodies of the invention were prepared, selected, and assayed as follows:

Immunization and hybridoma generation

Eight to ten week old XENOMOUSE™ mice were immunized intraperitoneally or in their hind footpads with human M-CSF (10 µg/dose/mouse). This dose was repeated five to seven times over a three to eight week period. Four days before fusion, the mice were given a final injection of human M-CSF in PBS. The spleen and lymph node lymphocytes from

immunized mice were fused with the non-secretory myeloma P3-X63-Ag8.653 cell line, and the fused cells were subjected to HAT selection as previously described (Galfre and Milstein, *Methods Enzymol.* 73:3-46, 1981). A panel of hybridomas all secreting M-CSF specific human IgG2 and IgG4 antibodies was recovered. Antibodies also were generated using
5 XENOMAX™ technology as described in Babcook, J.S. *et al.*, *Proc. Natl. Acad. Sci. USA* 93:7843-48, 1996. Nine cell lines engineered to produce antibodies of the invention were selected for further study and designated 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4, 8.10.3 and 9.7.2. The hybridomas were deposited under terms in accordance with the Budapest Treaty with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA
10 20110-2209 on August 8, 2003. The hybridomas have been assigned the following accession numbers:

	Hybridoma 3.8.3 (LN 15891)	PTA-5390
	Hybridoma 2.7.3 (LN 15892)	PTA-5391
	Hybridoma 1.120.1 (LN 15893)	PTA-5392
15	Hybridoma 9.7.2 (LN 15894)	PTA-5393
	Hybridoma 9.14.4 (LN 15895)	PTA-5394
	Hybridoma 8.10.3 (LN 15896)	PTA-5395
	Hybridoma 88-gamma (UC 25489)	PTA-5396
	Hybridoma 88-kappa (UC 25490)	PTA-5397
20	Hybridoma 100-gamma (UC 25491)	PTA-5398
	Hybridoma 100-kappa (UC 25492)	PTA-5399
	Hybridoma 252-gamma (UC 25493)	PTA-5400
	Hybridoma 252-kappa (UC 25494)	PTA-5401

25 EXAMPLE II

Gene Utilization Analysis

DNA encoding the heavy and light chains of monoclonal antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4, 8.10.3 and 9.7.2 was cloned from the respective hybridoma cell lines and the DNA sequences were determined by methods known to one skilled in the art. Additionally,
30 DNA from the hybridoma cell lines 9.14.4, 8.10.3 and 9.7.2 was mutated at specific framework regions in the variable domain and/or isotype-switched to obtain, for example, 9.14.4I, 8.10.3F, and 9.7.2IF, respectively. From nucleic acid sequence and predicted amino acid sequence of the antibodies, the identity of the gene usage for each antibody chain was determined ("VBASE"). Table 2 sets forth the gene utilization of selected antibodies in accordance with
35 the invention:

Table 2
Heavy and Light Chain Gene Utilization

Clone	Heavy Chain				Kappa Light Chain		
	SEQ ID NO:	V _H	D _H	J _H	SEQ ID NO:	V _K	J _K
252	1, 2	3-11	7-27	6	3, 4	O12	3
88	5, 6	3-7	6-13	4	7, 8	O12	3
100	9, 10	3-23	1-26	4	11, 12	L2	3
3.8.3	14	3-11	7-27	4	16	L5	3
2.7.3	18	3-33	1-26	4	20	L5	4
1.120.1	22	1-18	4-23	4	24	B3	1
9.14.4I	25, 26	3-11	7-27	4b	27, 28	O12	3
8.10.3F	29, 30	3-48	1-26	4b	31, 32	A27	4
9.7.2IF	33, 34	3-11	6-13	6b	35, 36	O12	3
9.14.4	37, 38	3-11	7-27	4b	27, 28	O12	3
8.10.3	29, 30	3-48	1-26	4b	43, 44	A27	4
9.7.2	45, 46	3-11	6-13	6b	47, 48	O12	3
8.10.3FG1	97, 98	3-48	1-26	4b	31, 32	A27	4
9.14.4G1	101, 102	3-11	7-27	4b	27, 28	O12	3
9.14.4C-Ser	54	3-11	7-27	4b	56	O12	3
9.14.4-CG2	74	3-11	7-27	4b	56	O12	3
9.14.4-CG4	78	3-11	7-27	4b	56	O12	3
8.10.3C-Ser	58	3-48	1-26	4b	60	A27	4
8.10.3-CG2	62	3-48	1-26	4b	60	A27	4
8.10.3-CG4	94	3-48	1-26	4b	60	A27	4
8.10.3-Ser	90	3-48	1-26	4b	43, 44	A27	4
9.7.2C-Ser	50	3-11	6-13	6b	52	O12	3
9.7.2-CG2	66	3-11	6-13	6b	52	O12	3
9.7.2-CG4	70	3-11	6-13	6b	52	O12	3
9.7.2-Ser	86	3-11	6-13	6b	47, 48	O12	3
9.14.4-Ser	82	3-11	7-27	4b	27, 28	O12	3

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Mutagenesis of specific residues of the heavy and light chains was carried out by designing primers and using the QuickChange Site Directed Mutagenesis Kit from Stratagene, according to the manufacturer's instructions. Mutations were confirmed by automated sequencing, and mutagenized inserts were subcloned into expression vectors. The expression vectors were transfected into HEK293 cells to produce enough of the antibodies for characterization.

EXAMPLE III

M-CSF Mouse Monocytic Cell Proliferation Assay

In vitro assays were conducted to measure M-CSF-dependent mouse monocytic cell proliferation in the presence of anti-M-CSF antibodies to determine the degree of inhibition by anti-M-CSF antibodies.

Mouse monocytic cells, M-NFS-60 cells, from American Type Culture Collection (ATCC) (Manassas, VA), were obtained and maintained in RPMI-1640 medium containing 2 mM L-glutamine (ATCC), 10% heat inactivated fetal bovine serum (FBS) (Invitrogen, Carlsbad, CA), 0.05 mM 2-mercaptoethanol (Sigma, St. Louis MO) (assay medium), with 15 ng/ml human M-CSF. M-NSF-60 cells were split to 5×10^4 for next day use or to 2.5×10^4 for use in 2 days. Prior to use in the assay, the cells were washed three times with RPMI-1640, counted and the volume adjusted with assay medium to yield 2×10^5 cells/ml. All conditions were conducted in triplicate in 96-well treated tissue culture plates (Corning, Corning, NY). To each well 50 μ l of the washed cells, either 100 pM or 1000 pM M-CSF in a volume of 25 μ l and test or control antibody at various concentrations in a volume of 25 μ l in acetate buffer (140 mM sodium chloride, 20 mM sodium acetate, and 0.2 mg/ml polysorbate 80, pH 5.5) to a final volume of 100 μ l was added. Antibodies of the invention were tested alone and with human M-CFS. The plates were incubated for 24 hours (hrs) at 37°C with 5% CO₂.

After 24 hrs, 10 μ l/well of 0.5 μ Ci ³H-thymidine (Amersham Biosciences, Piscataway, NJ) was added and pulsed with the cells for 3 hrs. To detect the amount of incorporated thymidine, the cells were harvested onto pre-wet unifilter GF/C filterplates (Packard, Meriden, CT) and washed 10 times with water. The plates were allowed to dry overnight. Bottom seals were added to the filterplates. Next, 45 μ l Microscint 20 (Packard, Meriden, CT) per well was added. After a top seal was added, the plates were counted in a Trilux microbeta counter (Wallac, Norton, OH).

These experiments demonstrate that anti-M-CSF antibodies of the invention inhibit mouse monocytic cell proliferation in response to M-CSF. Further, by using various concentrations of antibodies, the IC₅₀ for inhibition of mouse monocytic cell proliferation was determined for antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, and 9.7.2 (Cell Proliferation Assay, Table 3a and Table 3b).

Table 3a

Antibody	252	88	100	3.8.3	2.7.3	1.120.1
M-CSF Mouse Monocytic Cell Proliferation Assay [IC ₅₀ , M]	1.86 x 10 ⁻¹⁰	2.31 x 10 ⁻¹⁰	7.44 x 10 ⁻¹⁰	7.3 x 10 ⁻¹¹	1.96 x 10 ⁻¹⁰	1.99 x 10 ⁻¹⁰
Human Whole Blood Monocyte Activation Assay [IC ₅₀ , M]	8.67 x 10 ⁻¹⁰	5.80 x 10 ⁻¹⁰	1.53 x 10 ⁻¹⁰	8.6 x 10 ⁻¹¹	7.15 x 10 ⁻¹⁰	8.85 x 10 ⁻¹⁰
Receptor Binding Inhibition Assay [IC ₅₀ , M]	7.47 x 10 ⁻¹⁰	4.45 x 10 ⁻¹⁰	1.252 x 10 ⁻⁹	7.0 x 10 ⁻¹¹	3.08 x 10 ⁻¹⁰	1.57 x 10 ⁻¹⁰

Table 3b

Antibody	9.14.4I	8.10.3F	9.7.2IF	9.14.4	8.10.3	9.7.2
M-CSF Mouse Monocytic Cell Proliferation Assay [IC ₅₀ , M]	2.02 x 10 ⁻¹⁰	4.13 x 10 ⁻¹⁰	7.37 x 10 ⁻¹⁰	2.02 x 10 ⁻¹⁰	4.13 x 10 ⁻¹⁰	7.37 x 10 ⁻¹⁰
Human Whole Blood Monocyte Activation Assay [IC ₅₀ , M]	2.49 x 10 ⁻¹⁰	4.46 x 10 ⁻¹⁰	1.125 x 10 ⁻⁹	6.48 x 10 ⁻¹⁰	2.8 x 10 ⁻¹⁰	1.98 x 10 ⁻¹⁰
Receptor Binding Inhibition Assay [IC ₅₀ , M]	2.97 x 10 ⁻¹⁰	9.8 x 10 ⁻¹¹	5.29 x 10 ⁻¹⁰	4.1 x 10 ⁻¹¹	1.5 x 10 ⁻⁹	6 x 10 ⁻¹²

EXAMPLE IV**Human Whole Blood Monocyte Activation Assay**

In vitro assays were conducted to measure M-CSF dependent monocyte shape changes in the presence of anti-M-CSF antibodies to determine if the anti-M-CSF antibodies were

capable of inhibiting whole blood monocyte activation and their degree of inhibition of monocyte shape changes.

In individual wells of a 96-well tissue culture plate, 6 μ l of 1.7 nM anti-M-CSF and 94 μ l of whole human blood for a final concentration of 102 pM anti-M-CSF antibody were mixed. The plates were incubated at 37°C in a CO₂ tissue culture incubator. Next, the plates were removed from the incubator. To each well, 100 μ l of a fixative solution (0.5% formalin in phosphate buffered saline without MgCl₂ or CaCl₂) was added and the plates were incubated for 10 minutes at room temperature. For each sample, 180 μ l from each well and 1 ml of Red Cell Lysis Buffer were mixed. The tubes were vortexed for 2 seconds. Next, the samples were incubated at 37°C for 5 minutes in a shaking water bath to lyse the red blood cells, but to leave monocytes intact. Immediately following this incubation, the samples were read on a fluorescence-activated cell scanning (FACS) machine (BD Beckman FACS) and data was analyzed using FACS Station Software Version 3.4.

These experiments demonstrate that anti-M-CSF antibodies of the invention inhibit monocyte shape changes compared to control samples. Using the monocyte shape change assay, the IC₅₀ was determined for antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, and 9.7.2 (Human Whole Blood Monocyte Activation, Table 3a and Table 3b).

EXAMPLE V

c-fms Receptor Binding Inhibition Assay

In vitro assays were conducted to measure M-CSF binding to *c-fms* receptor in the presence of anti-M-CSF antibodies to determine if the anti-M-CSF antibodies were capable of inhibiting M-CSF binding to *c-fms* receptor and their degree of inhibition.

NIH-3T3 cells transfected with human *c-fms* or M-NSF-60 cells maintained in Dulbecco's phosphate buffered saline without magnesium or calcium were washed. NIH-3T3 cells were removed from tissue culture plates with 5 mM ethylene-diamine-tetra-acetate (EDTA), pH 7.4. The NIH-3T3 cells were returned to the tissue culture incubator for 1-2 minutes and the flask(s) were tapped to loosen the cells. The NIH-3T3 cells and the M-NSF-60 cells were transferred to 50 ml tubes and washed twice with reaction buffer (1x RPMI without sodium bicarbonate containing 50 mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), pH 7.4). Next, the NIH-3T3 cells were resuspended in reaction buffer for a final

concentration of 1.5×10^5 cell/ml. The M-NSF-60 cells were resuspended in a reaction buffer for a final concentration of 2.5×10^6 cells/ml.

For the assay, 9 μ l of a sterile 0.4 M sucrose solution, 100 μ l of 125 I-M-CSF (Amersham, IMQ7228v) at a final concentration of 200 pM in RPMI-1640 containing 50 mM HEPES (pH 7.4), 0.2% bovine serum albumin, and 100 μ l of unlabeled M-CSF at a final concentration of 200 nM were mixed in a binding tube. Next, 50 μ l/tube of increasing concentrations of a test antibody was added. In order to determine non-specific binding of the antibodies, we included samples to which we also added 200 nM M-CSF. To control tubes, we did not add antibody. Next, 15,000 NIH-3T3 cells or 250,000 M-NSF-60 cells were added per tube. All tubes were incubated at room temperature for 3 hrs and subjected to centrifugation at 10,000 rpm for 2 min. The tips of the tubes containing the cell pellets were cut off and the amount of M-CSF bound to the cells was determined using a Packard Cobra II Gamma counter. The specific binding was determined by subtracting non-specific binding from total binding. All assays were performed in duplicate. The binding data was analyzed using the computer program, Graph Pad Prism 2.01.

These experiments demonstrate that anti-M-CSF antibodies of the invention inhibit the binding of M-CSF to *c-fms* receptor compared to control samples. Further, by using various concentrations of antibodies, the IC_{50} for inhibition of receptor binding was determined for antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, and 9.7.2 (Receptor Binding Inhibition Assay, Table 3a and Table 3b).

EXAMPLE VI

Determination of Affinity Constants (K_D) of Anti-M-CSF

Monoclonal Antibodies by BIACORETM

Affinity measures of purified antibodies were performed by surface plasmon resonance using the BIACORETM 3000 instrument, following the manufacturer's protocols.

For antibodies 3.8.3, 2.7.3 and 1.120.1, the experiments were performed in a BIACORETM 3000 instrument at 25°C in Dulbecco's phosphate buffered saline containing 0.0005% Tween-20. Protein concentrations were obtained from sedimentation velocity experiments or by measuring the wavelength of the sample at 280 nm using theoretical extinction coefficients derived from amino acid sequences. For experiments measuring the binding of antibody to immobilized antigens, M-CSF was immobilized on a B1 chip by standard direct amine coupling procedures. Antibody samples were prepared at 0.69 μ M for

3.8.3, 2.7.3 and 1.120.1. These samples were diluted 3-fold serially to 8.5 nM or 2.8 nM for roughly a 100-fold range in concentrations. For each concentration, the samples were injected in duplicate at 5 μ l/min flow for 4 min. The dissociation was monitored for 2000 seconds. The data were fit globally to a simple 1:1 binding model using BIACORE™ Biaevaluation software. In all cases, this method was used to obtain k_{off} and it was found that this data set compared well to data obtained from global fit of association and dissociation data.

For antibodies 252, 88 and 100, the experiments were performed in a BIACORE™ 3000 instrument at 25°C in HBS-EP Buffer (0.01M HEPES, pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005% Surfactant P20). For experiments measuring the binding of antibody to immobilized antigens, a M-CSF was immobilized on a CM5 Research Grade Sensor chip by standard direct amine coupling procedures. Antibody samples were prepared at 12.5 nM for antibodies 252 and 100 and at 25.0 nM for antibody 88. These samples were two-fold serially diluted to 0.78 nM for roughly a 15-30 fold range in concentrations. For each concentration, the samples were injected in duplicate in random order at 30 μ l/min flow for 3 min. The dissociation was monitored for 300 sec. The data were fit globally to a simple 1:1 binding model using BIACORE™ Biaevaluation software. In all cases, this method was used to obtain k_{off} and it was found that this data set compared well to data obtained from global fit of association and dissociation data.

Table 4 shows results for antibodies 252, 88, 100, 3.8.3, 2.7.3 and 1.120.1.

Table 4

	252	88	100	3.8.3	2.7.3	1.120.1
K_D (M)	1.33×10^{-11}	1.33×10^{-9}	2.0×10^{-11}	4.0×10^{-10}	4.7×10^{-9}	5.4×10^{-9}
k_{off} (1/s)	1.03×10^{-6}	7.3×10^{-5}	1.7×10^{-5}			

EXAMPLE VII

Production of 8.10.3 antibodies from 8.10.3 hybridoma cells

Antibody 8.10.3 was produced in 3L sparged spinners. The 3L sparged spinner flask is a glass vessel where cultures are mixed with an impeller controlled by a magnetic platform. The spinner is connected to gas lines to provide 5% CO₂ and air. 8.10.3 hybridoma cells were initially thawed into T-25 cell culture flasks. The cells were progressively expanded until there was a sufficient number of cells to seed the sparged spinners.

Two 3L sparged spinner flasks were seeded with 8.10.3 hybridoma cells in Hybridoma Serum-Free Medium with the additions noted on Table 5, for the two sparged flasks. The concentrations for Ultra low IgG serum (Gibco cat# 16250-078), L-glutamine (JRH Biosciences cat# 59202-500M), Non-Essential Amino Acids (Gibco cat# 11140-050), Peptone (Difco cat# 211693), glucose (In-house stock prepared from JT Baker cat# 1920-07), and Anti-foam C (Sigma cat.# A-8011) are given at their final concentrations in the media. The balance of the volume in each reactor is Hybridoma Serum-Free Medium.

Table 5. Conditions for Growing Hybridoma 8.10.3 in two 3L sparged spinners.

Conditions	Spinner 1	Spinner 2
Seeding density (1×10^6 cells/ml)	0.16 ml	0.16 ml
Hybridoma Serum-Free Medium (Gibco cat# 12045-076)	Balance	Balance
Ultra low IgG serum (Gibco cat# 16250-078)	5%	5%
L-glutamine (JRH Biosciences cat# 59202-500M)	8 mmol/L	8mmol/L
Non-Essential Amino Acids (Gibco cat# 11140-050)	1%	1%
Peptone (Difco cat# 211693)	1g/L	1g/L
2M glucose (In-house stock prepared from JT Baker cat# 1920-07)	8g/L	8g/L
Anti-foam C (Sigma cat.# A-8011)	1ml/L	1ml/L

The cultures were grown for 15 days and were harvested when the viability was below 20%. Viability was determined by trypan blue exclusion method with an automated cell counter (Cedex, Innovatis). Harvesting was accomplished by centrifugation and subsequent filtration. Clarified supernatant was obtained after centrifugation for 15 minutes at 7000 rpm and subsequent filtration with a sterile 0.22 μ m 4" Opticap Millipore filter (cat# KVSCO4HB3) into a 10L sterile TC-Tech bag (cat # P/N 12420 Bag Style CC-10-112420). The filtrate was then purified in the following example.

EXAMPLE VIII

Purification of an Anti-M-CSF Antibody

A Protein A column (Amersham Pharmacia) was prepped by washing with 3 column volumes of 8M Urea, followed by an equilibration wash with 20 mM Tris (pH 8). The final filtrate from Example VII was spiked with 2% v/v of 1M Tris pH 8.3 and 0.02% NaN₃ before

being loaded onto the Protein A column via gravity-drip mode. After load was complete, the resin was washed with 5 column volumes of 20 mM Tris (pH 8), followed by 5 column volumes of the elution buffer (0.1 M Glycine pH 3.0). Any precipitation was noted, and then a 10% v/v spike of 1M Tris pH 8.3 was added to the eluted antibody. The eluted protein was then dialyzed into 100 fold the volume amount of eluted material of dialysis buffer (140 mM NaCl/20mM Sodium Acetate pH 5.5). Following dialysis, the antibody was sterile filtered with a 0.22 µm filter and stored until further use.

EXAMPLE IX

Monkey Treatment and Monocyte Counts

One male and one female cynomolgus monkey per dosage group were intravenously administered vehicle or antibody 8.10.3 (produced as describe in Examples VII and VIII) at 0, 0.1, 1, or 5 mg/kg in a dose volume of 3.79 mL/kg over an approximately 5 minute period. Blood samples for clinical laboratory analysis were collected at 24 and 72 hours postdose and weekly for 3 weeks. The monocyte counts were determined by light scatter using an Abbott Diagnostics Inc. Cell Dyn system (Abbott Park, Illinois).

A dose-related decrease (~25% to 85%) in total monocytes at all doses (Figures 1A and 1B) was observed. Monocyte counts at the 0.1 and 1 mg/kg appeared to rebound to near control levels by week 2, while monocyte counts at 5 mg/kg were still decreased at 3 weeks.

CD14+CD16+ monocyte subset analysis

Primate whole blood was drawn into Vacutainer tubes containing sodium heparin. 0.2 ml of each blood sample was added to a 15 ml conical polypropylene centrifuge tube containing 10 ml of red blood cell lysis buffer (Sigma), and incubated in a 37°C water bath for 15 minutes. The tubes were then centrifuged in a Sorvall RT7 centrifuge for 5 minutes at 1,200 rpm. The supernatant was aspirated, the pellet resuspended in 10 ml of 4°C FACS buffer (Hanks' Balanced Salt Solution/2%FBS/0.02% sodium azide), and the tube centrifuged again for 5 minutes at 1,200 rpm. The supernatant was aspirated and the pellet resuspended in an antibody cocktail consisting of 80 µl 4°C FACS buffer, 10 µl FITC-conjugated anti-human CD14 monoclonal antibody (BD Biosciences, San Diego, CA), 0.5 µl Cy5-PE-conjugated anti-human CD16 monoclonal antibody (BD Biosciences, San Diego, CA), and 10 µl PE-conjugated anti-human CD89 monoclonal antibody (BD Biosciences, San Diego, CA). The cell suspension was incubated on ice for 20 minutes, after which 10 ml of 4°C FACS buffer was added and the cells centrifuged as before. The supernatant was aspirated, and the cell pellet resuspended in 400 µl

FACS buffer and the cells analyzed on a FACSCaliber flow cytometer (BD Biosciences, San Jose, CA). Data for 30,000 cells were collected from each sample.

The monocyte population was identified by a combination of forward angle light scatter and orthogonal light scatter. Cells within the monocyte gate were further analyzed for expression of CD14 and CD16. Two distinct population of monocytes were observed, one expressing high levels of CD14 with little or no CD16 expression (CD14++CD16-) and the other expressing lower levels of CD14, but high levels of CD16 (CD14+CD16+), similar to the two monocyte subsets previously described in human peripheral blood (Ziegler-Heitbrock H.W., *Immunology Today* 17:424-428 (1996)). For each primate tested, the percentage of monocytes within the CD14+CD16+ subset was determined after each blood draw, on days 1, 3, 7, 14, and 21 after 8.10.3 injection.

In general, 8.10.3 treatment resulted in a reduction in the percentage of CD14+CD16+ monocytes (see Figures 2A and 2B). Monkeys not receiving 8.10.3 Antibody demonstrated relatively stable CD14+CD16+ monocyte levels. CD14+CD16+ monocytes have been termed "proinflammatory" because they produce higher levels of TNF- α and other inflammatory cytokines (Frankenberger, M.T., *et al.*, *Blood* 87:373-377 (1996)). It has also been reported that the differentiation of monocytes from the conventional CD14++CD16- phenotype to the proinflammatory phenotype is dependent on M-CSF (Saleh M.N., *et al.*, *Blood* 85: 2910-2917 (1995)).

EXAMPLE X

Monkey Treatment and Monocyte Counts

Three male cynomolgus monkeys per dosage group were intravenously administered vehicle (20 mM Sodium acetate, pH 5.5, 140 mM NaCl), purified antibody 8.10.3F, or purified antibody 9.14.4I at 0, 1, or 5 mg/kg in a dose volume of 3.79 mL/kg over an approximately 5 minute period. The monkeys were 4 to 9 years of age and weighed 6 to 10 kg. Blood samples for clinical laboratory analysis were collected at 2, 4, 8, 15, 23, and 29 days. Monocyte counts were determined by light scatter using an Abbott Diagnostics Inc. Cell Dyn system (Abbott Park, Illinois).

A decrease in the percentage change in total monocytes at all doses of antibody 8.10.3F and antibody 9.14.4I as compared to pre-test levels of monocytes (Figures 3A and 3B) was observed (see e.g., day 4, 8, 15, and 23 in Figures 3A and 3B).

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5 All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

10 The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

SEQUENCES

Key:

Signal peptide: underlined lower case
 CDRs 1,2,3: underlined UPPERCASE
 5 Variable domain: UPPER CASE
 Constant domain: lower case
 Mutations from germline in bold

10 SEQ ID NO: 1

252 Heavy Chain [Gamma chain] nucleotide sequence

atggagttggggctgtgctggatttcttggctattataaaagggtgccagtgtCAGGTGCAGCTGGTGGAGTCTGG
 GGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGAT
 15 TCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTG
GAGTGGATTTCATACATTAGTGGTAGTGGTAGTACCATATACTACGCAGACTCTGT
GAAGGGCCGATTACCATCTCCAGGGACAACGCCAAGAAGTCACTGTATCTGCAAA
 TGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGCCCTGGG
TGGGATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCTtccaccaaggg
 cccatccgttctccccctggcgccctgctctagaagcacctccgagagcacagcgccctgggctgctgtcaaggactacttccccg
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30 SEQ ID NO: 2

252 Heavy Chain [Gamma chain] protein sequence

melglcwiflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
 EWISYISGSGSTIYYADSVKGFRFTISRDNAKNSLYLQMNSLRAEDTAVYHCARALGGM
 35 DVWGQGTTVTVSSAstkgpsvfplapcsrcstsestaalgclvkdypcpvtvswngaltsgvhtfpavlqssglyslssvv
 tvpsnfgtqtynvdhkpnsntkvdktverkcvecppcpappvagpsvflfppkpkdtlmisrtpevtcvvvdvshedpevqfn
 wyvdgvevhnaktkpreeqfnstfrvsvltvvhqdwlngkeykckvsnkglpapiektisktkgqprepqvytlppsreemtkn
 qvsltelvkgfypsdiavewesngqpennyktpmldsdgsfflyskltvdksrwqqgnvfscsvmhleahnyhtqkslspsgk

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SEQ ID NO: 3

252 Light Chain [Kappa chain] nucleotide sequence

atgagggtcctgctcagctcctggggctcctgctactctggctccgaggtgccagatgtGACATCCAGATGACCCAGT
CTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCA
5 AGTCAGAGCATTAGCGGCTTTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCC
CTAAGCTCCTGATCTATGCTACATCCAGTTTGCAAAGTGGGGTCCCATTCAGGTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGA
AGATTTTGCAACTTATTACTGTCAACAGAGTTACAGTGTCCCATTCACTTTTCGGCCC
10 TGGGACCAAAGTGGATATCAAACGAactgtgctgcacatctgtcttcatcttcccgccatctgatgagcagttga
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t

SEQ ID NO: 4

252 Light Chain [Kappa chain] protein sequence

mrtpaqllgllllwlrgrcDIQMTQSPSSLSASVGDRVTITCRASQSISGFLNWYQQKPKAPKL
LIYATSSLSQSGVPRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSPFTFGPGTKVDIK
Rtvaapsvfifppsdeqlksgtasvcllnnfypreakvqwkvdnalqsgnsqesvteqdsdstyslssltliskadyekkhkvyace
20 vthqglsspvtksfnrgec

SEQ ID NO: 5

88 Heavy Chain [Gamma chain] nucleotide sequence

atggaatttgggctgtgctgggttttccctgtgtctattttagaagggtgtccagtgtGAGGTGCAGCTGGTGGAGTCTGG
25 GGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGAT
TCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTG
GAGTGGGTGGCCAAACATAAAGCAAGATGGAAGTGAGAAATACTATGTGGACTCTG
TGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAA
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30 AGCAGCTGGTAGGGCCTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCTtc
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SEQ ID NO: 6

88 Heavy Chain [Gamma chain] protein sequence

mefglcwvflvailegvqcEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKG
LEWVANIKQDGSEKYYVDSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCAPGIA
5 AAGRAYWGQGTLLTVSSAstkgpsvflapcsrstsestaalgcivkdyfpepvtvswngaltsgvhtfpavlqssgl
yslssvvtvpssnftqtynvdhkpnsntkvdkterkccvecpappvagsvflfppkpkdtlmisrtpevtcvvvdvshed
pevqfnwyvdgvevhnatkpreeqfnstfrvsvltvvhqdwlngkeykckvsnkglpapiektisktkgqprepvytlppsre
emtknqvsltlcvkgfypsdiavewesngqpennykttppmlsdsgsfflyskltvdksrwqqgnvfscsvmhealnhhtqksl
slspgk
10

SEQ ID NO: 7

88 Light Chain [Kappa chain] nucleotide sequence

atgagggtccctgctcagctcctggggctcctgctactctggctccgaggtgccagatgtGACATCCAGATGACCCAGT
CTCCATCCTCCCTGTCTGCATCTGTTGGAGACAGAGTCACCATCACTTGCCGGCCAA
15 GTCAGGACATTAGCAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCCT
AAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATTAAAGGTTTCAG
TGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAG
ATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCATTCACTTTCGGCCCTG
GGACCAAAGTGGATATCAAACGAactgtggctgcaccatctgttctcatcttccgccaatctgatgagcagttgaaat
20 ctggaactgctagcgttgtgtgcctgctgaataacttctatccagagaggccaaagtacagtggaaggtggataacgccctccaatcg
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SEQ ID NO: 8

88 Light Chain [Kappa chain] protein sequence

mrvpaqlglglwlrargcDIQMTQSPSSLSASVGDRTITCRPSQDISSYLNWYQQKPGKAPKL
LIYAASSLQSGVPLRFSGSGSGTDFTLTISLQPEDFATYYCQOSYSTPFTFGPGTKVDIK
Rtvaapsvfifppsdeqlksgtasvvcvlnnfypreakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhkvyace
30 vthqglsspvtksfnrgec

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SEQ ID NO: 9

100 Heavy Chain [Gamma chain] nucleotide sequence

atggagtttgggctccgctggattttcttggctattttaaaagggtgccagtgtGAGGTGCAGCTGTTGGAGTCTGG
GGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGAT
5 TCACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTG
GAATGGGTCTCAGCTATTAGTGGTTCGTGGTGGTAGGACATACTTCGCAGACTCCGT
GAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAA
TGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTTCTGTGCGGTAGAAGGCTA
TAGTGGGCGCTACGGATTTTGTGACTACTGGGGCCAGGGAACCCTAGTCACCGTCT
10 CCTCAGCCccaccaagggeccatcggtcttccccctggcgccctgctetagaagcacctccgagagcacagcggccctggget
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20 caagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccc
tgtctccgggtaaa

SEQ ID NO: 10

100 Heavy Chain [Gamma chain] protein sequence

mefglrwiflvailkgvqcEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMS WVRQAPGKGL
EWVSAISGRGGRTYFADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYFCAVEGYS
25 GRYGGFDYWGQGTLVTVSSAstkgpsvfplapcsrcstsestaaalgclvkdyfpepvtvswngaltsgvhtfpavqls
sglyslssvvtvpssnfgtqtytcnvdhkpstnkvdktverkcvecppcpappvagpsvflfppkpkdtlmisrtpetcvvvdvs
30 hedpevqfnwyvdgvevhnaktkpreeqfnstfrvsvltvvhqdwlngkeykckvsnkglpapiektisktkgprepqvylp
psreemtknqvsltlvkgfypsdiavewesngqpennyktpmldsdgsfflyskltvdksrwqqgnvfscsvmhleahnhyt
qkslspspgk

SEQ ID NO: 11

100 Light Chain [Kappa chain] nucleotide sequence

atggaagccccagctcagcttcttctcctcctgctactctggctcccagataaccactggaGAAATAGTGATGACGCAGT
CTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCC
35 AGTCAGAGTGTTAGCAGCAACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCC
40 CAGGCTCCTCATCTATGGTGCATCCACCAGGGCCAGTGGTATCCCAGACAGGATCA
GTGGCAGTGGGTCTGGAACAGAGTTCACCTCTCATCATCAGCAGCCTGCAGTCTGAA
GATTTTGCAGTTTATTACTGTGACAGTCTAATAACTGGCCATTCACTTTTCGGCCCT
GGGACCAAAGTGGATATCAAACGAactgtggctgcaccatctgtcttcatcttcccccatctgatgagcagttgaa
atctggaactgtagcgttggtgctgctgaataacttctatccagagaggccaaagtacagtggaggtggataacgcctccaatcg
45 gtaactcccagagagtgtagcagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgtgagcaaaagcaga
ctacgagaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgccacaaagagcttcaacaggggagagtg

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SEQ ID NO: 12

100 Light Chain [Kappa chain] protein sequence

meapaqlflflllwlpdttgEIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRL
LIYGASTRASGIPDRISGSGSGTEFTLISSSLQSEDFAVYYCQQSNNWPFTFGPGTKVDIK
5 Rtvaa⁵psvfifppsdeqlksgtasvvc¹⁰llnnfy¹⁵preakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhkvyace
vthqglsspvtksfnrgec

SEQ ID NO: 14

3.8.3 Heavy Chain [Gamma chain] protein sequence

10 mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWFSYISSSGSTIYYADSVKGRFTISRDNAKNSLSLQMNSLRAEDTAVYYCARGLTGD
YWGQGTLLTVSSAstk¹⁵gpsvf²⁰plapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtv
psnfgtqtytcnv²⁵dhkpsntkvdk³⁰verkccvecp³⁵pcpappvagsvflfppkpkdtl⁴⁰misrtpevtcvvvdvshedpevqfnw
yvdgvevhnakt⁴⁵kpreeqfnst⁵⁰frvsvltvvhqdwlngkeykckvsnkglp⁵⁵apiektisktkgqprepvytlppsreemtknqv
15 sltclvk⁶⁰gfypsdiavewesngqpennyk⁶⁵tpmldsdgsfflyskltvdksrwqqgnvfscsvmh⁷⁰ealhnhytqksls⁷⁵lspgk

SEQ ID NO: 16

3.8.3 Light Chain [Kappa chain] protein sequence

20 mdmrvpaqlglflllwfpgsrcDIQMTQSPSSVSASVGDRVTISCRASODISGWLAWYQQKPGKA
PKLLISATSSLHSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQTNSFPFTFGPGTKV
DIKRtva²⁵apsvfifppsdeqlksgtasvvc³⁰llnnfy³⁵preakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhk⁴⁰v
yacevthqglsspvtksfnrgec

SEQ ID NO: 18

2.7.3 Heavy Chain [Gamma chain] protein sequence

30 mefglswvflvallrgcqcQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKG
LEWVAFIWYDGSNKYYADSVKGRFTISRDN³⁵SKNTLYLQMNSLRAEDTAVYYCARGY
RVYFDYWGQGTLLTVSSAstk⁴⁰gpsvf⁴⁵plapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssgl
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slspgk

SEQ ID NO: 20

2.7.3 Light Chain [Kappa chain] protein sequence

40 mdmrvpaqlglflllwfpgsrcDIQMTQSPSSVSASVGDRVTITCRASODISSWLAWYQRKPGKAP
KLQIYAASSLESGVPSRFRNGSGSGTDFTLSISSLQPEDFATYYCQQTNSFPLTFGGGTKV
EIKRtva⁴⁵apsvfifppsdeqlksgtasvvc⁵⁰llnnfy⁵⁵preakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhk⁶⁰v
yacevthqglsspvtksfnrgec

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SEQ ID NO: 22

1.120.1 Heavy Chain [Gamma chain] protein sequence

mewtwsflflvaaatgahsQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQG
LEWMGWISAYNGNTNYAQKLQDRVTMTTDTSTTTAYMELRSLRSDDTAVYYCARRA
5 YGANFFDYWGQGTLVTVSSAstkgpsvfplapcsrcstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqs
sglyslssvvtvpssnfgtqytcnvdhkpstnkvdktverkccecpappvagsvflfppkpdltmisrtpevtcvvdvs
hedpevqfnwyvdgvevhnaktkpreeqfnstfrvsvltvvhqdwlngkeykckvsnkglpapiektisktkgpprepqvytlp
psreemtknqvslclvkgfypsdiavewesngqpennyktpmldsdgsfflyskltvdksrwqqgnvfscsvmhcalhnhyt
10 qkslspsgk

SEQ ID NO: 24

1.120.1 Light Chain [Kappa chain] protein sequence

mvlqtqvflislllwisgaygDIVMTQSPDSLAVSLGERATINCKSSQSILFFSNKNLYLAWYRQKP
15 GQPPNLLIYWASTRESGVPDFRSGSGSGTDFTLTISSLQAEDVAVYYCQOYYSSPWTFG
QGTVKVEIKRtvaapsvfifppsdeqlksgtasvcllnnfypreakvqwkvdnalqsgnsqesvteqskdstylsstltlska
dyekhkvyacevthqglsspvtksfnrgec

SEQ ID NO: 25

9.14.4I Heavy Chain [Gamma Chain] nucleotide sequence

atggagtttgggctgagctgggtttcttctgttgcattataaaaggtgtCCAGTGTCAAGGTGCAGCTGGTGGAGTC
TGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG
GATTCACCTTCAGTGACTACTATATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGA
CTGGAGTGGGTTTCATACATTAGTAGTAGTGGTAGTACCATATACTACGCAGACTC
25 TGTGAAGGGCCGATTACCATCTCCAGGGACAACGCCAAGAACTCACTGTATCTGC
AAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGGCCT
AACTGGGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCTTccaccaaggg
cccatcctcttccccctggcgccctgctctagaagcacctccgagagcacagcgccctgggctgcttgtaaggactacttccccg
aaccggtagcgtgtcgtggaactcaggcgctctgaccagcggtgcacacctccagctgtctacagtcctcaggactctactccc
30 tcagcagcgtggtgacctgcccctccagcaacttcggcacccagacctacacctgcaacgtagatcacaagcccagcaacaccaagg
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aaaacccaaggacacctcatgatctcccgaccctgaggtcacgtgctggtggtagctgagccacgaagaccccaggtcca
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35 agaaaacctatccaaaacaaaggcgagccccgagaaccacaggtgtacacctgccccateccgggaggagatgaccaagaac
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aacgtcttctcatgtctcgtgatgcatgaggtctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa

SEQ ID NO: 26

9.14.4I Heavy Chain [Gamma Chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGLTGD
45 YWGQGTLVTVSSAstkgpsvfplapcsrcstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtv
pssnfgtqytcnvdhkpstnkvdktverkccecpappvagsvflfppkpdltmisrtpevtcvvdvshedpevqfnw
yvdgvevhnaktkpreeqfnstfrvsvltvvhqdwlngkeykckvsnkglpapiektisktkgpprepqvytlppsreemtknqv
slclvkgfypsdiavewesngqpennyktpmldsdgsfflyskltvdksrwqqgnvfscsvmhcalhnhytqkslspsgk

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SEQ ID NO: 27

9.14.4, 9.14.4I, 9.14.4-Ser and 9.14.4-G1 Light Chain [Kappa Chain] nucleotide sequence

atggacatgaggggtccccgctcagctcctggggctcctgctactctggctccgaggtgccagatg TGACATCCAGATGAC
CCAGTCTCCATCCTCCCTGTCTGCATCTGTTCGGAGACAGAGTCAACCATCACTTGCCG
5 GCCAAGTCAGATCATTAGCAGTTTATTAAATTGGTATCAGCAGAAACCAGGGAAAG
CCCCTAAGCTCCTGATCCATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGG
TTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGTAGTCTGCAACC
TGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCATTCACCTTTCGG
CCCTGGGACCAAAGTGGATATCAAACGA actgtggctgcaccatctgtcttcatcttcccgccatctgatgagca
10 gttgaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtgggaaggtgataacgccctcc
aatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcacctgacgtgagcaaag
cagactacgagaaacacaaagtctacgcctgcgaagtcaccatcagggcctgagctgccccgcacaaagagcttaacaggggaga
gtgt

SEQ ID NO: 28

9.14.4, 9.14.4I, 9.14.4-Ser and 9.14.4-G1 Light Chain [Kappa Chain] protein sequence

mdmrvpaqlglglwlrgrc DIQMTQSPSSLSASVGDRTITCRPSQIISLLN WYQQKPKGKAPK
LLIHAASSLQSGVPSRFSGSGSGTDFLT ISSLPEDFATYYCQSYSTPFTFGPGTKVDI
20 KRtvaapsvfifppsdeqlksgtasvcllnfybreakvqwkvdnalqsgnsqesvteqdsdstylsstltlskadyekhkvy
cevtqglsspvtksfnrgec

SEQ ID NO: 37

9.14.4 Heavy Chain [Gamma Chain] nucleotide sequence

atggagttlgggctgagctgggttttcttctgtgctattataaaagggtg CCAGTGTCAAGGTGCAGCTGGTGGAGTC
TGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG
GATTCACCTTCAGTGACTACTATATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGA
CTGGAGTGGGTTTCATACATTAGTAGTAGTGGTAGTACCATATACTACGCAGACTC
30 TGTGAAGGGCCGATTACCATCTCCAGGGACAACGCCAAGAACTCACTGTATCTGC
AAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGGCCT
AACTGGGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCT tccaccaaggg
cccatccgtcttccccctggcgccctgctctagaagcacctccgagagcacagcgccctgggctgctgtgtaaggactacttccccg
aaccggtagcgggtgctgtggaactcagcgctctgaccagcggcgtgcacaccttcccagctgtctacagtcctcaggactctactccc
35 tcagcagcgtggtgacctgcccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaaggt
ggacaagagagltgagtcacaaataggtcccccatgccatcatgccagcacctgagttcctggggggaccatcagttcttctgttcccc
ccaaaacccaaggacactctcatgatctcccggaccctgaggtcacgtgcgtggtggtggacgtgagccaggaagaccccagggtcc
agttcaactggtacgtggatggcgtggaggtgcataatgccaaagacaaagccgaggaggagcagttcaacagcacgtaccgtgtggt
cagcgtctcaccgtcctgcaccaggactggtgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgctctccatcg
40 agaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacacctgcccccatcccaggaggagatgaccaagaac
caggtcagcctgacctgcctgtgcaaaaggcttaccaccagcgacatcgccgtggagtgaggagagcaatgggcagccggagaacaact
acaagaccacgcctcccgctgctggactccgacggctccttctctacagcaggctaaccgtggacaagagcaggtggcaggaggg
gaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtctccgggtaaa

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SEQ ID NO: 38

9.14.4 Heavy Chain [Gamma Chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARGLTGD
5 YWGQGTLVTVSSAstkgpsvflapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtv
pssslgktytcnvdhkpntkvdkrveskygppcpapeflggpsvflfppkpkdtlmsrtpevtcvvvdvsqedpevfqnw
yvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiectiskakgqprepvytlppsqeemtknq
vsltlvkgfypsdiavewesngqpennykttppvldsdgsfflysrltvdksrwqegnvfscsvmhealhnhytqkslslspgk

SEQ ID NO: 54

9.14.4C-Ser Heavy Chain [Gamma chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARGLTGD
15 YWGQGTLVTVSSAstkgpsvflapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtv
pssslgktytcnvdhkpntkvdkrveskygppcpapeflggpsvflfppkpkdtlmsrtpevtcvvvdvsqedpevfqnw
yvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiectiskakgqprepvytlppsqeemtknq
vsltlvkgfypsdiavewesngqpennykttppvldsdgsfflysrltvdksrwqegnvfscsvmhealhnhytqkslslspgk

SEQ ID NO: 56

9.14.4C-Ser, 9.14.4-CG2 and 9.14.4-CG4 Light Chain [Kappa chain] protein sequence

mdmrvpaqlglglwlrargcDIQMTQSPSSLSASVGDRVTITCRPSQIISLLNWYQQKPGKAPK
LLIYAASSLQSGVPSRFRSGSGSGTDFTLTTISSLOPEDFATYYCQQSYSTPFTFGPGTKVDI
25 KRtvaapsvfifppsdeqlksgtasvvcllnnfyreakvqwkdnalqsgnsqesvteqdskdstyslssltliskadyekhkvyva
cevthqglsspvtksfnrgec

SEQ ID NO: 74

9.14.4-CG2 Heavy Chain [Gamma chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARGLTGD
30 YWGQGTLVTVSSAstkgpsvflapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtv
pssnfgtqtytcnvdhkpntkvdkterkccvecppcpappvagpsvflfppkpkdtlmsrtpevtcvvvdvshedpevfqnw
35 yvdgvevhnaktkpreeqfnstfrvvsvltvvhqdwlngkeykckvsnkglpapiektisktkgqprepvytlppsreemtknq
sltlvkgfypsdiavewesngqpennykttppmldsdgsfflysrltvdksrwqqgnvfscsvmhealhnhytqkslslspgk

SEQ ID NO: 78

9.14.4-CG4 Heavy Chain [Gamma chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARGLTGD
40 YWGQGTLVTVSSAstkgpsvflapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtv
pssslgktytcnvdhkpntkvdkrveskygppcpapeflggpsvflfppkpkdtlmsrtpevtcvvvdvsqedpevfqnw
45 yvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiectiskakgqprepvytlppsqeemtknq
vsltlvkgfypsdiavewesngqpennykttppvldsdgsfflysrltvdksrwqegnvfscsvmhealhnhytqkslslspgk

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SEQ ID NO: 82

9.14.4-Ser Heavy Chain [Gamma chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGLTGD
YWGQGTLVTVSSAstkgpsvflapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtv
pssslgtkytencvdkhpsntkvdkrveskygppcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnw
yvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepvytlppsqeemtknq
vsltlvkgfypsdiavewesngqpennykttppvldsdsfflysrltvdksrwqegnvfscsvmhleahnhytqkslspsgk

SEQ ID NO. 101

9.14.4G1 Heavy chain (gamma chain) nucleotide sequence

atggagtttgggctgagctgggtttcttctgtgctattataaaaggtgtccagtgtCAGGTGCAGCTGGTGGAGTCTGG
GGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGAT
TCACCTTCAGTGACTACTATATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGACTG
GAGTGGGTTTCATACATTAGTAGTAGTGGTAGTACCATATACTACGCAGACTCTGT
GAAGGGCCGATTACCATCTCCAGGGACAACGCCAAGAAGTCACTGTATCTGCAAA
TGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGGCCTAAC
TGGGGACTACTGGGGCCAGGGAACCCCTGGTCACCGTCTCCTCAGCTiccaccaagggcccat
cggctctccccctggcaccctctccaagagcacctctgggggcacagcgccctgggctgctggtcaaggactactccccgaaccg
gtgacgggtgctgtggaactcaggcgccctgaccagcggcggtgcacacctccccggctgtcctacagtcctcaggactctactccctcagc
agcgtgggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggaca
agaaagttgagcccaaatctgtgacaaaactcacatgccaccgtgccagcacctgaactctggggggaccgtcagttctctctt
ccccccaaaacccaaggacacctcatgatctcccgaccctgaggtcacatgcgtggtgggtggacgtgagccacgaagacctgag
gtcaagttcaactggtacgtggacggcggtggaggtgcataatgccaagacaaagccgcgaggagcagtagaacagcacgtaccgt
gtggtcagcgtcctcaccgtctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacacctgccccatccccgggatgagctgaccaa
gaaccaggtcagcctgacctgctgtaaggtctatcccagcgacatcgccgtggagtgaggagcaatgggcagccggagaa
caactacaagaccagcctcccgctgctggactccgagggctctctctctacagcaagctaccgtggacaagagcaggtggcagc
aggggaacgtctctcatgctcctgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaatag

SEQ ID NO 102

9.14.4G1 Heavy chain (gamma chain) protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGLTGD
YWGQGTLVTVSSAstkgpsvflapsskstsggtaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvt
vpssslgtqtyicnvnhkpsntkvdkkvepkscdkthtppcpapellggpsvflfppkpkdtlmisrtpevtcvvvdvshdpevk
fnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkalpapiektiskakgqprepvytlppsrdehtk
nqvsltlvkgfypsdiavewesngqpennykttppvldsdsfflyskltvdksrwqqgnvfscsvmhleahnhytqkslspsgk

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SEQ ID NO: 29

8.10.3 and 8.10.3F Heavy Chain [Gamma chain] nucleotide sequence

atggagttgggctgtgctgggttttctgttgctatttagaaggtgtccagtgtGAGGTGCAGCTGGTGGAGTCTGG
5 GGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGAT
TCACCTTCAGTAGTTTTAGTATGACCTGGGTCCGCCAGGCTCCAGGAAAGGGGCTG
GAGTGGGTTTCATACATTAGTAGTAGAAGTAGTACCATATCCTACGCAGACTCTGT
GAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAACTCACTGTATCTGCAAA
10 TGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTACTGTGCGAGAGATCCTCTT
CTAGCGGGAGCTACCTTCTTTGACTACTGGGGGCCAGGGAACCCTGGTCACCGTCTC
CTCAGCCtccaccaagggcccatcggtcttccccctggcgccctgtccaggagcacctccgagagcacageggccctgggctg
cctggtaaggactacttccccgaaccgggtgacgggtgctgtggaactcaggcgctctgaccagcggcggtgcacaccttccagctgtcct
acagtctcaggacttactccctcagcagcgtggtgaccgtgcccctccagcaacttcggcaccagacctacacctgcaacgtagatca
caagcccagcaacaccaaggtggacaagacagtlgagcgcaaatgttgtgtcagtgcccaccgtgccagcaccacctgtggcagga
15 ccgtcagttcttcttcccccaaaaaccaagacacctcatgatctccggaccctgaggtcacgtgcgtggtggtggacgtgagc
cacgaagacccccgaggtccagttcaactggtacgtggacggcggtggaggtgcataatgccaagacaaagccacgggaggagcagttc
aacagcacgttccgtgtggtcagcgtctcaccgttgtgcaccaggactggctgaacggcaaggagtacaagtgaaggtctcaacaa
aggcctccagcccccatcgagaaaacctctccaaaaccaagggcagccccgagaaccacaggtgtacacctgccccatccccg
ggaggagatgaccaagaaccaggtcagcctgacctgctggtcaaaggcttctaccccagcgacatcgccgtggagtgaggagagcaat
20 gggcagccggagaacaactacaagaccacacctcccatgctggactccgacggctccttctctctacagcaagctcaccgtggacaa
gagcaggtggcagcaggggaacgtcttctcatgctcgtgatgcagggctctgcacaaccactacacgcagaagagcctctccctgt
ctccgggtaaa

SEQ ID NO: 30

8.10.3 and 8.10.3F Heavy Chain [Gamma chain] protein sequence

melglcwvflvailegvqcEVQLVESGGGLVQPGGSLRLSCAASGFTFSSFSMTWVRQAPGKGL
EWVSYISSRSSTISYADSVKGRFTISRDNANKNSLYLQMNSLRDEDTA VYYCARDPLLA
30 GATFFDYWGQGTLLTVSSAstkgpsvflapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssg
lylssvvtvpssnfgtqytncvndhkpnsntkvdktverkecveppcpappvagpsvflfppkpkdtlmisrtpevtcvvvdvshe
dpevqfnwyvdgvevhnaktkpreeqfnstfrvsvltvvhqdwlngkeyckvsnkglpapiektisktkgqprepvytlppsr
eemtqnqvsltclvkgyfypsdiavewesngqpennyktpmldsdgsfflyskltvdksrwqqgnvfscsvmhcalhnhytqks
lslspgk

SEQ ID NO: 31

8.10.3FG1 and 8.10.3F Light Chain [Kappa chain] nucleotide sequence

atggaacccccagcgcagcttcttctctctgctactctggctcccagataccaccggaGAATTTGTGTTGACGCAGT
CTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGGCC
40 AGTCAGAGTGTTAGCAGCAGTTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGC
TCCCAGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGT
TCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCT
GAAGATTTTGCAGTGTATTACTGTGTCAGCAGTATGGTAGCTCACCTCTCACTTTCGGC
GGAGGGACCAAGGTGGAGATCAAACGAactgtggctgcaccatctgttctcatcttcccgcctctgatgagca
45 gttgaaatctggaactgcctctgttgtgctgctgaataactctatcccagagaggccaaagtacagtgaaggtggataacgccctcc
aatcgggtaactcccaggagagtgctacagagcaggacagcaaggacagcacctacagcctcagcagcacctgacgtgagcaaaag
cagactacgagaaacacaaagctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggaga
gtgt

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metpaqlflflllwlpdttgEiVLTQSPGTLSPGGERATLSCRASQSVSSSYLAWYQQKPGQAPRL
LIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIK
Rtvaapsvfifppsqdeqlksgtasvcllnfyfreakvqwkvdnalqsgnsqesvteqskdstyslsstltlskadyekhkvyace
vthqglsspvtksfnrgec

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SEQ ID NO: 62

8.10.3-CG2 Heavy Chain [Gamma chain] protein sequence

melglcwvflvailegvqcEVQLVESGGGLVQPGGSLRLSCAASGFTFSFSMTWVRQAPGKGL
EWVSYISSRSSTISYADSVKGRFTISRDNANKNSLYLQMNSLRDEDTAVYYCARD**DPLLA**
5 GATFFDYWGQGTLVTVSSAstkgpsvfplapcsrcstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssg
lylssvvtvpssnfgtqytcnvdhkpntkvdkverkccepcppappvagpsvflfppkpkdtlmisrtpevtcvvvdvshe
dpevqfnwyvdgvevhnaktkpreeqfnstfrvsvltvvhqdwlngkeykckvsnkglpapiektisktkgqprepvytlpps
eemtknqvsltclvkgyfypsdiavewesngqpennykttpmldsdgsfflyskltvdksrwqqgnvfscsvmhealhnhytqks
10 lslspgk

SEQ ID NO: 90

8.10.3-Ser Heavy Chain [Gamma chain] protein sequence

melglcwvflvailegvqcEVQLVESGGGLVQPGGSLRLSCAASGFTFSFSMTWVRQAPGKGL
15 EWVSYISSRSSTISYADSVKGRFTISRDNANKNSLYLQMNSLRDEDTAVYYCARD**DPLLA**
GATFFDYWGQGTLVTVSSAstkgpsvfplapcsrcstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssg
lylssvvtvpssslgtktytcnvdhkpntkvdkrveskygppcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqe
dpevqfnwyvdgvevhnaktkpreeqfnstyrvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepvytlpps
qeemtknqvsltclvkgyfypsdiavewesngqpennykttpvldsdgsfflysrvtvdksrwqegnvfscsvmhealhnhytqks
20 lslspgk

SEQ ID NO: 94

8.10.3-CG4 Heavy Chain [Gamma chain] protein sequence

25 melglcwvflvailegvqcEVQLVESGGGLVQPGGSLRLSCAASGFTFSFSMTWVRQAPGKGL
EWVSYISSRSSTISYADSVKGRFTISRDNANKNSLYLQMNSLRDEDTAVYYCARD**DPLLA**
GATFFDYWGQGTLVTVSSAstkgpsvfplapcsrcstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssg
lylssvvtvpssslgtktytcnvdhkpntkvdkrveskygppcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqe
dpevqfnwyvdgvevhnaktkpreeqfnstyrvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepvytlpps
30 qeemtknqvsltclvkgyfypsdiavewesngqpennykttpvldsdgsfflysrvtvdksrwqegnvfscsvmhealhnhytqks
lslspgk

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SEQ ID NO: 97

8.10.3FG1 Heavy Chain nucleotide sequence

atggagttggggctgagctgggttttcttggtgctattataaaagggtccagtgtGAGGTGCAGCTGGTGGAGTCTG
GGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA
5 TTCACCTTCAGTAGTTTTAGTATGACCTGGGTCCGCCAGGCTCCAGGAAAGGGGCT
GGAGTGGGTTCATACATTAGTAGTAGAAGTAGTACCATATCCTACGCAGACTCTG
TGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAACTCACTGTATCTGCAA
ATGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTACTGTGCGAGAGATCCTCT
10 TCTAGCGGGAGCTACCTTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCT
CCTCAGCCtccaccaaggggcccatcggttctccccctggcaccctctccaagagcacctctgggggcacageggccctgggt
gcttggtcaaggactacttccccgaaccggtgacggtgctgtggaactcagcgccctgaccageggcgtgcacacctccccgctgtc
ctacagtctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcaccagacctacatctgcaacgtgaat
cacaagcccagcaacaccaagggtggacaagaaagttgagcccaaatctgtgacaaaactcacacatgccaccgtgccagcacctg
aactctggggggaccgtcagtcttctcttcccccaaaacccaaggacacctcatgatctccggaccctgaggtcacatgctgtg
15 tgggtggacgtgagccacgaagaccctgaggtcaagtcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcg
ggaggagcagtagaacagcacgtaccgtgtggtcagcgtcctcaccgtctgcaccaggactggctgaatggcaaggagtacaagtgc
aaggtctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacacc
ctgcccccatccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtaaaaggcttctatcccagegacatcgccgtgga
gtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgctgctggactccgacggctcttcttctctacagcaag
20 ctaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaa
gagcctctccctgtctccgggtaaatag

SEQ ID NO: 98

8.10.3FG1 Heavy chain (gamma chain) protein sequence

melglcwwflvailegvqcEVQLVESGGGLVQPGGSLRLSCAASGFTFSSFSMTWVRQAPGKGL
EWVSYISSRSSTISYADSVKGRFTISRDNANKNSLYLQMNSLRDEDTAVYYCARD**DPLLA**
GATFFDYWGQGTLVTVSSAstkgpsvflapsskstsggtaalglvkdypcpvtvswngaltsgvhtfpavqlss
glyslssvvtvpssslgtqtienvnhkpsntkvdkkvepkscdkthtppcpapellggpsvflfppkpkdtlmisrtpevtcvvvd
30 vshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeykckvsnkalpapiektiskakgqprepvy
tlppsrdeitknqvslclvkgyfypsdiavewesngqpennyktpvldsdgsfflyskltvdksrwqqgnvfscsvmhealnhhy
tqkslspsgk

SEQ ID NO: 33

9.7.2IF Heavy Chain [Gamma chain] nucleotide sequence

5 atggagtttgggctgagctgggttttcttgttgcattataaaagggtgccagtgtcAGGTGCAGCTGGTGGAGTCTGG
GGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGAT
TCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTG
GAGTGGGTTTCATACATTAGTAGTAGTGGTAGTACCATATACTACGCAGACTCTGT
GAAGGGCCGATTCAACATCTCCAGGGACAACGCCAAGAATTCAGTGTATCTGCAAA
TGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGGCGTATAGG
10 AGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCTtcaccaaggg
cccatccgtctccccctggcgccctgctctagaagcacctccgagagcacagcgccctgggctgcttgtaaggactacttccccg
aacccgtgacggtgtctggaactcaggegtctgaccagcggtgcacacctccagctgtctacagtcctcaggactctactccc
tcagcagcgtggtgaccgtgcccctccagcaacttcggcaccagacctacacctgcaacgtagatcacaagcccagcaacaccaaggt
ggacaagacagttgagcgcaaatgtgtgtagtgcccaccgtgcccagcaccacctgtggcaggaccgtcagtttcttcttcccc
15 aaaaaccaaggacacctcatgatctccccgaccctgaggtcacgtgctggtggtggacgtgagccacgaagaccccaggtcca
gttcaactggtacgtggacggcgtggaggtgcataatgccaagacaagccacgggaggagcagttcaacagcacgttccgtgtggtc
agcgtcctcaccgttgtgaccaggactggctgaacggcaaggagtacaagtgaaggttccaacaaggcctccagccccatcg
agaaaaccatctccaaaaccaaaagggcagccccgagaaccacaggtgtacacctgccccatccccgggaggagatgaccaagaac
caggtcagcctgacctgcctggtcaaaggcttctaccccagcgacatcgccgtggagtgaggagcaatgggcagccggagaacaact
acaagaccacacctccatgctggactccgacggctccttctctacagaagctcaccgtggacaagagcaggtggcagcagggg
20 aacgtcttctcatgctccgtgatgcatgaggtctgcacaaccactacacgcagaagagcctctcctgtctccgggtaaa

SEQ ID NO: 34

9.7.2IF Heavy Chain [Gamma Chain] protein sequence

25 mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARRIGGM
DVWGQGTTVTVSSAstkgpsvfplapcsrstsestaalgclvdyfpepvtvswngaltsgvhtfpavlqssglyslssvv
tvpsnfgtqtytenvdhkpnsntkvdkterkccveppcpappvagpsvflfppkpkdtlmisrtpetvvdvshedpevqfn
wyvdgvevhnaktkpreeqfnstfrvsvltvvhqdwlngkeykckvsnkglpapiektisktkgqprepqvylppsreemtkn
30 qvsltelvkgfypsdiavewesngqpennyktpmldsdgsfflyskltvdksrwqqgnvfscsvmhealhnhytqkslspsgk

SEQ ID NO: 35

9.7.2IF Light Chain [Kappa chain] nucleotide sequence

35 atggacatgaggggtccccgctcagctcctggggctcctgctactctggctccgaggtgccagatgtGACATCCAGATGACC
CAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCCGG
GCAAGTCAGAGCATTAGCGGCTTTTAAATTTGGTATCAGCAGAGACCAGGGAAGC
CCCTAAGCTCCTGATCTATGCTACATCCAGTTTACAAAGTGGGGTCCCATCAAGGTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTG
40 AAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCAATTCATTTTCGGCC
CTGGGACCAAAGTGGATATCAAACGAactgtggtgcaccatctgtcttcatcttcccgcacatctgatgagcagtt
gaaatctggaactgectctgtgtgctgctgaataacttctatcccagagaggccaaagtacagtggagggtgataacgccctccaat
cgggtaactcccaggagagtgctacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgtgagcaaaagca
gactacgagaaacaaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcctgcacaaagagcttcaacaggggagagt
45 gt

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SEQ ID NO: 36

9.7.2IF Light Chain [Kappa chain] protein sequence

mdmrvpaqllgllllwlrgarcDIQMTQSPSSLSASVGDRVTITCRASQSISGFLIWYQQRPGKAPK
LLIYATSSLOSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQOQSYSTPFTFGPGTKVDI
5 KRtvaapsvfifppsdeqlksgtasvvcllnnfybreakvqwkvdnalqsgnsqesvteqdskdstyslstltskadyekhkvyv
cevtqhglsspvtksfnrgec

SEQ ID NO: 45

9.7.2 Heavy Chain [Gamma chain] nucleotide sequence

atggagtttgggctgagctgggttttcctgttgcattataaaagggtgccagtgtcAGGTGCAGCTGGTGGAGTCTGG
GGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGAT
TCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTG
GAGTGGGTTTCATACATTAGTAGTAGTGGTAGTACCATATACTACGCAGACTCTGT
15 GAAGGGCCGATTACCATCTCCAGGGACAACGCCAAGAATTCACTGTATCTGCAAA
TGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGGCCGTATAGG
AGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCTtccaccaaggg
ccatccgtcttccccctggcgccctgctctagaagcacctccgagagcacagcgccctgggctgcctggtcaaggactacttccccg
aaccggtgacggtgctgctggaactcaggcgctctgaccagcggcggtgcacaccttccagctgtcctacagtcctcaggactctactccc
20 tcagcagcgtggtgaccgtgccccccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaaggt
ggacaagagagtgtagtccaaatatggtcccccatgccatcatgccagcacctgagttcctggggggaccatcagttcttctgttcccc
ccaaaacccaaggacactctcatgatctccccggaccctgaggtcacgtgcgtggtgggtggacgtgagccaggaagaccccagaggtcc
agttcaactggtacgtggatggcggtggaggtgcataatgccaaagacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggt
cagcgtctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgtctccatcg
25 agaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacacctgcccccatccaggaggagatgaccaagaac
caggtcagcctgacctgcctgggtcaaaggcttctaccccagcgacatcgccgtggagtgaggagcaatgggcagccggagaaact
acaagaccacgcctcccgtgctggactccgacggctccttctctacagcaggctaaccgtggacaagagcaggtggcaggaggg
gaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacagaagagcctctcctgtctccgggtaaa

SEQ ID NO: 46

9.7.2 Heavy Chain [Gamma Chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARRIGGM
35 DVWGQGTTVTVSSAstkgpsvfplapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvv
tvpssslgtktytcnvdhkpsntkvdkrveskygppcpsepapeflggpsvflfppkpkdtlmisrtevtcvvvdvsqedpevqfn
wyvdgvevhnaktkpreeqfnstyrvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqvylppsqeemtkn
qvsltelvkgfypsdiavewesngqpennykttpvldsdgsfflysrltvdksrwqegnvfscsvmhcalnhhtqkslsispk

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SEQ ID NO: 47

9.7.2 and 9.7.2-Ser Light Chain [Kappa chain] nucleotide sequence

atggacatgaggggtccccgctcagctcctggggctcctgctactctggctccgaggtgccagatgtGACATCCAGATGACC
CAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGG
5 GCAAGTCAGAGCATTAGCGGCTTTTAAATTTGGTATCAGCAGAGACCAGGGGAAAGC
CCCTAAGCTCCTGATCTATGCTACATCCAGTTTACAAAGTGGGGTCCCATTAAAGGTT
CAGTGGCAGTGAATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTG
AAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCATTCACCTTCGGCC
10 CTGGGACCAAAGTGGATATCAAACGAactgtggctgcaccatctgttctccttcccgccatctgatgagcagtt
gaaatctggaactgcctctgtgtgtgcctgctgaataacttctatccagagaggccaaagtacagtgggaaggtggataacgacctccaat
cgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagca
gactacgagaaacacaaagtctacgctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttaacaggggagagt
gt

SEQ ID NO: 48

9.7.2 and 9.7.2-Ser Light Chain [Kappa chain] protein sequence

mdmrvpaqlglglwlgarcDIQMTQSPSSLSASVGDRVTITCRASQISGFLIWYQQRPGKAPK
LLIYATSSLQSGVPLRFSGSESGTDFTLTISSLQPEDFATYYCQOQSYSTPFTFGPGTKVDI
20 KRtvaapsvfifppsdeqlksgtasvcllnfybreakvqwkvdnalqsgnsqesvteqdsdstylsstltlskadyekhhkvy
cevtqglsspvtksfnrgec

SEQ ID NO: 50

9.7.2C-Ser Heavy Chain [Gamma chain] protein sequence

25 mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCAIRIGGMD
VWGQGTTVTVSSAstkgpsvfplapcsrcstestaalglvkdypfepvtvswngaltsgvhtfpavlqssglyslssvvtv
pssslgtktytcnvdhkpnsntkvdkrveskygppeppcpapeflggpsvflfppkpkdtlmsrtpevtcvvdvsqedpevfqnw
yvdgvevhnaktkpreeqfnstyrvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepvytlppsqeemtknq
30 vslclvkgyfypsdiavewesngqpennykttpvldsdgsfflysrlytdksrwqegnvfscsvmhcalhnhytqkslsispkg

SEQ ID NO: 52

9.7.2C-Ser, 9.7.2-CG2 and 9.7.2-CG4 Light Chain [Kappa chain] protein sequence

35 mdmrvpaqlglglwlgarcDIQMTQSPSSLSASVGDRVTITCRASQISGFLIWYQQKPGKAPK
LLIYATSSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQOQSYSTPFTFGPGTKVDI
KRtvaapsvfifppsdeqlksgtasvcllnfybreakvqwkvdnalqsgnsqesvteqdsdstylsstltlskadyekhhkvy
cevtqglsspvtksfnrgec

SEQ ID NO: 66

9.7.2-CG2 Heavy Chain [Gamma chain] protein sequence

40 mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCAIRIGGMD
VWGQGTTVTVSSAstkgpsvfplapcsrcstestaalglvkdypfepvtvswngaltsgvhtfpavlqssglyslssvvtv
45 pssnfgtqtytcnvdhkpnsntkvdktkvercccveppcpappvagpsvflfppkpkdtlmsrtpevtcvvdvshedpevfqnw
yvdgvevhnaktkpreeqfnstfrvsvltvvhqdwlngkeykckvsnkglpapiektisktkgqprepvytlppsreemtknqv
sltclvkgyfypsdiavewesngqpennyktpmldsdgsfflyskltvdksrwqqgnvfscsvmhcalhnhytqkslsispkg

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SEQ ID NO: 70

9.7.2-CG4 Heavy Chain [Gamma chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARRIGGMD
5 VWGQGTTVTVSSAstkgpsvfplapcsrcstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvtv
pssslgtktytcnvdhkpntkvdkrveskygppcpapeflggpsvflfppkpkdtlmisrtpvtecvvdvsqedpevqfnw
yvdgvevhnaktkpreeqfnstyrvsvltvlhqdwlngkeykckvsnkglpssiectiskakgqprepvytlppsqeemtknq
vsltlvkgfypsdiavewesngqpennykttpvldsdgsfflysrltvdksrwqegnvfscsvmhealhnhytqkslsispkg

10 SEQ ID NO: 86

9.7.2-Ser Heavy Chain [Gamma chain] protein sequence

mefglswvflvaiikgvqcQVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGL
EWVSYISSSGSTIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARRIGGM
15 DVWGQGTTVTVSSAstkgpsvfplapcsrcstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssv
tvpssslgtktytcnvdhkpntkvdkrveskygppcpapeflggpsvflfppkpkdtlmisrtpvtecvvdvsqedpevqfn
wyvdgvevhnaktkpreeqfnstyrvsvltvlhqdwlngkeykckvsnkglpssiectiskakgqprepvytlppsqeemtkn
qvsltlvkgfypsdiavewesngqpennykttpvldsdgsfflysrltvdksrwqegnvfscsvmhealhnhytqkslsispkg

The claims defining the invention are as follows:

1. A human monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion blocks binding to *c-fms* and binds to M-CSF with a K_D of 1.0×10^{-7} M or less.
2. A human monoclonal antibody 8.10.3F or an antigen-binding portion thereof that specifically binds to M-CSF.
3. A human monoclonal antibody 9.14.4I or an antigen-binding portion thereof that specifically binds to M-CSF.
4. A human monoclonal antibody or an antigen-binding portion thereof that binds specifically to and inhibits human M-CSF, wherein the antibody or portion has at least one property selected from the group consisting of:
 - a) cross-competes for binding to M-CSF with an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1;
 - b) competes for binding to M-CSF with an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1;
 - c) binds to the same epitope of M-CSF as an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1;
 - d) binds to M-CSF with substantially the same K_D as an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1; and

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e) binds to M-CSF with substantially the same off rate as an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1.

5. A monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody is selected from the group consisting of:

- a) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 2 and the light chain amino acid sequence set forth in SEQ ID NO: 4 without the signal sequences;
- b) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 6 and the light chain amino acid sequence set forth in SEQ ID NO: 8 without the signal sequences;
- c) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 10 and the light chain amino acid sequence set forth in SEQ ID NO: 12 without the signal sequences;
- d) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 14 and the light chain amino acid sequence set forth in SEQ ID NO: 16 without the signal sequences;
- e) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 18 and the light chain amino acid sequence set forth in SEQ ID NO: 20 without the signal sequences;
- f) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 22 and the light chain amino acid sequence set forth in SEQ ID NO: 24 without the signal sequences;
- g) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 26 and the light chain amino acid sequence set forth in SEQ ID NO: 28 without the signal sequences;
- h) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 38 and the light chain amino acid sequence set forth in SEQ ID NO: 28 without the signal sequences;

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- i) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 54 and the light chain amino acid sequence set forth in SEQ ID NO: 56 without the signal sequences;
- j) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 74 and the light chain amino acid sequence set forth in SEQ ID NO: 56 without the signal sequences;
- k) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 78 and the light chain amino acid sequence set forth in SEQ ID NO: 56 without the signal sequences;
- l) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 82 and the light chain amino acid sequence set forth in SEQ ID NO: 28 without the signal sequences;
- m) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 102 and the light chain amino acid sequence set forth in SEQ ID NO: 28 without the signal sequences;
- n) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30 and the light chain amino acid sequence set forth in SEQ ID NO: 32 without the signal sequences;
- o) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30 and the light chain amino acid sequence set forth in SEQ ID NO: 44 without the signal sequences;
- p) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 58 and the light chain amino acid sequence set forth in SEQ ID NO: 60 without the signal sequences;
- q) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 62 and the light chain amino acid sequence set forth in SEQ ID NO: 60 without the signal sequences;
- r) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 90 and the light chain amino acid sequence set forth in SEQ ID NO: 44 without the signal sequences;
- s) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 94 and the light chain amino acid sequence set forth in SEQ ID NO: 60 without the signal sequences;

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- t) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 98 and the light chain amino acid sequence set forth in SEQ ID NO: 32 without the signal sequences;
- u) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 34 and the light chain amino acid sequence set forth in SEQ ID NO: 36 without the signal sequences;
- v) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 46 and the light chain amino acid sequence set forth in SEQ ID NO: 48 without the signal sequences;
- w) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 50 and the light chain amino acid sequence set forth in SEQ ID NO: 52 without the signal sequences;
- x) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 66 and the light chain amino acid sequence set forth in SEQ ID NO: 52 without the signal sequences;
- y) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 70 and the light chain amino acid sequence set forth in SEQ ID NO: 52 without the signal sequences; and
- z) an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 86 and the light chain amino acid sequence set forth in SEQ ID NO: 48 without the signal sequences.

6. A monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises:

- a) a heavy chain comprising the heavy chain CDR1, CDR2 and CDR3 of an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1; or
- b) the heavy chain of a) and a light chain comprising the light chain CDR1, CDR2 and CDR3 of the selected antibody.

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7. A monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises:
- a) a heavy chain comprising the amino acid sequence from the beginning of the CDR1 through the end of the CDR3 of the heavy chain of an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1; or
 - b) the heavy chain of a) and a light chain comprising the amino acid sequence from the beginning of the CDR1 through the end of the CDR3 of the selected antibody.
8. The monoclonal antibody or antigen-binding portion according to claim 7, wherein the antibody or portion comprises:
- a) a heavy chain variable domain (V_H) amino acid sequence of an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1; or
 - b) the V_H amino acid sequence of a) and a light chain variable domain (V_L) amino acid sequence of the selected antibody.
9. The monoclonal antibody or antigen-binding portion according to claim 6, wherein the antibody or portion comprises any one or more of the FR1, FR2, FR3 and FR4 amino acid sequences of an antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1; wherein the CDR and FR amino acid sequences are selected from the same antibody.
10. The human monoclonal antibody or antigen-binding portion according to claim 1, wherein the antibody or portion comprises:

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- a) a heavy chain amino acid sequence of a monoclonal antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, and 9.14.4G1, without the signal sequence; or
- b) the heavy chain amino acid sequence of a) and a light chain amino acid sequence of the selected monoclonal antibody.

- 11. A monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a light chain comprising SEQ ID NO: 32 and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a heavy chain comprising SEQ ID NO: 30.
- 12. A monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the heavy chain variable domain of antibody 8.10.3F and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the light chain variable domain of antibody 8.10.3F.
- 13. A monoclonal antibody that specifically binds to M-CSF, wherein the heavy chain amino acid sequence of said antibody is SEQ ID NO: 30 without the signal sequence, and the light chain amino acid sequence of said antibody is SEQ ID NO: 32 without the signal sequence.
- 14. A monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a light chain comprising SEQ ID NO: 28 and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a heavy chain comprising SEQ ID NO: 26.
- 15. A monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the heavy chain variable domain of antibody

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9.14.4I and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the light chain variable domain of antibody 9.14.4I.

16. A monoclonal antibody that specifically binds to M-CSF, wherein the heavy chain amino acid sequence of said antibody is SEQ ID NO: 26 without the signal sequence, and the light chain amino acid sequence of said antibody is SEQ ID NO: 28 without the signal sequence.

17. The monoclonal antibody or antigen-binding portion according to claim 1 or 10, wherein the C-terminal lysine of the heavy chain of the antibody or portion is not present.

18. The monoclonal antibody or antigen-binding portion according to any one of claims 2 to 9, 11, 12, 14, and 15, wherein the C-terminal lysine of the heavy chain of the antibody or portion is not present.

19. The monoclonal antibody or antigen-binding portion according to any one of claims 1, 10, and 17, wherein the antibody or portion possesses at least one of the following properties:

- a) binds to human secreted isoforms of M-CSF and membrane bound isoforms of M-CSF;
- b) has selectivity for M-CSF that is at least 100 times greater than its selectivity for GM-CSF or G-CSF; and
- c) has an off rate (K_{off}) for M-CSF of $2.0 \times 10^{-4} \text{ s}^{-1}$ or smaller.

20. The monoclonal antibody or antigen-binding portion according to any one of claims 2 to 9, 11, 12, 14, 15, and 18, wherein the antibody or portion possesses at least one of the following properties:

- a) binds to human secreted isoforms of M-CSF and membrane bound isoforms of M-CSF;
- b) has selectivity for M-CSF that is at least 100 times greater than its selectivity for GM-CSF or G-CSF;
- c) binds to M-CSF with a K_D of $1.0 \times 10^{-7} \text{ M}$ or less;
- d) has an off rate (K_{off}) for M-CSF of $2.0 \times 10^{-4} \text{ s}^{-1}$ or smaller; and
- e) binds to human M-CSF in the presence of human *c-fms*.

21. An isolated polypeptide selected from the group consisting of:

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- a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 without the signal sequence;
- b) a polypeptide comprising the amino acid sequence of SEQ ID NO: 6 without the signal sequence;
- c) a polypeptide comprising the amino acid sequence of SEQ ID NO: 10 without the signal sequence;
- d) a polypeptide comprising the amino acid sequence of SEQ ID NO: 14 without the signal sequence;
- e) a polypeptide comprising the amino acid sequence of SEQ ID NO: 18 without the signal sequence;
- f) a polypeptide comprising the amino acid sequence of SEQ ID NO: 22 without the signal sequence;
- g) a polypeptide comprising the amino acid sequence of SEQ ID NO: 26 without the signal sequence;
- h) a polypeptide comprising the amino acid sequence of SEQ ID NO: 30 without the signal sequence;
- i) a polypeptide comprising the amino acid sequence of SEQ ID NO: 34 without the signal sequence;
- j) a polypeptide comprising the amino acid sequence of SEQ ID NO: 38 without the signal sequence;
- k) a polypeptide comprising the amino acid sequence of SEQ ID NO: 46 without the signal sequence;
- l) a polypeptide comprising the amino acid sequence of SEQ ID NO: 50 without the signal sequence;
- m) a polypeptide comprising the amino acid sequence of SEQ ID NO: 54 without the signal sequence;
- n) a polypeptide comprising the amino acid sequence of SEQ ID NO: 58 without the signal sequence;
- o) a polypeptide comprising the amino acid sequence of SEQ ID NO: 62 without the signal sequence;
- p) a polypeptide comprising the amino acid sequence of SEQ ID NO: 66 without the signal sequence;
- q) a polypeptide comprising the amino acid sequence of SEQ ID NO: 70 without the signal sequence;

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- r) a polypeptide comprising the amino acid sequence of SEQ ID NO: 74 without the signal sequence;
- s) a polypeptide comprising the amino acid sequence of SEQ ID NO: 78 without the signal sequence;
- t) a polypeptide comprising the amino acid sequence of SEQ ID NO: 82 without the signal sequence;
- u) a polypeptide comprising the amino acid sequence of SEQ ID NO: 86 without the signal sequence;
- v) a polypeptide comprising the amino acid sequence of SEQ ID NO: 90 without the signal sequence;
- w) a polypeptide comprising the amino acid sequence of SEQ ID NO: 94 without the signal sequence;
- x) a polypeptide comprising the amino acid sequence of SEQ ID NO: 98 without the signal sequence; and
- y) a polypeptide comprising the amino acid sequence of SEQ ID NO: 102 without the signal sequence.

22. The isolated polypeptide according to claim 21 comprising the amino acid sequence of SEQ ID NO: 30 without the signal sequence.

23. The isolated polypeptide according to claim 21 comprising the amino acid sequence of SEQ ID NO: 26 without the signal sequence.

24. An isolated polypeptide selected from the group consisting of:

- a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 4 without the signal sequence;
- b) a polypeptide comprising the amino acid sequence of SEQ ID NO: 8 without the signal sequence;
- c) a polypeptide comprising the amino acid sequence of SEQ ID NO: 12 without the signal sequence;
- d) a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 without the signal sequence;
- e) a polypeptide comprising the amino acid sequence of SEQ ID NO: 20 without the signal sequence;

- f) a polypeptide comprising the amino acid sequence of SEQ ID NO: 24 without the signal sequence;
- g) a polypeptide comprising the amino acid sequence of SEQ ID NO: 28 without the signal sequence;
- h) a polypeptide comprising the amino acid sequence of SEQ ID NO: 36 without the signal sequence;
- i) a polypeptide comprising the amino acid sequence of SEQ ID NO: 44 without the signal sequence;
- j) a polypeptide comprising the amino acid sequence of SEQ ID NO: 48 without the signal sequence;
- k) a polypeptide comprising the amino acid sequence of SEQ ID NO: 52 without the signal sequence;
- l) a polypeptide comprising the amino acid sequence of SEQ ID NO: 56 without the signal sequence; and
- m) a polypeptide comprising the amino acid sequence of SEQ ID NO: 60 without the signal sequence.

25. The isolated polypeptide according to claim 24 comprising the amino acid sequence of SEQ ID NO: 28 without the signal sequence.

26. A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to any one of claims 1 to 20, and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition according to claim 26, wherein the monoclonal antibody is monoclonal anti-M-CSF antibody 9.14.4I or 8.10.3F.

28. A method for treating a condition selected from the group consisting of arthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion

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injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn, and conjunctivitis shock in a subject comprising the step of administering to said subject in need thereof a therapeutically effective amount of the monoclonal antibody or antigen-binding portion according to any one of claims 1, 10, 17, and 19.

29. A method for treating a condition selected from the group consisting of arthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn, and conjunctivitis shock in a subject, comprising the step of administering to said subject the monoclonal antibody or antigen-binding portion according to any one of claims 2 to 9, 11, 12, 14, 15, 18, and 20, wherein the antibody or portion inhibits M-CSF binding to *c-fms*.

30. A method for treating a solid tumor such as a sarcoma, a carcinoma or a lymphoma, in a subject, comprising the step of administering to said subject the monoclonal antibody or antigen-binding portion according to any one of claims 1, 10, 17, and 19.

31. A method for treating a solid tumor such as a sarcoma, a carcinoma or a lymphoma, in a subject, comprising the step of administering to said subject the monoclonal antibody or antigen-binding portion according to any one of claims 2 to 9, 11, 12, 14, 15, 18, and 20, wherein the antibody or portion inhibits M-CSF binding to *c-fms*.

32. Use of the monoclonal antibody or antigen-binding portion according to any one of claims 1, 10, 17, and 19, for the preparation of a pharmaceutical composition.

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33. Use of the monoclonal antibody or antigen-binding portion according to any one of claims 2 to 9, 11, 12, 14, 15, 18, and 20, wherein the antibody or portion inhibits M-CSF binding to *c-fms*, for the preparation of a pharmaceutical composition.
34. The method according to claim 28 or 29, wherein the condition is rheumatoid arthritis.
35. The method according to any one of claims 28 to 34, wherein the antibody utilized is monoclonal anti-M-CSF antibody 8.10.3F or 9.14.4I.
36. An isolated cell line that produces the monoclonal antibody or antigen-binding portion according to any one of claims 1 to 20, or the heavy chain of the antibody or portion.
37. The isolated cell line according to claim 36 that produces a monoclonal antibody selected from the group consisting of: antibodies 252, 88, 100, 3.8.3, 2.7.3, 1.120.1, 9.14.4I, 8.10.3F, 9.7.2IF, 9.14.4, 8.10.3, 9.7.2, 9.7.2C-Ser, 9.14.4C-Ser, 8.10.3C-Ser, 8.10.3-CG2, 9.7.2-CG2, 9.7.2-CG4, 9.14.4-CG2, 9.14.4-CG4, 9.14.4-Ser, 9.7.2-Ser, 8.10.3-Ser, 8.10.3-CG4, 8.10.3FG1, 9.14.4G1, and an antibody that has the same amino acid sequence as one of the foregoing antibodies.
38. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain, or an antigen-binding portion thereof, or both the heavy chain and light chain, or an antigen-binding portion thereof, of the monoclonal antibody according to any one of claims 1 to 20.
39. A vector comprising the nucleic acid molecule according to claim 38, wherein the vector optionally comprises an expression control sequence operably linked to said nucleic acid molecule.
40. An isolated host cell comprising the vector according to claim 39 or the nucleic acid molecule according to claim 38.
41. The isolated host cell according to claim 40 comprising a nucleic acid molecule encoding the heavy chain and a nucleic acid molecule encoding the light chain of the antibody or antigen-binding portion according to any one of claims 1 to 20.

42. A method of making an anti-M-CSF antibody or antigen-binding portion thereof, comprising culturing the host cell according to claim 40 or the cell line according to claim 36 under suitable conditions and recovering the antibody or portion.

Dated: 11 August 2009

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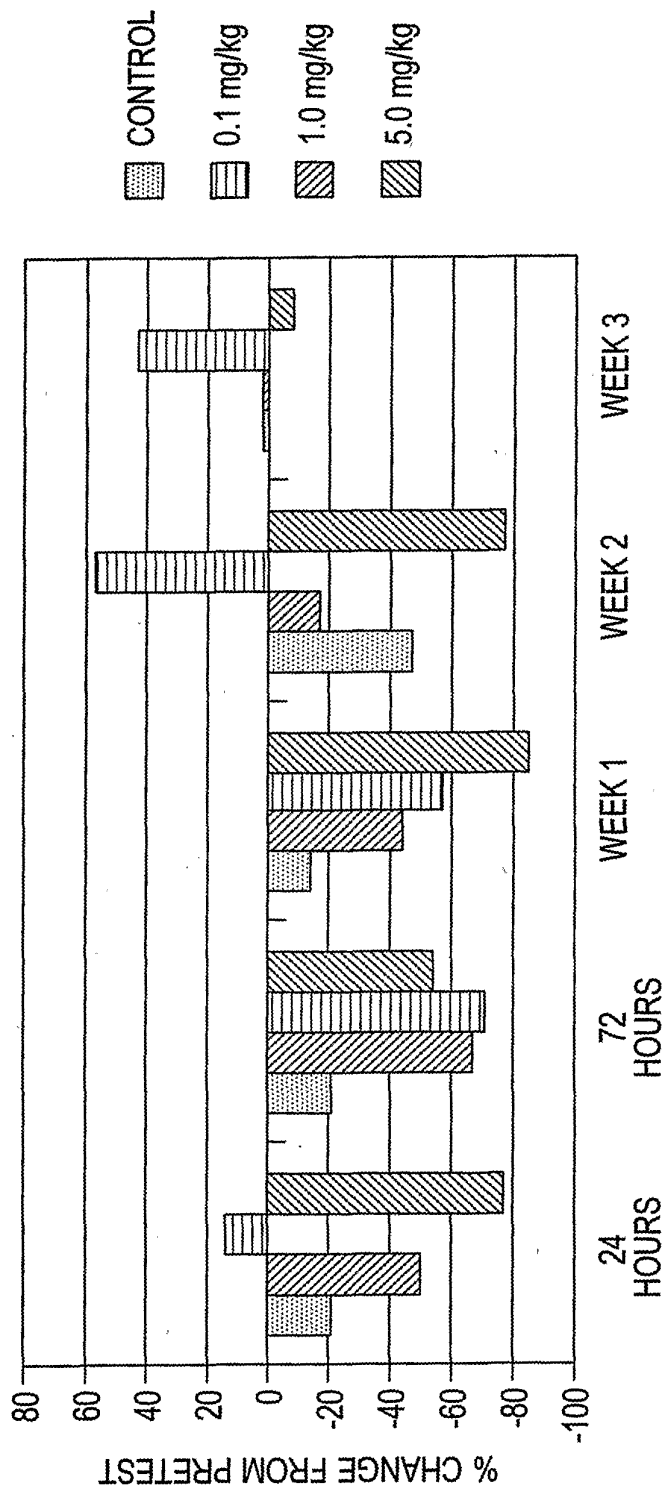


FIG. 1A

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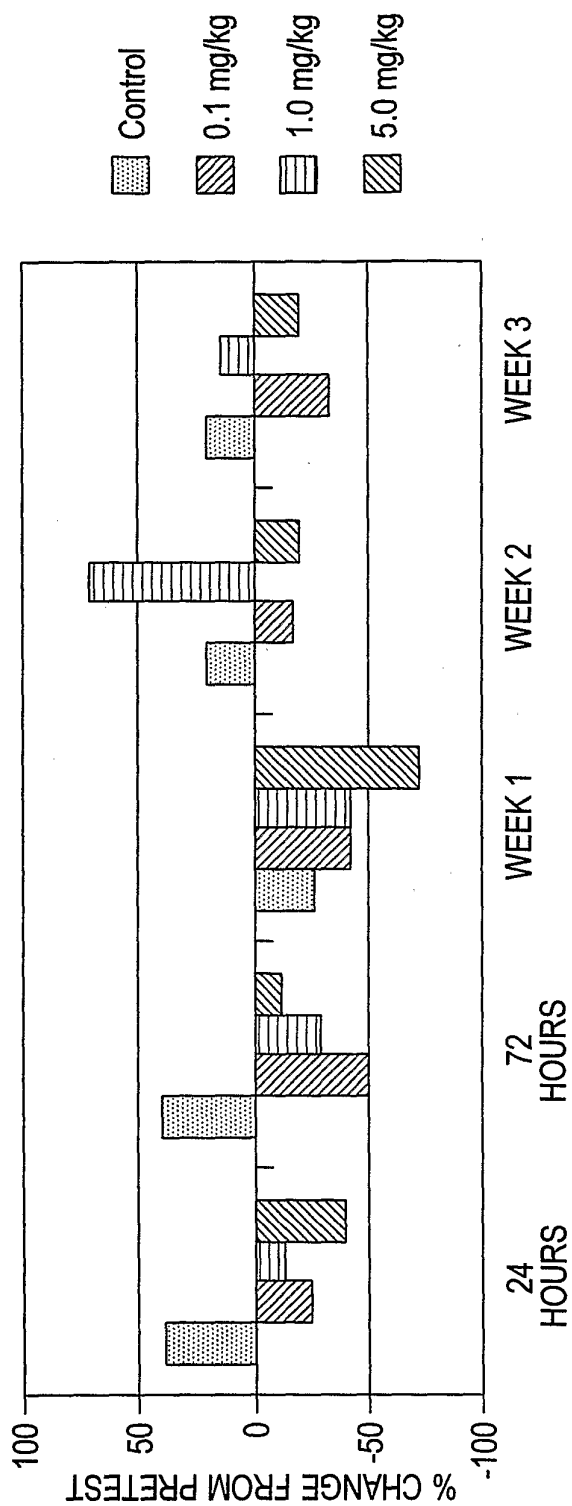
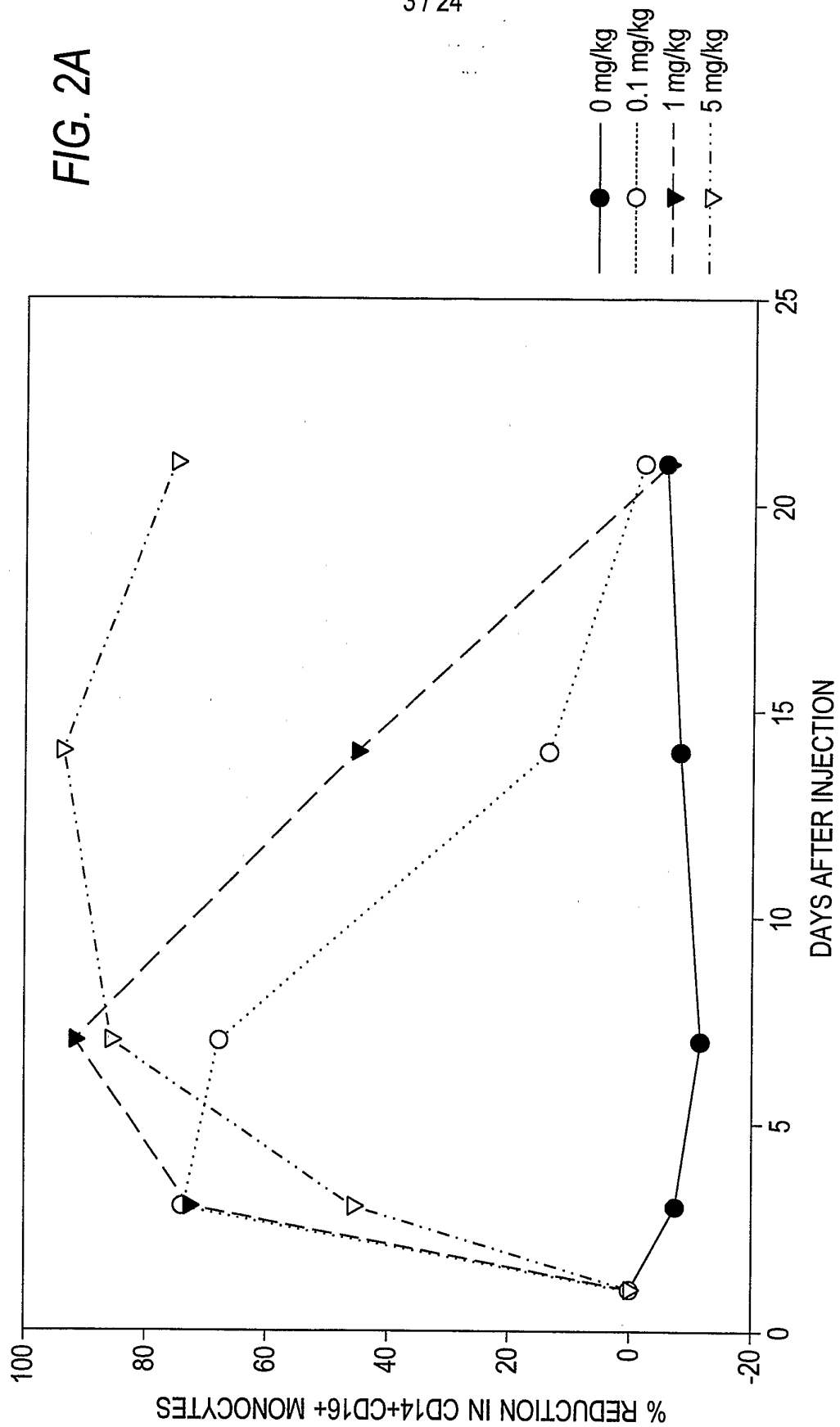


FIG. 1B

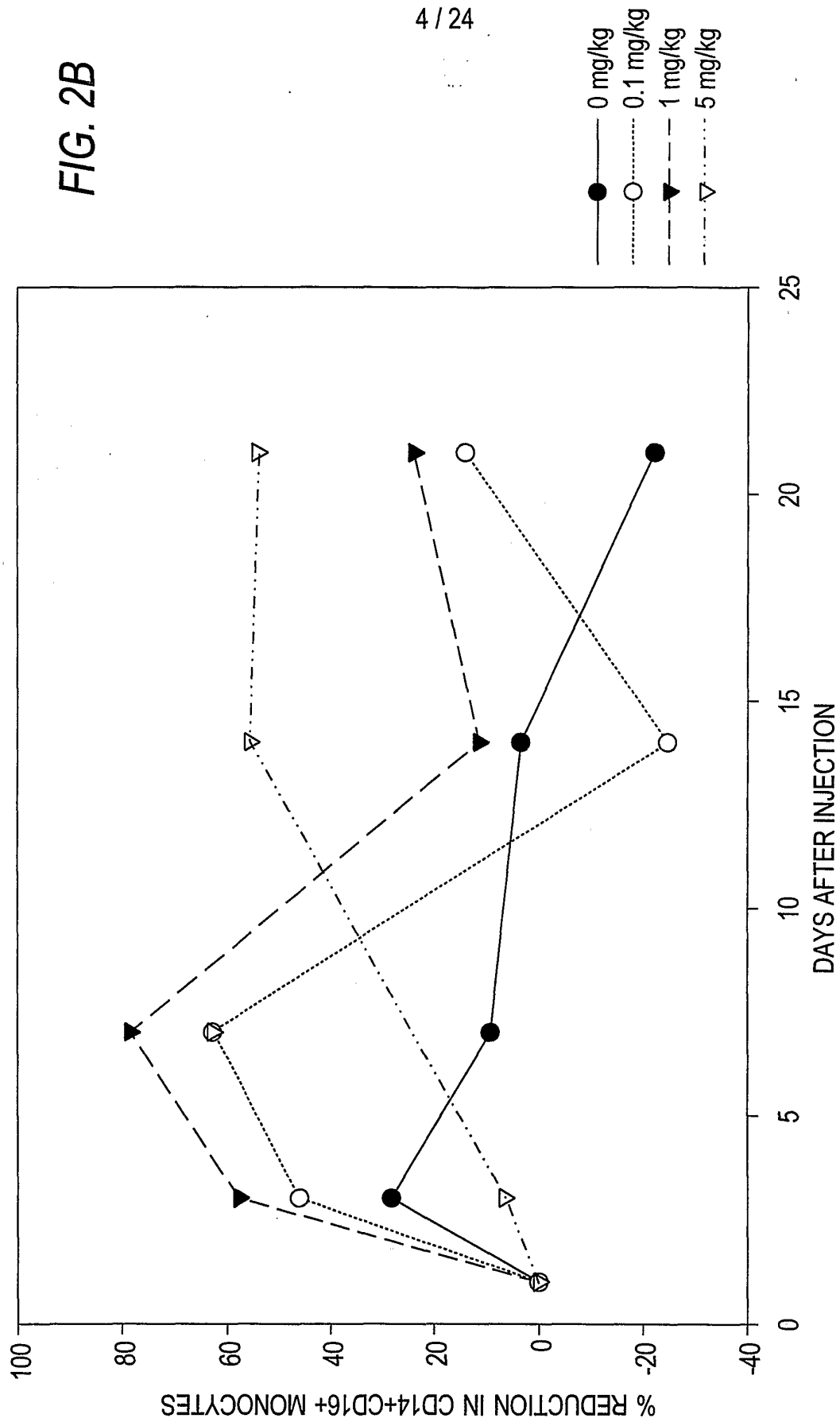
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FIG. 2A



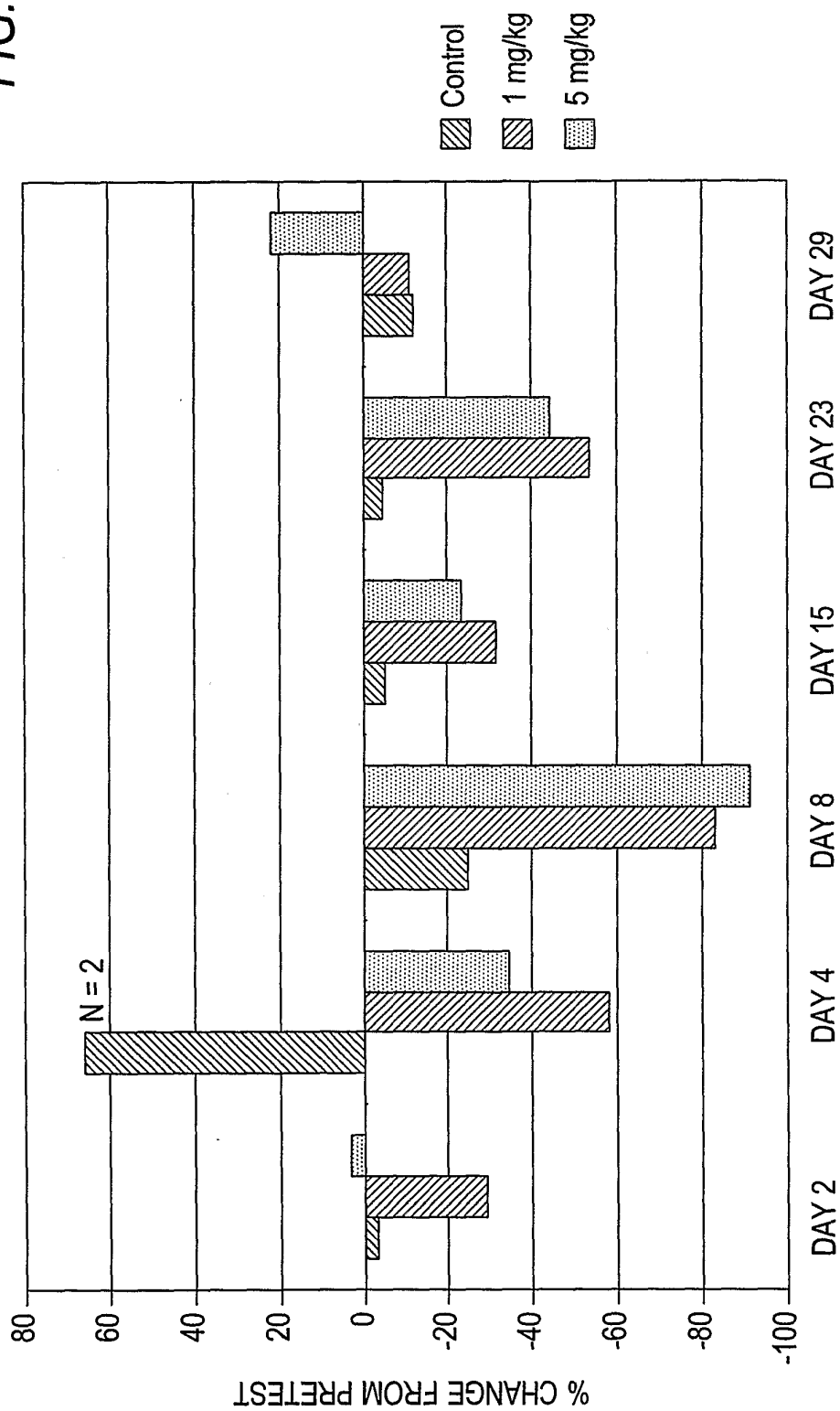
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FIG. 2B



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FIG. 3A



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FIG. 3B

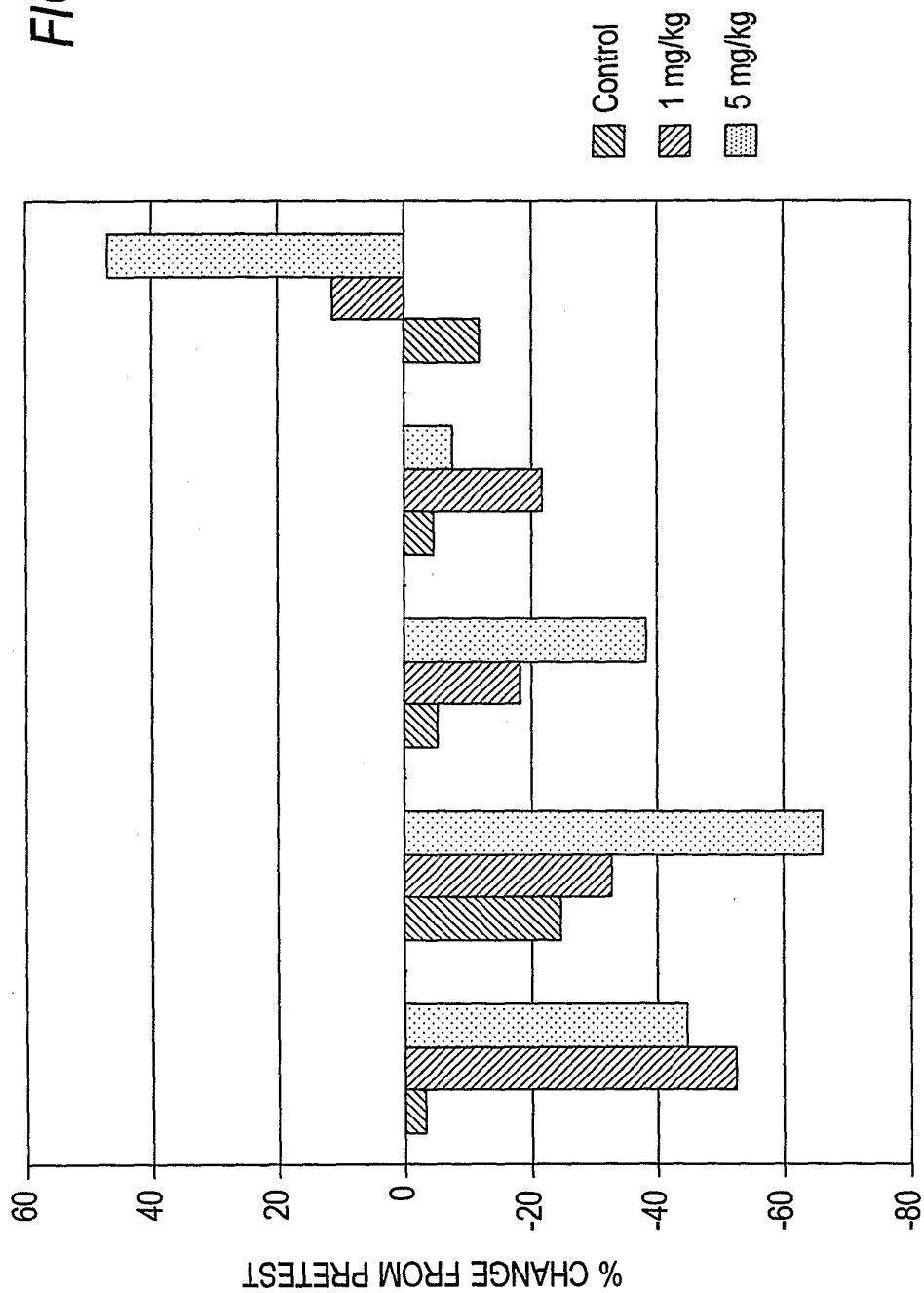


FIG. 4A

Germline V=O12, J=JK3

252

-----GF-----T-----F-----V-----
DIQMTQSPSSLSASVGDRTITC RASQSISSYLN WYQOKPGKAPKLLIY AASLQS GVPSRFGSGSGTDFTLTITSSIQPEDFATYYC QQSYSTPFT
FR1 CDR1 FR2 CDR2 FR3 CDR3

----- (residues 21-127 of SEQ ID NO: 4)

Germ FGPGTKVDIK (SEQ ID NO: 103)
J

FIG. 4B

Germline V=O12, J=JK3

88

-----P-D-----L-----
DIQMTQSPSSLSASVGDRTITC RASQSISSYLN WYQOKPGKAPKLLIY AASLQS GVPSRFGSGSGTDFTLTITSSIQPEDFATYYC QQSYSTPFT
FR1 CDR1 FR2 CDR2 FR3 CDR3

----- (residues 21-127 of SEQ ID NO: 8)

Germ FGPGTKVDIK (SEQ ID NO: 103)
J

FIG. 4C

Germline V=L2, J=JK3

100

-----D-I-----S-----
EIVMTQSPATLSVSPGERATLSC RASQSVSSNLA WYQOKPGQAPRLLIY GASTRAF GIPARFSGSGSGTEFTLTITSSIQSEDFAVYYC QQYNNWPFT
FR1 CDR1 FR2 CDR2 FR3 CDR3

----- (residues 21-127 of SEQ ID NO: 12)

Germ FGPGTKVDIK (SEQ ID NO: 107)
J

FIG. 4D

Germline V=L5, J=JK3

3.8.3

(residues 23-130 of SEQ ID NO: 16)

Germ

(SEQ ID NO: 109)

DIQMTQSPSSVSASVGDRVTITC RASQGISSWLA WYQOKPGKAPKLLIY AASSLOS GVPSRFGSGSGTDFLTITSSLPEDFATYYC QGANSEFET EGPGTKVDIKR
 FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4E

Germline V=L5, J=JK4

2.7.3

(residues 23-130 of SEQ ID NO: 20)

Germ

(SEQ ID NO: 117)

DIQMTQSPSSVSASVGDRVTITC RASQGISSWLA WYQOKPGKAPKLLIY AASSLOS GVPSRFGSGSGTDFLTITSSLPEDFATYYC QGANSEFLT EGGCTKVEIKR
 FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4F

Germline V=B3, J=JK1

1.120.1

1.120.1

Germ

(residues 21-134 of SEQ ID NO: 24)

EGGCTKVEIKR (SEQ ID NO: 112)

DIQMTQSPDLSAVSLGERATINC KSSQSVLYSSNNKNYLA WYQOKPGQPPKLLIY WASTRES GVPDFSGSGSGTDFLTITSSLPQAEADVAVYC QQYYSTPWT
 FR1 CDR1 FR2 CDR2 FR3 CDR3

FIG. 4G

Germline V=3-11, D=D7-27, J=JH6

252

	-----I-----	-----G-----	-----H-----
252			
Germ	<u>QVQLVESGGGLVKPGGSLRLS</u> <u>CAAS</u>	<u>GFTFSDYYMS</u>	<u>WIRQAPGKGLEWVS</u>
	FR1	CDR1	FR2
			<u>YISSSGSTIYYADSVKG</u>
			CDR2
			<u>RTTISRDNAKNSLYLQMNSLR</u> <u>AEDTAVYYCAR</u>
			FR3
			CDR3
			<u>ALGGMVDV</u>

Germ	FR1	CDR1	FR2	CDR2	FR3	CDR3
ALGGMVD						
QVQLVESGGGLVKPGGSLRLS		GFTFSDYYMS	WIRQAPGKGLEWVS	YTSSSGSTIYYADSVK	RFTTISRDNAKNSLYLQ	NSRAEDTAVYYCAR

FR3

CDR2

FR2

252 ----- (residues 20-136 of SEQ ID NO: 2)

Germ WQGGTTTVSSA (SEQ ID NO: 106)
FR4

FIG. 4H

FIG. 4H

Germline V=3-7. D=6-13, J=JH4

88

	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	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	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542
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Germ
<u>EVQLVESGGGLVQPGGSLRLSCAAS</u>
FR1 CDR1
<u>GFTFSSYWMS</u>
FR2 CDR2
<u>WVRQAPAGGLEWVA</u>
NIKODGSEKYVDVKVG FR3
<u>RETISRDNAKNSLYLQMISLRADTAVYYCAR</u>
GIAAAGYFDY CDR3

ER3

CDR2

ER2

88 ----- (residues 20-138 of SEQ ID NO: 6)

Germ WGQGTlVTVSSA (SEQ ID NO: 105)
FR4

FIG. 4I

Germline V=3-23, D=D1-26, J=JH4
100

	-----R-R-F-----F-V EG--R-GF----
Germine V-3-ZS, D-DI-26, O-OH4	
100	
Germ	EVQLLESGGLVQPGGSLRLSCAAS GFTSSYAMS WVRQAPKGLEWVS AISGGSTYYADSVKGR FTISRDN SKNTLYIQMNSLR AEDTAVYYCAK # YSGSYVYFDY CDR3
	FR1 FR2 CDR1 CDR2

Germ	FR1	CDR1	FR2	CDR2	FR3	CDR3
	EVQLLESGGGLVQPGGSLRLSCAAS	GFTESSYAMS	WVROAPGKGLEWVS	AISGGSGSTYYADSVKG	RFTISRDNKNTLYIQMNSLR	AEADTAVYYCAK
						##YSGSYVYFDY

FR3

CDR2

FR2

100 ----- (residues 20-141 of SEQ ID NO: 10)

FIG. 4J

GermLine V=3-11, D=D7-27, J=JH4

3.8.3

-----F-----S-----G-----

Germ QVQLVESGGGVKPGGSLRLSCAAS GETFSDYYMS WIRQAPGKGLEWVS YISSSGSTIYYADSVKG RETISRDNAKNSLYLQMNSLRAEDTAVYYCAR #LTGDY
FR1 CDR1 FR2 CDR2 FR3 CDR3

3.8.3 ----- (residues 20-135 of SEQ ID NO: 14)

Germ WGGTGLVTVSSA (SEQ ID NO: 108)
FR4

FIG. 4K

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GermLine V=3-33, D=D1-26, J=JH4

2.7.3

-----F-----RV-----

Germ QVQLVESGGGVVQPGRLRLSCAAS GETFSSYGMH WVRQAPGKGLEWVA VIWYDGSNKYYADSVKG RETISRDNKNTLYLQMNSLRAEDTAVYYCAR GYS#YFDY
FR1 CDR1 FR2 CDR2 FR3 CDR3

2.7.3 ----- (residues 20-137 of SEQ ID NO: 18)

Germ WGGTGLVTVSSA (SEQ ID NO: 110)
FR4

FIG. 4L

GermLine V=1-18, D=D4-23, J=JH4

1.120.1

-----D-----T-----R RA--A-F-----

Germ QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYGIS WVRQAPGGGLEWMG WISAYNGNTNVAQKIQ RVMTTDTSTSTAYMELRSLRSDDTAVYYCA# #DYGGNYFDY
FR1 CDR1 FR2 CDR2 FR3 CDR3

1.120.1 ----- (residues 20-139 of SEQ ID NO: 22)

Germ WGGTGLVTVSSA (SEQ ID NO: 111)
FR4

FIG. 4N

Germline V=012. J=JK3

(residual)

Germ

DDIQMTQSPSSLSASVGDRVTTC RASQISSYLN WYQKPGKAPKLLIY AASSLQ GVPSRFSGSGGTDFLTITSSLPEDFATYYC QQSYPFT FGPGKVDIKR
 (3) FR1 CDR1 FR2 CDR2 FR3 CDR3 J

(SEQ ID NO: 103)

[illegible]

8.10.3

(SEQ ID NO: 103)

	FR1	FR2	CDR2	FR3	CDR3	J
(J3)						
(J3)						

(SEQ ID NO: 103)

FR1	FR2	CDR2	FR3	CDR3	J
3)					

(SEQ ID NO: 103)

Germ
(SEQ ID NO: 103)

DIQMTQSPFSLASVGDRTITC	RASQISSYLN	WYQQKPGAPKLLIY	AASSLQS	GVPSRFSGSGGTDFLTISLPEDFAITYYC	QQSYSTPFT
FR1	CDR1	FR2	CDR2	FR3	CDR3
					J

FGPGPKVDIKR

FIG. 4P

Germline V=VH3-11, D=D7-27, J=JH4b
9.14.4

Germ QVQLVESGGGLVKPGGSLRLSCAAS GFTFSDYMS WIRQAPGKGLEWVS YISSSGSTIYYADSVKG RTTISRDNAKNSLYLQMNSLRAEDTAVYYCAR #LTGDY CDR3

9.14.4 ----- (residues 20-135 of SEQ ID NO: 38)

Germ WQQGTLVTVSSA (SEQ ID NO: 116)
J

FIG. 4Q

Germline V=012, J=JK3

9.7.2 -----
(residues 23-130 of SEQ ID NO: 48)
Germ DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQQKPKAPKLLIY AASSLQS GVPSPRFGSGSGTDFTLTISSLPEDFATYYC QQSYSTPFT FGPSTKVDIKR CDR3
(SEQ ID NO: 103) FR1 CDR1 FR2 FR3

FIG. 4R

Germline V=VH3-11, D=D6-13, J=JH6b
9.7.2

Germ QVQLVESGGGLVKPGGSLRLSCAAS GFTFSDYMS WIRQAPGKGLEWVS YISSSGSTIYYADSVKG RTTISRDNAKNSLYLQMNSLRAEDTAVYYCA# #I#GMDV CDR3

9.7.2 ----- (residues 20-136 of SEQ ID NO: 46)

Germ WQQGTTVTVSSA (SEQ ID NO: 115)
J

FIG. 4S

Germline V=012, J=JK3
 9.14.4I
 (residues 23-130 of SEQ ID NO: 28)

-----P-I-L-----H-----

Germ DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQQKPKAPKLLIY AASSLQS GVPSRFGSGSGTDFTLTISSLOPEDEATYYC QOSYSTPFT EGPGTKVDIKR
 (SEQ ID NO: 103) FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4T

Germline V=VH3-11, D=D7-27, J=JH4b
 9.14.4I

-----G-----

Germ QVQLVESGGGLVKPGGSLRLSCAAS GETFSDYMS WIRQAPGKLEWVS YISSSGSTIYYADSVKG RETISRDNAKNSLYLQMNSLRAEDTAVYYCAR #LTGDY
 (residues 20-135 of SEQ ID NO: 26) FR1 CDR1 FR2 CDR2 FR3 CDR3

Germ WCGQTLVTVSSA (SEQ ID NO: 116) J

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FIG. 4U

Germline V=A27, J=JK4
 8.10.3F

-----F-----

Germ EIVLTQSPGTLISLSPGERATLSC RASQSVSSSYLA WYQQKPGQAPRLLIY GASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC
 (residues 21-129 of SEQ ID NO: 32) FR1 CDR1 FR2 CDR2 FR3

Germ QQYGSSPLT EGGGTKVEIKR (SEQ ID NO: 114) J
 CDR3

FIG. 4W

[illegible]

FIG. 4X

	Germ	V=VH3-11, D=D6-13, J=JH6b 9.7.2IF-----R R-G-
	Germ	QVLVESGGGLVKPGGSLRLSCAAS GFTFSDYMS WIRQA PGKGLEWVS YISSGSTIYYADSVKG RTTISRDNAKNSLYLQMNSLR AEDTA VYYCA# #I#GMVD CDR3
	9.7.2IF	(residues 20-136 of SEQ ID NO: 34)
	Germ	WGQGTTVTTVSSA (SEQ ID NO: 115) .J

FIG. 4Y

Germline V=012, J=JK3
 9.7.2C-Ser
 (residues 23-130 of SEQ ID NO: 52)
 FR1 CDR1 FR2 CDR2 FR3 CDR3 J
 Germ DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQOKPGKAPKLLIY AASSLQS GVPSRFSGSGSGTDFTLTITSSLPEDFATYYC QQSYSTPFT FGPGTKVDIKR
 (SEQ ID NO: 103) FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4Z

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Germline V=VH3-11, D=D6-13, J=JH6b
 9.7.2C-Ser
 (residues 20-136 of SEQ ID NO: 50)
 FR1 CDR1 FR2 CDR2 FR3 CDR3 R-G
 Germ QVQLVESGGGLVKPGGSLRLSCAAS GFTFSDYYMS WIRQAPGKGLEWVS YISSSGSTIYYADSVKG RFTISRDNAKNSLYLQMNLSRAEDTAVYYCA #I#GMDV
 (residues 20-136 of SEQ ID NO: 50) FR1 CDR1 FR2 CDR2 FR3 CDR3
 Germ WGQGTITVTVSSA (SEQ ID NO: 115) J

FIG. 4AA

Germline V=012, J=JK3
 9.14.4C-Ser
 (residues 23-130 of SEQ ID NO: 56)
 FR1 CDR1 FR2 CDR2 FR3 CDR3 J
 Germ DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQOKPGKAPKLLIY AASSLQS GVPSRFSGSGSGTDFTLTITSSLPEDFATYYC QQSYSTPFT FGPGTKVDIKR
 (SEQ ID NO: 103) FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4BB

Germline V=VH3-11, D=D7-27, J=JH4b

9.14.4C-Ser

QVQLVESGGGLVKPGGSLRLSCAAS GTFESDYMS WIRQAPGKGLEWVS YISSSGSTIYYADSVKG RFTISRDNAKNSLYLQMNLSLRAEDTAVYYCAR #LTGDY
FR1 CDR1 FR2 CDR2 FR3 CDR3

9.14.4C-Ser (residues 20-135 of SEQ ID NO: 54)

Germ WGQGTLLVTVSSA (SEQ ID NO: 116)

J

FIG. 4CC

Germline V=A27, J=JK4

8.10.3C-Ser

EIVLTQSPGTLSPGERATLSC RASQSVSSSYLA WYQKPGQAPRLLIY GASSRAT GIPDRFSGSGGTDFLTISRLEPEDFAVYYC
FR1 CDR1 FR2 CDR2 FR3

Germ QQYGSPLT FGGTKVEIKR (residues 21-129 of SEQ ID NO: 60)

J

8.10.3 (SEQ ID NO: 114)

FIG. 4DD

Germline V=VH3-48, D=D1-26, J=JH4b

8.10.3C-Ser

EVQLVESGGGLVQPGGSLRLSCAAS GTFESSYSMN WVRQAPGKGLEWVS YISSSSTIYYADSVKG RFTISRDNAKNSLYLQMNLSLRAEDTAVYYCAR ###IVG##FDY
FR1 CDR1 FR2 CDR2 FR3 CDR3

8.10.3C-Ser (residues 20-141 of SEQ ID NO: 58)

Germ WGQGTLLVTVSSA (SEQ ID NO: 113)

J

FIG. 4EE

Germline V=A27, J=JK4

8.10.3-CG2

Germ EIVLTQSPGTLISLSPGERATLSC RASQSVSSSYLA WYQOKPGQAPRLLIY GASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC
FR1 CDR1 FR2 CDR2 FR3

8.10.3-CG2 (residues 21-129 of SEQ ID NO: 60)

Germ QQYGSSPLT FGGGTKVEIKR (SEQ ID NO: 114)
CDR3 J

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FIG. 4FF

Germline V=VH3-48, D=D1-26, J=JH4b

8.10.3-CG2

Germ EVOLVESGGGLVQPGGSLRLS CAAS GETFSSYSMN WVRQAPGKLEWVS YISSSSTIYYADSVKG RETISRDNAKNSLYLQMNSLRDEDTAVYYCAR ###IVG##FDY
FR1 CDR1 FR2 CDR2 CDR3 DPLIA-ATF

8.10.3-CG2 (residues 20-141 of SEQ ID NO: 62)

Germ WGQGTLLVTVSSA (SEQ ID NO: 113)
J

FIG. 4GG

Germline V=012, J=JK3

9.7.2-CG2

(residues 23-130 of SEQ ID NO: 52)
FR1

Germ DIQMTQSPSSLSASVGDRVTITC RASQISSYLN WYQOKPGKAPKLLIY AASSLQS GVPSRFSGSGSGTDFTLTISLSLQPEDFAVYYC QQSYSTPFT FGPGTKVDIKR
FR1 CDR1 FR2 CDR2 CDR3 J

FIG. 4HH

Germline V=VH3-11, D=D6-13, J=JH6b
9.7.2-CG2
(residues 20-136 of SEQ ID NO: 66)

Germ QVQLVESGGGLVKPGGSLRLSCAAS GFTFSDYYMS WIRQAPGKGLEWVS YISSSGSTIYADSVKG RFTISRDNAKNSLYLQMNLSRAEDTAVYYCA #I#GMDV
(SEQ ID NO: 115) FR1 CDR1 FR2 CDR2 FR3 CDR3 R-G

9.7.2-CG2

Germ WGQGTITVTVSSA
J

FIG. 4II

Germline V=012, J=JK3
9.7.2-CG4
(residues 23-130 of SEQ ID NO: 52)

Germ DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQOKPGKAPKLLIY AASSLOS GVPSRFSGSGSGTDFTLTITSSLOPEDFATYYC QQSISTPFT FGPGTKVDIKR
(SEQ ID NO: 103) FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4JJ

Germline V=VH3-11, D=D6-13, J=JH6b
9.7.2-CG4

Germ QVQLVESGGGLVKPGGSLRLSCAAS GFTFSDYYMS WIRQAPGKGLEWVS YISSSGSTIYADSVKG RFTISRDNAKNSLYLQMNLSRAEDTAVYYCA #I#GMDV
(SEQ ID NO: 115) FR1 CDR1 FR2 CDR2 FR3 CDR3 R-G

9.7.2-CG4 (residues 20-135 of SEQ ID NO: 70)

Germ WGQGTITVTVSSA (SEQ ID NO: 115)
J

FIG. 4KK

Germline V=012, J=JK3
 9.14.4-CG2 -----
 (residues 23-130 of SEQ ID NO: 56)

 -P-I-L-

 Germ DIQMTQSPSSLSASVGDRVTTC RASQSISSYLN WYQQKPGKAPKLLIY AASSLQS GVPSRFGSGSGTDFTLTISSLPEDFATYYC QQSSTPFT FGPGTKVDIKR
 (SEQ ID NO: 103) FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4LL

Germline V=VH3-11, D=D7-27, J=JH4b
 9.14.4-CG2 -----
 (residues 23-130 of SEQ ID NO: 56)

 -P-I-L-

 Germ QVQLVESGGGLVPGGSLRLSCAAS GFTFSDYMS WIRQAPGKGLEWVS YISSSGSTIYYADSVKG RFTISRDNAKNSLYLQMNSLRAEDFATYYCAR #LTGDY
 (SEQ ID NO: 103) FR1 CDR1 FR2 CDR2 FR3 CDR3 G

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9.14.4-CG2 ----- (residues 20-135 of SEQ ID NO: 74)

Germ WGQGLTVTVSSA (SEQ ID NO: 116)

FIG. 4MM

Germline V=012, J=JK3
 9.14.4-CG4 -----
 (residues 23-130 of SEQ ID NO: 56)

 -P-I-L-

 Germ DIQMTQSPSSLSASVGDRVTTC RASQSISSYLN WYQQKPGKAPKLLIY AASSLQS GVPSRFGSGSGTDFTLTISSLPEDFATYYC QQSSTPFT FGPGTKVDIKR
 (SEQ ID NO: 103) FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4NN

Germ V=VH3-11, D=D7-27, J=JH4b
9.14.4-CG4

-----G-----
Germ QVQLVESGGGLVKPGGSLRLSCAAS GFTFSDYMS WIRQAPGKGLEWVS YISSSGSTIYYADSVKG RTISRDNAKNSLYIQMNSLRAEDTAVYYCAR #LTGDY CDR3
FR1 FR2 CDR2

9.14.4-CG4 ----- (residues 20-135 of SEQ ID NO: 78)

Germ WGQGLVTVSSA (SEQ ID NO: 116)
J

FIG. 400

Germ V=012, J=JK3
9.14.4-Ser
(residues 23-130 of SEQ ID NO: 28)

-----P-I-I-----H-----
Germ DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQOKPGKAPKLLIY AASSLQS GVPFRFSGSGGTDFTLTITSSIQPEDEFTYYC QQSYSTPFT FGPGTKVDIKR CDR3
FR1 FR2 CDR2 CDR3 J

FIG. 4PP

Germ V=VH3-11, D=D7-27, J=JH4b
9.14.4-Ser

-----G-----
Germ QVQLVESGGGLVKPGGSLRLSCAAS GFTFSDYMS WIRQAPGKGLEWVS YISSSGSTIYYADSVKG RTISRDNAKNSLYIQMNSLRAEDTAVYYCAR #LTGDY CDR3
FR1 FR2 CDR2 CDR3

9.14.4-Ser ----- (residues 20-135 of SEQ ID NO: 82)

Germ WGQGLVTVSSA (SEQ ID NO: 116)
J

FIG. 4QQ

Germline V=012, J=JK3
 9.7.2-Ser -----
 (residues 23-130 of SEQ ID NO: 48)
 FR1 CDR1 FR2 FR3 CDR3 J
 DIQMTQSPSSLSASVGDRVTTC RASQSISSYLN WYQOKPKAPKLLIY AASSLOS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSISTPFT FGPGTKVDIKR
 (SEQ ID NO: 103) FR1 CDR1 FR2 FR3 CDR3 J

FIG. 4RR

Germline V=VH3-11, D=D6-13, J=JH6b
 9.7.2-Ser -----
 (residues 20-136 of SEQ ID NO: 50)
 FR1 CDR1 FR2 FR3 CDR2 FR3 R-G
 QVQLVESGGGLVKPGGSLRLSCAAS GFTFSYYMS WIRQAPKGLEWVS YISSSGSTIYYADSVKG RTISRDNAKNSLYIQMNSLRAEDTAVYYCA #I#GMDV
 (SEQ ID NO: 115) FR1 CDR1 FR2 FR3 CDR2 FR3 CDR3

FIG. 4SS

Germline V=A27, J=JK4
 8.10.3-Ser -----
 (residues 21-129 of SEQ ID NO: 44)
 FR1 CDR1 FR2 FR3 CDR2 FR3 V
 EIVLTQSPGTLSPGERATLSC RASQSVSSYLA WYQOKPGQAPRLIY GASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAYYC
 (SEQ ID NO: 114) FR1 CDR1 FR2 FR3 CDR2 FR3
 QQYGSPLT FGGTKVEIKR (SEQ ID NO: 114)
 CDR3 J

FIG. 4TT

Germline V=VH3-48, D=D1-26, J=JH4b
 8.10.3-Ser
 -----F-T-----R-S-----DPLLA-ATF-----
 Germ EVQLVESGGGLVQPGGSLRLSCAAS GFTSSYSMN WVRQAPGKGLEWVS YISSSSTIYYADSVKG RTISRDNAKNSLYIQMNSLRDEDTAVYYCAR ###IVG##FDY
 FR1 FR2 CDR1 CDR2 FR3 CDR3
 8.10.3-Ser ----- (residues 20-141 of SEQ ID NO: 90)
 Germ WGQGTILVTVSSA (SEQ ID NO: 113)
 J

FIG. 4UU

Germline V=A27, J=JK4
 8.10.3-CG4

 Germ EIVLTQSPGTLISLSPGERATLSC RASQSVSSSYLA WYQOKPGQAPRLLIY GASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDEFAVYYC
 FR1 FR2 CDR1 CDR2 FR3
 8.10.3-CG4 ----- (residues 21-129 of SEQ ID NO: 60)
 Germ QQYGSPLT FGGGKVEIKR (SEQ ID NO: 114)
 CDR3 J

FIG. 4VV

Germline V=VH3-48, D=D1-26, J=JH4b
 8.10.3-CG4
 -----F-T-----R-S-----DPLLA-ATF-----
 Germ EVQLVESGGGLVQPGGSLRLSCAAS GFTSSYSMN WVRQAPGKGLEWVS YISSSSTIYYADSVKG RTISRDNAKNSLYIQMNSLRDEDTAVYYCAR ###IVG##FDY
 FR1 FR2 CDR1 CDR2 FR3 CDR3
 8.10.3-CG4 ----- (residues 20-141 of SEQ ID NO: 94)
 Germ WGQGTILVTVSSA (SEQ ID NO: 113)
 J

FIG. 4WW

Germline V=012, J=JK3
 9.14.4G1
 (residues 23-130 of SEQ ID NO: 28)

-----P-I-L-----H-----

 Germ DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQOKPGKAPKILLY AASSIQS GVPSEFSGSGSGTDFTLTITSSLPQPEDEATYYC QQSISTPFT FGPGTKVDIKR
 (SEQ ID NO: 103) FR1 CDR1 FR2 CDR2 FR3 CDR3 J

FIG. 4XX

Germline V=VH3-11, D=D7-27, J=JH4b
 9.14.4G1

 Germ QVQLVESGGGLVKPGGSLRLSCAAS GFTFSDYYMS WIRQAPGKGLEWVS VISSSGSTIYVADSVKG RETISRDNAKNSIYLQMNLSLRAEDTAVYYCAR #LTGDY
 (residues 20-135 of SEQ ID NO: 102) FR1 CDR1 FR2 CDR2 FR3 CDR3
 9.14.4G1
 Germ WQQGTLTVTSSA (SEQ ID NO: 116) J

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FIG. 4YY

Germline V=A27, J=JK4
 8.10.3FG1

-----F-----

 Germ EIVLTQSPGTLSPGERATLSC RASQVSSSYLA WYQOKPGQAPRILLY GASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC
 (residues 21-129 of SEQ ID NO: 32) FR1 CDR1 FR2 CDR2 FR3
 8.10.3FG1
 Germ QQYGSSPLT FCGGTKVEIKR (SEQ ID NO: 114) J
 CDR3

FIG. 4ZZ

Germline V=VH3-48, D=D1-26, J=JH4b
8.10.3FG1

-----F--T-----R--S-----DPLLA-ATF-----

Germ EVQLVESGGGLVQPGGSLRLSCAAS GFTFSSYSMN WVRQAPGKGLEWVS YISSSSTIYYADSVKG RTTISRDNAKNSLYLQMNSLRDEDTAVYYCAR ###IVG##FDY
FR1 CDR1 FR2 CDR2 CDR3

8.10.3FG1 ----- (residues 20-141 of SEQ ID NO: 98)

Germ WGQGTLLVTVSSA (SEQ ID NO: 113)
J

SEQUENCE LISTING

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DEVALARAJA, MADHAV NARASIMHA
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KELLERMANN, SIRID-AIMEE
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gcagctggta gggcctactg gggccaggga accctgggtca ccgtctcctc agcttccacc 420
aagggcccat ccgtcttccc cctggcgccc tgctctagaa gcacctccga gagcacagcg 480
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aacgtagatc acaagcccag caacaccaag gtggacaaga cagttgagcg caaatgttgt 720
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gggcagccgg agaacaacta caagaccaca cctcccatgc tggactccga cggctccttc 1260
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1320
tgctccgtga tgcattgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1380
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<210> 6

<211> 463

<212> PRT

<213> Homo sapiens

<400> 6

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Met Glu Phe Gly Leu Cys Trp Val Phe Leu Val Ala Ile Leu Glu Gly
 1             5             10             15

Val Gln Cys Glu Val Gln Leu Val 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 Thr Phe
      35             40             45

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

Glu Trp Val Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val
      65             70             75             80

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

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

```

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

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 420 425 430

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

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455 460

<210> 7
 <211> 702
 <212> DNA
 <213> Homo sapiens

<400> 7
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 atcacttgcc ggccaagtca ggacattagc agttatttaa attggtatca gcagaaacca 180
 gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccat 240
 aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 300
 gaagattttg caacttacta ctgtcaacag agttacagta ccccatcac tttcggccct 360
 gggaccaaag tggatatcaa acgaactgtg gctgcaacct ctgtcttcat cttcccgcca 420
 tctgatgagc agttgaaatc tgggaactgt agcggtgtgt gcctgctgaa taacttctat 480
 ccagagaggg ccaaagtaca gtggaagggt gataacgccc tccaatcggg taactcccag 540
 gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 600
 ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 660
 ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 702

<210> 8
 <211> 234
 <212> PRT
 <213> Homo sapiens

<400> 8
 Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Arg
 1 5 10 15

Gly Ala 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 Pro 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 Ala Ser Ser Leu Gln Ser Gly Val Pro Leu
 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 Ser Tyr
 100 105 110

Ser Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
 115 120 125
 Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 130 135 140
 Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 145 150 155 160
 Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 165 170 175
 Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 180 185 190
 Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 195 200 205
 His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 210 215 220
 Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230

<210> 9

<211> 1398

<212> DNA

<213> Homo sapiens

<400> 9

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 tgtgcagcct ctggattcac ctttagcagc tatgccatga gctgggtccg ccaggctcca 180
 ggggaaggggc tggaatgggt ctcagctatt agtggtcgtg gtggtaggac atacttcgca 240

 gactccgtga agggccggtt caccatctcc agagacaatt ccaagaacac gctgtatctg 300
 caaatgaaca gcctgagagc cgaggacacg gccgtatatt tctgtgcggt agaaggctat 360
 agtgggcgct acggattttt tgactactgg ggccaggga ccctagtcac cgtctcctca 420
 gcctccacca agggcccatc ggtcttcccc ctggcgccct gctctagaag cacctccgag 480
 agcacagcgg ccctgggctg cctgggtcaag gactacttcc ccgaaccggt gacgggtgtc 540
 tggaactcag gcgctctgac cagcggcggt cacaccttcc cagctgtcct acagtccctca 600
 ggactctact ccctcagcag cgtgggtgacc gtgccctcca gcaacttcgg caccagacc 660
 tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 720
 aaatgttggt tggagtgtcc accgtgcccc gcaccacctg tggcaggacc gtcagtcttc 780
 ctcttcccc caaaaccctc ggacaccctc atgatctccc ggaccctga ggtcacgtgc 840
 gtgggtgggt acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 900
 gtggagggtc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 960
 gtggtcagcg tctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 1020
 aaggcttcca acaaaggcct cccagcccc atcgagaaaa ccactctcaa aaccaaaggg 1080
 cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac 1140
 caggtcagcc tgacctgcct ggtcaaaggc ttctaccca gcgacatcgc cgtggagtgg 1200
 gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1260
 ggctccttct tctctacag caagctcacc gtggacaaga gcagggtggc gcagggggaa 1320
 gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380
 tccctgtctc cgggtaaa 1398

<210> 10
 <211> 466
 <212> PRT
 <213> Homo sapiens

<400> 10

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Met Glu Phe Gly Leu Arg Trp Ile Phe Leu Val Ala Ile Leu Lys Gly
 1           5           10           15

Val Gln 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 Thr Phe
          35           40           45

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

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

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

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

Tyr Phe Cys Ala Val Glu Gly Tyr Ser Gly Arg Tyr Gly Phe Phe Asp
          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
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
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> 11

<211> 702

<212> DNA

<213> Homo sapiens

<400> 11

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gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 120
ctctcctgca gggccagtc gaagtgttagc agcaacttag cctgggtacca gcagaaacct 180
ggccaggctc ccaggctcct catctatggg gcatccacca gggccagtg tatccagac 240
aggatcagtg gcagtgggtc tggaacagag ttcactctca tcatcagcag cctgcagtct 300
gaagattttg cagtttatta ctgtcagcag tctaataact ggccattcac tttcggccct 360
gggaccaaag tggatatcaa acgaactgtg gctgcacccat ctgtcttcat cttcccgcga 420
tctgatgagc agttgaaatc tggaactgct agcgttgtgt gcctgctgaa taacttctat 480
cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccga 540

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gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 600
 ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 660
 ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 702

<210> 12

<211> 234

<212> PRT

<213> Homo sapiens

<400> 12

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
 1 5 10 15

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

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

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

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

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

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

Asn Trp Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
 115 120 125

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

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

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 180 185 190

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

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 210 215 220

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

12/77

<210> 13

<400> 13

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<210> 14

<211> 460

<212> PRT

<213> Homo sapiens

<400> 14

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
 1 5 10 15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

Glu Trp Phe Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
 65 70 75 80

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

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

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

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
 145 150 155 160

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 165 170 175

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

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 195 200 205

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
 210 215 220

Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
 225 230 235 240

<400> 15
000

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<210> 16
<211> 236
<212> PRT
<213> Homo sapiens
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<400> 16
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp

1	5	10	15
Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser	20	25	30
Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser	35	40	45
Gln Asp Ile Ser Gly Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys	50	55	60
Ala Pro Lys Leu Leu Ile Ser Ala Thr Ser Ser Leu His Ser Gly Val	65	70	75
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
Thr Asn Ser Phe Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp 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
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> 17

<400> 17
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<210> 18
<211> 463
<212> PRT
<213> Homo sapiens

<400> 18

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
 1 5 10 15

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

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

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

 Glu Trp Val Ala Phe Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
 65 70 75 80

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

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

 Tyr Tyr Cys Ala Arg Gly Tyr Arg Val Tyr Phe Asp Tyr Trp Gly Gln
 115 120 125

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

 Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 145 150 155 160

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

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

 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 195 200 205

 Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
 210 215 220

 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
 225 230 235 240

 Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
 245 250 255

 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 260 265 270

 Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
 275 280 285

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

290		295		300
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser				
305		310		315 320
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys				
	325		330	335
Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile				
	340		345	350
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro				
	355		360	365
Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu				
	370		375	380
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn				
385		390		395 400
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser				
	405		410	415
Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg				
	420		425	430
Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu				
	435		440	445
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys				
	450		455	460

<210> 19

<400> 19
000

<210> 20

<211> 236

<212> PRT

<213> Homo sapiens

<400> 20

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp				
1		5		10 15
Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser				
	20		25	30
Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser				
	35		40	45
Gln Asp Ile Ser Ser Trp Leu Ala Trp Tyr Gln Arg Lys Pro Gly Lys				
	50		55	60

Ala Pro Lys Leu Gln Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val
 65 70 75 80
 Pro Ser Arg Phe Asn Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser
 85 90 95
 Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
 100 105 110
 Thr Asn Ser Phe Pro Leu 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> 21

<400> 21

000

<210> 22

<211> 464

<212> PRT

<213> Homo sapiens

<400> 22

Met Glu Trp Thr Trp Ser Phe Leu Phe Leu Val Ala Ala Ala Thr Gly
 1 5 10 15
 Ala His Ser Gln 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 Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu

50	55	60
Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala		
65	70	75 80
Gln Lys Leu Gln Asp Arg Val Thr Met Thr Thr Asp Thr Ser Thr Thr		
	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 Arg Ala Tyr Gly Ala Asn Phe Phe Asp Tyr Trp		
	115 120	125
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro		
	130 135	140
Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr		
	145 150	155 160
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr		
	165 170	175
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro		
	180 185	190
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr		
	195 200	205
Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp		
	210 215	220
His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys		
	225 230	235 240
Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser		
	245 250	255
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		
	260 265	270
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		
	275 280	285
Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
	290 295	300
Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val		
	305 310	315 320
Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
	325 330	335
Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr		
	340 345	350

Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 355 360 365
 Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
 370 375 380
 Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 385 390 395 400
 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp
 405 410 415
 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
 420 425 430
 Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 435 440 445
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455 460

<210> 23

 <400> 23
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<210> 24

<211> 240

<212> PRT

<213> Homo sapiens

<400> 24

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
 1 5 10 15
 Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
 20 25 30
 Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
 35 40 45
 Ile Leu Phe Phe Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Arg Gln
 50 55 60
 Lys Pro Gly Gln Pro Pro Asn Leu Leu Ile Tyr Trp Ala Ser Thr Arg
 65 70 75 80
 Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
 85 90 95
 Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
 100 105 110

Tyr Cys Gln Gln Tyr Tyr Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr
 115 120 125
 Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
 130 135 140
 Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
 145 150 155 160
 Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
 165 170 175
 Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
 180 185 190
 Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
 195 200 205
 Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
 210 215 220
 Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235 240

<210> 25

<211> 1380

<212> DNA

<213> Homo sapiens

<400> 25

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 tgtgcagcct ctggattcac cttcagtgac tactatatga gctggatccg ccaggctcca 180
 gggaaggac tggagtgggt ttcatacatt agtagtagtg gtagtaccat atactacgca 240
 gactctgtga agggccgatt caccatctcc agggacaacg ccaagaactc actgtatctg 300
 caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgagag aggcctaact 360
 ggggactact ggggccaggg aaccctggtc accgtctcct cagcttccac caagggccca 420
 tccgtcttcc cctggcgcc ctgctctaga agcacctccg agagcacagc ggccctgggc 480
 tgccctggtca aggactactt cccgaaccg gtgacgggtg cgtggaactc aggcgctctg 540
 accagcggcg tgcacacctt cccagctgtc ctacagtcct caggactcta ctccctcagc 600
 agcgtggtga ccgtgccttc cagcaacttc ggcacccaga cctacacctg caacgtagat 660
 cacaagccca gcaacaccaa ggtggacaag acagttgagc gcaaagtgtg tgtcgagtgc 720
 ccaccgtgcc cagcaccacc tgtggcagga ccgtcagctt tcctcttccc cccaaaaccc 780
 aaggacaccc tcatgatctc cgggacccct gaggtcacgt gcgtgggtgg ggacgtgagc 840
 cacgaagacc ccgaggtcca gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 900
 aagacaaagc caggggagga gcagttcaac agcacgttcc gtgtgggtcag cgtcctcacc 960
 gttgtgcacc aggatgggt gaacggcaag gactacaagt gcaaggtctc caacaaaggc 1020
 ctcccagccc ccctcgagaa aaccatctcc aaaaccaaag ggcagccccg agaaccacag 1080
 gtgtacaccc tgcccccatc cggggaggag atgaccaaga accaggtcag cctgacctgc 1140
 ctgggtcaaag gcttctaccc cagcgacatc gccgtggagt gggagagcaa tgggcagccc 1200
 gagaacaact acaagaccac acctcccatg ctggactccg acggctcctt ctctctctac 1260

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<400> 26
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
  1          5          10          15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
          50          55          60

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

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

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

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

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
          145          150          155          160

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
          165          170          175

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

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
          195          200          205

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
          210          215          220

Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
          225          230          235          240

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe

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245										250				255			
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val		
			260					265					270				
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe		
		275					280					285					
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro		
		290					295					300					
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr		
305					310					315					320		
Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val		
				325					330					335			
Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr		
				340					345					350			
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg		
			355					360					365				
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly		
			370					375					380				
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro		
385					390					395					400		
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser		
				405					410					415			
Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln		
			420					425					430				
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His		
			435					440					445				
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						
			450					455					460				

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<210> 27
<211> 708
<212> DNA
<213> Homo sapiens
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<400> 27						
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agatgtgaca	tccagatgac	ccagtcctca	tcctccctgt	ctgcatctgt	cggagacaga	120
gtcaccatca	cttgccggcc	aagtcagatc	attagcagtt	tattaaattg	gtatcagcag	180
aaaccaggga	aagccccctaa	gctcctgatc	catgctgcat	ccagtttgca	aagtggggtc	240
ccatcaaggt	tcagttggcag	tggatctggg	acagatttca	ctctcaccat	cagtagtctg	300
caacctgaag	atatttgcaac	ttactactgt	caacagagtt	acagtatccc	attcactttc	360
ggccctggga	ccaaagtgga	tatcaaacga	actgtggctg	caccatctgt	cttcactctc	420
cgcccatctg	atgagcagtt	gaaatctgga	actgcctctg	ttgtgtgcct	gctgaataac	480

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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

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<210> 28

<211> 236

<212> PRT

<213> Homo sapiens

<400> 28

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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 Pro Ser
      35              40              45

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

Ala Pro Lys Leu Leu Ile His Ala Ala Ser Ser Leu Gln 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

Ser Tyr Ser Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp 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

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<210> 29
 <211> 1398
 <212> DNA
 <213> Homo sapiens

<400> 29
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 gtgcagctgg tggagtctgg gggaggcttg gtacagcctg gggggtcctt gagactctcc 120
 tgtgcagcct ctggattcac cttcagtagt tttagtatga cctgggtccg ccaggctcca 180
 ggaaaggggc tggagtgggt ttcatacatt agtagtagaa gtagtaccat atcctacgca 240
 gactctgtga agggccgatt caccatctcc agagacaatg ccaagaactc actgtatctg 300
 caaatgaaca gcctgagaga cgaggacacg gctgtgtatt actgtgagag agatcctctt 360
 ctagcgggag ctaccttctt tgactactgg ggccagggaa ccctgggtcac cgtctcctca 420
 gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 480
 agcacagcgg ccctgggctg cctgggtcaag gactacttcc ccgaaccggt gacggtgtcg 540
 tggaaactcag gcgctctgac cagcggcggt cacaccttcc cagctgtcct acagtctcca 600
 ggactctact ccctcagcag cgtggtgacc gtgcctcca gcaacttcgg caccagacc 660
 tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 720
 aaatgttgtg tcgagtgcc accgtgcccc gcaccacctg tggcaggacc gtcagtcttc 780
 ctcttcccc caaaacccaa ggacacctc atgatctccc ggacctctga 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 ccagaccccc atcgagaaaa ccatctccaa aaccaaaggg 1080
 cagccccgag aaccacaggt gtacacctg cccccatccc gggaggagat gaccaagaac 1140
 caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1200
 gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1260
 ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcagggggaa 1320
 gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380
 tccctgtctc cgggtaaa 1398

<210> 30
 <211> 466
 <212> PRT
 <213> Homo sapiens

<400> 30
 Met Glu Leu Gly Leu Cys Trp Val Phe Leu Val Ala Ile Leu Glu Gly
 1 5 10 15
 Val Gln Cys Glu Val Gln Leu Val 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 Thr Phe
 35 40 45
 Ser Ser Phe Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60
 Glu Trp Val Ser Tyr Ile Ser Ser Arg Ser Ser Thr Ile Ser Tyr Ala
 65 70 75 80
 Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
 85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val
 100 105 110
 Tyr Tyr Cys Ala Arg Asp Pro Leu Leu Ala Gly Ala Thr Phe Phe Asp
 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> 31
 <211> 705
 <212> DNA
 <213> Homo sapiens

<400> 31
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 gaatttgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 120
 ctctcctgca gggccagtca gagtgttagc agcagttact tagcctggta ccagcagaaa 180
 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 240
 gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 300
 cctgaagatt ttgcagtgtg ttactgtcag cagtatggta gctcacctct cactttcggc 360
 ggagggacca aggtggagat caaacgaact 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 caccatcag 660
 ggcttgagct cgcccgtcac aaagagcttc aacaggggag agtgt 705

<210> 32
 <211> 235
 <212> PRT
 <213> Homo sapiens

<400> 32
 Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Trp Leu Pro
 1 5 10 15

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

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
 35 40 45

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

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

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
 85 90 95
 Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
 100 105 110
 Gly Ser Ser 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> 33

<211> 1383

<212> DNA

<213> Homo sapiens

<400> 33

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 gtgcagctgg tggagtctgg gggaggcttg gtcaagcctg gaggtgccct gagactctcc 120
 tgtgcagcct ctggattcac cttcagtgac tactacatga gctggatccg ccaggctcca 180
 gggaaagggg tggagtgggt ttcatatatt agtagtagtg gtagtaccat atactacgca 240
 gactctgtga agggccgatt caccatctcc agggacaacg ccaagaattc actgtatctg 300
 caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgctgag gcgtatagga 360
 ggtatggacg tctggggcca agggaccacg gtcaccgtct cctcagcttc caccaagggc 420
 ccatccgtct tccccctggc gccctgctct agaagcacct ccgagagcac agcggccctg 480
 ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgctgtggaa ctcaggcgct 540
 ctgaccagcg gcgtgcacac cttcccagct gtcctacagt cctcaggact ctactccctc 600
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 gatcacaagc ccagcaacac caaggtggac aagacagttg agcgcaaagt ttgtgtcgag 720
 tgcccaccgt gccagcacc acctgtggca ggaccgtcag tcttcctctt cccccaaaa 780
 cccaaggaca cctcatgat ctcccggacc cctgaggtca cgtgcgtggg ggtggacgtg 840
 agccacgaag accccgaggt ccagttcaac tggtagctgg acggcgtgga ggtgcataat 900
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 accgttgtgc accagactg gctgaacggc aaggagtaca agtgcaaggt ctccaacaaa 1020
 ggctccag ccccatcga gaaaaccatc tccaaaacca aagggcagcc ccgagaacca 1080
 caggtgtaca cctgcccc atcccgggag gagatgacca agaaccaggt cagcctgacc 1140

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tgccctgggtca aaggcttcta cccagcgac atcgccgtgg agtgggagag caatgggcag 1200
ccggagaaca actacaagac cacacctccc atgctggact ccgacggctc cttcttcctc 1260
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcattgctcc 1320
gtgatgcatg aggtcttgca caaccactac acgcagaaga gcctctccct gtctccgggt 1380
aaa 1383

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<210> 34

<211> 461

<212> PRT

<213> Homo sapiens

<400> 34

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Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
  1             5             10             15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
  50             55             60

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

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

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

Tyr Tyr Cys Ala Arg Arg Ile Gly Gly Met Asp Val Trp Gly Gln Gly
          115            120            125

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
          130            135            140

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
          145            150            155            160

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
          195            200            205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
          210            215            220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
          225            230            235            240

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Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	
				245					250					255		
Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	
				260					265					270		
Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	
				275					280					285		
Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	
				290					295					300		
Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	
				305					310					315		
Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	
				325					330					335		
Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	
				340					345					350		
Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	
				355					360					365		
Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	
				370					375					380		
Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	
				385					390					395		
Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	
				405					410					415		
Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	
				420					425					430		
Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	
				435					440					445		
His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys				
				450					455					460		

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<210> 35
<211> 708
<212> DNA
<213> Homo sapiens
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<400> 35						
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gtcaccatca	cttgccgggc	aagtcaagac	attagcggct	ttttaatttg	gtatcagcag	180
agaccaggga	aagcccccta	gctcctgatc	tatgctacat	ccagtttaca	aagtggggtc	240
ccatcaaggt	tcagtgccag	tgatctctgg	acagatttca	ctctcaccat	cagcagtctg	300
caacctgaag	attttgcaac	tactactctg	caacagagtt	acagtacccc	attcactttc	360
ggccctggga	ccaaagtgga	tatcaaacga	actgtggctg	caccatctgt	cttcactctc	420

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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

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<210> 36

<211> 236

<212> PRT

<213> Homo sapiens

<400> 36

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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 Ser Ile Ser Gly Phe Leu Ile Trp Tyr Gln Gln Arg Pro Gly Lys
 50              55              60

Ala Pro Lys Leu Leu Ile Tyr Ala Thr Ser Ser Leu Gln 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

Ser Tyr Ser Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp 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

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<210> 37
 <211> 1383
 <212> DNA
 <213> Homo sapiens

<400> 37
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 gtgcagctgg tggagtctgg gggaggcttg gtcaagcctg gagggtcctt gagactctcc 120
 tgtgcagcct ctggattcac cttcagtgac tactatatga gctggatccg ccaggctcca 180
 gggaaggggac tggagtgggt ttcatacatt agtagtagtg gtagtaccat atactacgca 240
 gactctgtga agggccgatt caccatctcc agggacaacg ccaagaactc actgtatctg 300
 caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgagag aggcctaact 360
 ggggactact ggggccaggg aaccctggtc accgtctcct cagcttccac caagggccca 420
 tccgtcttcc ccctggcgcc ctgctctaga agcacctccg agagcacagc ggccctgggc 480
 tgcctggtca aggactactt ccccgaaaccg gtgacgggtg cgtggaactc aggcgtctg 540
 accagcggcg tgcacacctt cccagctgtc ctacagtcct caggactcta ctccctcagc 600
 agcgtggtag ccgtgccctc cagcagcttg ggcacgaaga cctacacctg caacgtagat 660
 cacaagccca gcaacaccaa ggtggacaag agagttgagt ccaaataatg tcccccatgc 720
 ccatcatgcc cagcacctga gttcctgggg ggaccatcag tcttcctggt cccccaaaaa 780
 cccaaggaca ctctcatgat ctcccgacc cctgaggtca cgtgcgtggg ggtggacgtg 840
 agccaggaag accccgaggt ccagttcaac tggtagctgg atggcgtgga ggtgcataat 900
 gccaagacaa agccgcggga ggagcagttc aacagcacgt accgtgtggg cagcgtcctc 960
 accgtcctgc accaggactg gctgaacggc aaggagtaca agtgcaagggt ctccaacaaa 1020
 ggcctcccgt cctccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagagcca 1080
 caggtgtaca ccctgcccc atcccaggag gagatgacca agaaccaggt cagcctgacc 1140
 tgcctgggtca aaggcttcta cccagcgac atcgccgtgg agtgggagag caatgggcag 1200
 ccggagaaca actacaagac cagcctccc gtgctggact ccgacggctc cttctctc 1260
 tacagcaggc taaccgtgga caagagcagg tggcaggagg ggaatgtctt ctcatgctcc 1320
 gtgatgcatg aggtcttgca caaccactac acacagaaga gcctctccct gtctccgggt 1380
 aaa 1383

<210> 38
 <211> 461
 <212> PRT
 <213> Homo sapiens

<400> 38
 Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
 1 5 10 15
 Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
 20 25 30
 Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 35 40 45
 Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60
 Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
 65 70 75 80
 Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
 85 90 95

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

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

<210> 39

<400> 39
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<210> 40

<400> 40
000

<210> 41

<400> 41
000

<210> 42

<400> 42
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<210> 43

<211> 705

<212> DNA

<213> Homo sapiens

<400> 43

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gaatttgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 120
ctctcctgca gggccagtc gagtgtagc agcagttact tagcctggta ccagcagaaa 180
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 240
gacaggttca gtggcagtg gtctgggaca gacttcactc tcaccatcag cagactggag 300
cctgaagatt ttgtagtgt ttactgtcag cagtatggta gctcacctct cactttcggc 360
ggagggacca aggtggagat caaacgaact gtggctgcac catctgtctt catcttcccg 420
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 480
tatcccagag aggcctaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 540
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccttg 600
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 660

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ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt

705

<210> 44

<211> 235

<212> PRT

<213> Homo sapiens

<400> 44

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
 1 5 10 15

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

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
 35 40 45

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

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

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

Ser Arg Leu Glu Pro Glu Asp Phe Val Val Tyr Tyr Cys Gln Gln Tyr
 100 105 110

Gly Ser Ser 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> 45

<211> 1386

<212> DNA

<213> Homo sapiens

<400> 45

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gtgcagctgg tggagtctgg gggaggcttg gtcaagcctg gaggggccct gagactctcc 120
tgtgcagcct ctggattcac cttcagtgac tactacatga gctggatccg ccagggtcca 180
gggaaggggc tggagtgggt ttcatacatt agtagtagtg gtagtaccat atactacgca 240
gactctgtga agggccgatt caccatctcc agggacaacg ccaagaattc actgtatctg 300
caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgagag gcgtatagga 360
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctcagcttc caccaagggc 420
ccatccgtct tccccctggc gccctgctct agaagcacct ccgagagcac agcggccctg 480
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgct 540
ctgaccagcg gcgtgcacac cttcccagct gtcctacagt cctcaggact ctactccctc 600
agcagcgtgg tgaccgtgcc ctccagcagc ttgggcacga agacctacac ctgcaacgta 660
gatcacaagc ccagcaacac caagggtggc aagagagttg agtccaaata tgggtcccca 720
tgcccatcat gccagcacc tgagttcctg gggggaccat cagtcttctt gttcccca 780
aaaccaagg acactctcat gatctcccgg accctgagg tcacgtgcgt ggtggtggac 840
gtgagccagg aagaccccga ggtccagttc aactggtagc tggatggcgt ggaggtgcat 900
aatgccaaaga caaagccgag ggaggagcag ttcaacagca cgtaccgtgt ggtcagcgct 960
ctcaccgtcc tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac 1020
aaaggcctcc cgtcctccat cgagaaaacc atctccaaag ccaaagggca gccccgagag 1080
ccacaggtgt acaccctgcc cccatcccag gaggagatga ccaagaacca ggtcagcctg 1140
acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg 1200
cagccggaga acaactacaa gaccacgcct cccgtgctgg actccgacgg ctccttcttc 1260
ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt cttctcatgc 1320
tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctccg 1380
ggtaaa

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<210> 46

<211> 462

<212> PRT

<213> Homo sapiens

<400> 46

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Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
  1             5             10             15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
      50             55             60

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

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

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

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

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
 420 425 430

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

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455 460

<210> 47
 <211> 708
 <212> DNA
 <213> Homo sapiens

<400> 47
 atggacatga ggggtccccgc tcagctcctg ggggtcctgc tactctggct ccgaggtgcc 60
 agatgtgaca tccagatgac ccagttccca tcctccctgt ctgcatctgt aggagacaga 120
 gtcaccatca cttgccgggc aagtcagagc attagcggct ttttaatttg gtatcagcag 180
 agaccaggga aagcccctaa gctcctgata tatgtacat ccagtttaca aagtgggggc 240
 ccattaaggt tcagtggcag tgaatctggg acagatttca ctctcaccat cagcagtctg 300
 caacctgaag attttgcaac ttactactgt caacagagtt acagtacccc attcactttc 360
 ggccctggga ccaaagtgga tatcaaacga actgtggctg 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> 48
 <211> 236
 <212> PRT
 <213> Homo sapiens

<400> 48
 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 Ser Ile Ser Gly Phe Leu Ile Trp Tyr Gln Gln Arg Pro Gly Lys
 50 55 60

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

Pro Leu Arg Phe Ser Gly Ser Glu 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
Ser Tyr Ser Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp 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> 49

<400> 49

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<210> 50

<211> 462

<212> PRT

<213> Homo sapiens

<400> 50

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15
Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45
Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60
Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
65 70 75 80
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

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

<400> 51
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<400> 52

Met 1	Asp	Met	Arg	Val 5	Pro	Ala	Gln	Leu	Leu 10	Gly	Leu	Leu	Leu	Leu 15	Trp
Leu	Arg	Gly	Ala 20	Arg	Cys	Asp	Ile	Gln 25	Met	Thr	Gln	Ser	Pro 30	Ser	Ser
Leu	Ser	Ala 35	Ser	Val	Gly	Asp	Arg 40	Val	Thr	Ile	Thr	Cys 45	Arg	Ala	Ser
Gln	Ser 50	Ile	Ser	Gly	Phe	Leu 55	Ile	Trp	Tyr	Gln	Gln 60	Lys	Pro	Gly	Lys
Ala 65	Pro	Lys	Leu	Leu	Ile 70	Tyr	Ala	Thr	Ser	Ser 75	Leu	Gln	Ser	Gly	Val 80
Pro	Ser	Arg	Phe	Ser 85	Gly	Ser	Gly	Ser	Gly 90	Thr	Asp	Phe	Thr	Leu 95	Thr
Ile	Ser	Ser	Leu 100	Gln	Pro	Glu	Asp	Phe 105	Ala	Thr	Tyr	Tyr	Cys 110	Gln	Gln
Ser	Tyr 115	Ser	Thr	Pro	Phe	Thr	Phe 120	Gly	Pro	Gly	Thr	Lys 125	Val	Asp	Ile
Lys 130	Arg	Thr	Val	Ala	Ala	Pro 135	Ser	Val	Phe	Ile	Phe 140	Pro	Pro	Ser	Asp
Glu 145	Gln	Leu	Lys	Ser	Gly 150	Thr	Ala	Ser	Val	Val 155	Cys	Leu	Leu	Asn 160	Asn
Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu

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

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455 460

<210> 55

<400> 55
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<210> 56
 <211> 236
 <212> PRT
 <213> Homo sapiens

<400> 56
 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 Pro Ser
 35 40 45
 Gln Ile Ile Ser Ser Leu Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
 50 55 60
 Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln 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
 Ser Tyr Ser Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp 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> 57

<400> 57
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<210> 58
 <211> 467
 <212> PRT
 <213> Homo sapiens

<400> 58
 Met Glu Leu Gly Leu Cys Trp Val Phe Leu Val Ala Ile Leu Glu Gly
 1 5 10 15
 Val Gln Cys Glu Val Gln Leu Val 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 Thr Phe
 35 40 45
 Ser Ser Phe Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60
 Glu Trp Val Ser Tyr Ile Ser Ser Arg Ser Ser Thr Ile Ser Tyr Ala
 65 70 75 80
 Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
 85 90 95
 Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val
 100 105 110
 Tyr Tyr Cys Ala Arg Asp Pro Leu Leu Ala Gly Ala Thr Phe Phe Asp
 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 Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
 210 215 220
 Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
 225 230 235 240
 Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
 245 250 255
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 260 265 270
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
 275 280 285
 Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 290 295 300
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
 305 310 315 320
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 325 330 335
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
 340 345 350
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 355 360 365
 Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
 370 375 380
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 385 390 395 400
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 405 410 415
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
 420 425 430
 Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
 435 440 445
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 450 455 460
 Pro Gly Lys
 465

<210> 59

<400> 59

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<210> 60

<211> 235

<212> PRT

<213> Homo sapiens

<400> 60

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
 1 5 10 15

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

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
 35 40 45

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

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

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

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

Gly Ser Ser 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> 61

<400> 61

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<210> 62

<211> 466

<212> PRT

<213> Homo sapiens

<400> 62

Met Glu Leu Gly Leu Cys Trp Val Phe Leu Val Ala Ile Leu Glu Gly
 1 5 10 15

Val Gln Cys Glu Val Gln Leu Val 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 Thr Phe
 35 40 45

Ser Ser Phe Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

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

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

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

Tyr Tyr Cys Ala Arg Asp Pro Leu Leu Ala Gly Ala Thr Phe Phe Asp
 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> 63

 <400> 63
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<210> 64

 <400> 64
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<210> 65

<400> 65
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<210> 66
<211> 461
<212> PRT
<213> Homo sapiens

<400> 66
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

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

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

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

Tyr Tyr Cys Ala Ile Arg Ile Gly Gly Met Asp Val Trp Gly Gln Gly
115 120 125

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
130 135 140

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145 150 155 160

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
195 200 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
210 215 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225 230 235 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
 245 250 255
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 260 265 270
 Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
 275 280 285
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 290 295 300
 Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
 305 310 315 320
 Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 325 330 335
 Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 340 345 350
 Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 355 360 365
 Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 370 375 380
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 385 390 395 400
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
 405 410 415
 Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 420 425 430
 Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 435 440 445
 His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455 460

<210> 67

 <400> 67
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<210> 68

 <400> 68
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<210> 69

<400> 69
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<210> 70
<211> 461
<212> PRT
<213> Homo sapiens

<400> 70
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15
Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45
Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60
Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
65 70 75 80
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Ala Arg Ile Gly Gly Met Asp Val Trp Gly Gln Gly Thr
115 120 125
Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
130 135 140
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
145 150 155 160
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
165 170 175
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
180 185 190
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
195 200 205
Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
210 215 220
Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys
225 230 235 240
Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
245 250 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 260 265 270
 Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
 275 280 285
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 290 295 300

 Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 305 310 315 320
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 325 330 335
 Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
 340 345 350
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 355 360 365
 Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 370 375 380
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 385 390 395 400
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 405 410 415
 Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
 420 425 430
 Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 435 440 445
 His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455 460

<210> 71

 <400> 71
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<210> 72

 <400> 72
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<210> 73

<400> 73
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<210> 74
<211> 460
<212> PRT
<213> Homo sapiens

<400> 74
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15
Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45
Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60
Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
65 70 75 80
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Ala Arg Gly Leu Thr Gly Asp Tyr Trp Gly Gln Gly Thr
115 120 125
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
130 135 140
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
145 150 155 160
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
165 170 175
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
180 185 190
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
195 200 205
Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
210 215 220
Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
225 230 235 240
Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
245 250 255

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 260 265 270
 Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
 275 280 285
 Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 290 295 300
 Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
 305 310 315 320
 Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 325 330 335
 Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
 340 345 350
 Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 355 360 365
 Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 370 375 380
 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 385 390 395 400
 Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
 405 410 415
 Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 420 425 430
 Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 435 440 445
 Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455 460

<210> 75

 <400> 75
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<210> 76

 <400> 76
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<210> 77

 <400> 77
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<210> 78
 <211> 461
 <212> PRT
 <213> Homo sapiens

<400> 78

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Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
 1           5           10           15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
          50           55           60

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

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

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

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

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
          145          150          155          160

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
          165          170          175

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

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
          195          200          205

Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
          210          215          220

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

Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
          245          250          255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu

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260	265	270
Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln		
275	280	285
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys		
290	295	300
Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu		
305	310	315
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys		
	325	330
		335
Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys		
	340	345
		350
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser		
	355	360
		365
Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys		
	370	375
		380
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln		
385	390	395
		400
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly		
	405	410
		415
Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln		
	420	425
		430
Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn		
	435	440
		445
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
	450	455
		460

<210> 79

<400> 79

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<210> 80

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<210> 81

<400> 81

000

<210> 82

<211> 461

<212> PRT

<213> Homo sapiens

<400> 82

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
 1 5 10 15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

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

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

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

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

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
 145 150 155 160

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 165 170 175

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

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 195 200 205

Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
 210 215 220

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

Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
 245 250 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 260 265 270

Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
 275 280 285
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 290 295 300
 Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 305 310 315 320
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 325 330 335
 Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
 340 345 350
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 355 360 365
 Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 370 375 380
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 385 390 395 400
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 405 410 415
 Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
 420 425 430
 Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 435 440 445
 His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455 460

<210> 83

 <400> 83
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<210> 84

 <400> 84
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<210> 85

 <400> 85
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<210> 86

<211> 462

<212> PRT

<213> Homo sapiens

<400> 86

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
 1 5 10 15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

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

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

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

Tyr Tyr Cys Ala Arg Arg Ile Gly Gly Met Asp Val Trp Gly Gln Gly
 115 120 125

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 130 135 140

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
 145 150 155 160

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 195 200 205

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
 210 215 220

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
 225 230 235 240

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
 245 250 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 260 265 270

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val

275	280	285
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr		
290	295	300
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val		
305	310	315
320		
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys		
325	330	335
Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser		
340	345	350
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro		
355	360	365
Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val		
370	375	380
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly		
385	390	395
400		
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp		
405	410	415
Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp		
420	425	430
Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His		
435	440	445
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
450	455	460

<210> 87

<400> 87

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<210> 88

<400> 88

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<210> 89

<400> 89

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<210> 90

<211> 467

<212> PRT

<213> Homo sapiens

<400> 90

Met Glu Leu Gly Leu Cys Trp Val Phe Leu Val Ala Ile Leu Glu Gly
 1 5 10 15

Val Gln Cys Glu Val Gln Leu Val 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 Thr Phe
 35 40 45

Ser Ser Phe Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

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

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

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

Tyr Tyr Cys Ala Arg Asp Pro Leu Leu Ala Gly Ala Thr Phe Phe Asp
 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 Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
 210 215 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
 225 230 235 240

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
 245 250 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
 275 280 285
 Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 290 295 300
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
 305 310 315 320
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 325 330 335
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
 340 345 350
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 355 360 365
 Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
 370 375 380
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 385 390 395 400
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 405 410 415
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
 420 425 430
 Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
 435 440 445
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 450 455 460
 Pro Gly Lys
 465

<210> 91

 <400> 91
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<210> 92

 <400> 92
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<210> 93

 <400> 93
 000

<210> 94

<211> 467

<212> PRT

<213> Homo sapiens

<400> 94

Met Glu Leu Gly Leu Cys Trp Val Phe Leu Val Ala Ile Leu Glu Gly
 1 5 10 15

Val Gln Cys Glu Val Gln Leu Val 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 Thr Phe
 35 40 45

Ser Ser Phe Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

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

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

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

Tyr Tyr Cys Ala Arg Asp Pro Leu Leu Ala Gly Ala Thr Phe Phe Asp
 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 Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
 210 215 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
 225 230 235 240

Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly
 245 250 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

260	265	270
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln		
275	280	285
Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val		
290	295	300
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr		
305	310	315
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly		
325	330	335
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile		
340	345	350
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val		
355	360	365
Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser		
370	375	380
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu		
385	390	395
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro		
405	410	415
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val		
420	425	430
Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met		
435	440	445
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser		
450	455	460
Pro Gly Lys		
465		

<210> 95

<400> 95
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<210> 96

<400> 96
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<210> 97

<211> 1413

<212> DNA

<213> Homo sapiens

<400> 97

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tgtgcagcct ctggattcac cttcagtagt tttagtagta cctgggtccg ccaggctcca 180
ggaaaggggc tggagtgggt ttcatacatt agtagtagaa gtagtaccat atcctacgca 240
gactctgtga agggccgatt caccatctcc agagacaatg ccaagaactc actgtatctg 300
caaatgaaca gcctgagaga cgaggacacg gctgtgtatt actgtgcgag agatcctctt 360
ctagcgggag ctaccttctt tgactactgg ggccaggga ccttggtcac cgtctcctca 420
gcctccacca agggcccatc ggtcttcccc ctggcacctt cctccaagag cacctctggg 480
ggcacagcgg ccctgggctg cctgggtcaag gactacttcc ccgaaccggt gacggtgtcg 540
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ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg caccagacc 660
tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc 720
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ccgtcagctc tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccgaccctc 840
gaggtcacat gcgtgggtgg ggacgtgagc cacgaagacc ctgagggtcaa gttcaactgg 900
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 960
agcacgtacc gtgtgggtcag cgtcctcacc gtcctgcacc aggactgggt gaatggcaag 1020
gagtacaagt gcaagggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 1080
aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggatgag 1140
ctgaccaaga accagggtcag cctgacctgc ctgggtcaaag gcttctatcc cagcgacatc 1200
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 1260
ctggactccg acgggtcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1320
cagcagggga acgtcttctc atgtccctg atgcatgagg ctctgcacaa ccactacacg 1380
cagaagagcc tctccctgtc tccgggtaaa tag 1413

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<210> 98

<211> 470

<212> PRT

<213> Homo sapiens

<400> 98

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Met Glu Leu Gly Leu Cys Trp Val Phe Leu Val Ala Ile Leu Glu Gly
 1              5              10              15

Val Gln Cys Glu Val Gln Leu Val 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 Thr Phe
      35              40              45

Ser Ser Phe Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
      50              55              60

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

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

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

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Tyr Tyr Cys Ala Arg Asp Pro Leu Leu Ala Gly Ala Thr Phe Phe Asp
 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 Ser Ser Lys Ser Thr Ser Gly
 145 150 155 160
 Gly 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 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
 210 215 220
 Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
 225 230 235 240
 Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
 245 250 255
 Leu Leu Gly 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 Lys Phe Asn Trp Tyr Val Asp Gly
 290 295 300
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
 305 310 315 320
 Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 325 330 335
 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
 340 345 350
 Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 355 360 365
 Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu 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 Val 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> 99

<400> 99
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<210> 100

<400> 100
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<210> 101

<211> 1395

<212> DNA

<213> Homo sapiens

<400> 101

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 gtgcagctgg tggagtctgg gggaggcttg gtcaagcctg gaggggccct gagactctcc 120
 tgtgcagcct ctggattcac cttcagtgac tactatatga gctggatccg ccagggtcca 180
 ggggaaggac tggagtgggt ttcatacatt agtagtagtg gtagtaccat atactacgca 240
 gactctgtga agggccgatt caccatctcc agggacaacg ccaagaactc actgtatctg 300
 caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgagag aggcctaact 360
 ggggactact ggggcccagg aaccctgggc accgtctcct cagcttccac caagggccca 420
 tcggtcttcc ccctggcacc ctctccaag agcacctctg ggggcacagc ggccctgggc 480
 tgcctgggtca aggactactt cccgaaccg gtgacgggtg cgtggaactc aggcgccttg 540
 accagcggcg tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc 600
 agcgtgggtga ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat 660
 cacaagccca gcaacaccaa ggtggacaag aaagttgagc ccaaactctg tgacaaaact 720
 cacacatgcc caccgtgccc agcacctgaa ctcttggggg gaccgtcagt cttctcttcc 780

ccccaaaaac ccaaggacac cctcatgata tcccggaccc ctgaggtcac atgcgtggtg 840
 gtggacgtga gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag 900
 gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc 960
 agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc 1020
 tccaacaaag ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc 1080
 cgagaaccac aggtgtacac cctgccccca tcccgggatg agctgaccaa gaaccaggtc 1140
 agcctgacct gcctgggtcaa aggcctctat cccagcgaca tcgccgtgga gtgggagagc 1200
 aatgggcagc cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc 1260
 ttcttctctc acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc 1320
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<210> 102

<211> 464

<212> PRT

<213> Homo sapiens

<400> 102

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Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
 1           5           10           15

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

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

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
      50           55           60

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

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

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

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

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

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

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
      165          170          175

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

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
      195          200          205

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
      210          215          220

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

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
      245          250          255

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg

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<400> 103
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 Ser 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

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Tyr Ala Ala Ser Ser Leu Gln 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 Ser Tyr Ser Thr Pro Phe
 85 90 95
 Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 104
 <211> 120
 <212> PRT
 <213> Homo sapiens

<400> 104
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Tyr Ser Gly Ser Tyr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser Ala
 115 120

<210> 105
 <211> 119
 <212> PRT
 <213> Homo sapiens

<400> 105
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95
 Arg Gly Ile Ala Ala Ala Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser Ala
 115

<210> 106
 <211> 117
 <212> PRT
 <213> Homo sapiens

<400> 106
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
 20 25 30
 Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ala Leu Gly Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
 100 105 110
 Thr Val Ser Ser Ala
 115

<210> 107
 <211> 107
 <212> PRT
 <213> Homo sapiens

<400> 107

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Phe
 85 90 95
 Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 108
 <211> 115
 <212> PRT
 <213> Homo sapiens

<400> 108
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
 20 25 30
 Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Leu Thr Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
 100 105 110
 Ser Ser Ala
 115

<210> 109
 <211> 108
 <212> PRT

<213> Homo sapiens

<400> 109

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln 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 Ala Asn Ser Phe Pro Phe
 85 90 95
 Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
 100 105

<210> 110

<211> 117

<212> PRT

<213> Homo sapiens

<400> 110

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Gly Tyr Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser Ala
 115

<210> 111
 <211> 118
 <212> PRT
 <213> Homo sapiens

<400> 111
 Gln 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 Ser Tyr
 20 25 30
 Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
 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 Asp Tyr Gly Gly Asn Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser Ala
 115

<210> 112
 <211> 114
 <212> PRT
 <213> Homo sapiens

<400> 112
 Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
 20 25 30
 Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60
 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
 85 90 95
 Tyr Tyr Ser Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile

100 105 110
 Lys Arg

 <210> 113
 <211> 116
 <212> PRT
 <213> Homo sapiens

 <400> 113
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

 Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ile Val Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110
 Val Ser Ser Ala
 115

 <210> 114
 <211> 109
 <212> PRT
 <213> Homo sapiens

 <400> 114
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

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<210> 115
<211> 114
<212> PRT
<213> Homo sapiens
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<400> 115
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
  1          5          10          15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
      20          25          30

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

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
      50          55          60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
      65          70          75          80

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

Ala Ile Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
      100          105          110

Ser Ala

```

```
<210> 116
<211> 115
<212> PRT
<213> Homo sapiens
```

<400> 116
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Leu Thr Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
 100 105 110
 Ser Ser Ala
 115

<210> 117
 <211> 108
 <212> PRT
 <213> Homo sapiens

<400> 117
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln 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 Ala Asn Ser Phe Pro Leu
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
 100 105