(19) DANMARK

(10) DK/EP 3337829 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 K 16/44 (2006.01)* *A 61 K 39/395 (2006.01)* *A 61 P 35/04 (2006.01)* *G 01 N 33/574 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2020-02-17**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2020-01-08**

(86) Europæisk ansøgning nr.: **17708098.3**

(86) Europæisk indleveringsdag: **2017-02-16**

(87) Den europæiske ansøgnings publiceringsdag: **2018-06-27**

(86) International ansøgning nr.: **US2017018185**

(87) Internationalt publikationsnr.: **WO2017143073**

(30) Prioritet: **2016-02-19 US 201662297744 P** **2016-11-22 US 201662425495 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Siwa Corporation, 400 East Randolph 3913, Chicago, Illinois 60601, USA**

(72) Opfinder: **GRUBER, Lewis, S., 400 East Randolph 3911, Chicago, Illinois 60601, USA**

(74) Fuldmægtig i Danmark: **Budde Schou A/S, Hausergade 3, 1128 København K, Danmark**

(54) Benævnelse: **FREMGANGSMÅDE OG SAMMENSÆTNING TIL BEHANDLING AF CANCER, DRAB AF METASTATISKE CANCERCELLER OG FOREBYGGELSE AF CANCERMETASTASE VED HJÆLP AF ANTISTOFFER MOD AVANCEREDE GLYKERINGSSLUTPRODUKTER (age)**

(56) Fremdragne publikationer:
EP-A1- 1 415 997
WO-A1-2017/065837
VAN HEIJST JEROEN W J ET AL: "Advanced glycation end products in human cancer tissues: detection of Nepsilon-(carboxymethyl)lysine and argpyrimidine.", June 2005 (2005-06), ANNALS OF THE NEW YORK ACADEMY OF SCIENCES JUN 2005, VOL. 1043, PAGE(S) 725 - 733, XP008184426, ISSN: 0077-8923 the whole document
KOBAYASHI SHINJIRO ET AL: "Overproduction of N(epsilon)-(carboxymethyl)lysine-induced neovascularization in cultured choroidal explant of aged rat.", BIOLOGICAL & PHARMACEUTICAL BULLETIN JAN 2007, vol. 30, no. 1, January 2007 (2007-01), pages 133-138, XP55369124, ISSN: 0918-6158
D. FOSTER ET AL: "AGE Metabolites: A Biomarker Linked to Cancer Disparity?", CANCER EPIDEMIOLOGY, BIOMARKERS AND PREVENTION., vol. 23, no. 10, 22 July 2014 (2014-07-22) , pages 2186-2191, XP055369101, US ISSN: 1055-9965, DOI: 10.1158/1055-9965.EPI-14-0564
ABDUL ROUF MIR ET AL: "Structural changes in histone H2A by methylglyoxal generate highly immunogenic amorphous aggregates with implications in auto-immune response in cancer", GLYCOBIOLOGY, vol. 26, no. 2, 26 September 2015 (2015-09-26), pages 129-141, XP055369061, US ISSN: 0959-6658, DOI: 10.1093/glycob/cwv082

Fortsættes ...

SHUN-YAO KO ET AL: "Cell Migration Is Regulated by AGE-RAGE Interaction in Human Oral Cancer Cells In Vitro", PLOS ONE, vol. 9, no. 10, 16 October 2014 (2014-10-16), page e110542, XP055369069, DOI: 10.1371/journal.pone.0110542
HANBEI CHEN ET AL: "Advanced glycation end products increase carbohydrate responsive element binding protein expression and promote cancer cell proliferation", MOLECULAR AND CELLULAR ENDOCRINOLOGY., vol. 395, no. 1-2, 1 September 2014 (2014-09-01), pages 69-78, XP055369075, IE ISSN: 0303-7207, DOI: 10.1016/j.mce.2014.07.021
MERCADO-PIMENTEL MELANIA E ET AL: "The S100P/RAGE signaling pathway regulates expression of microRNA-21 in colon cancer cells", FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 589, no. 18, 17 July 2015 (2015-07-17), pages 2388-2393, XP029256898, ISSN: 0014-5793, DOI: 10.1016/J.FEBSLET.2015.07.010
Anonymous: "Carboxymethyl Lysine Antibody MAB3247", , 13 October 2015 (2015-10-13), XP55292706, Retrieved from the Internet: URL:https://resources.rndsystems.com/pdfs/ datasheets/mab3247.pdf [retrieved on 2016-08-02]

DESCRIPTION

BACKGROUND

[0001] Senescent cells are cells that are partially-functional or non-functional and are in a state of proliferative arrest. Senescence is a distinct state of a cell, and is associated with biomarkers, such as activation of the biomarker $p16^{Ink4a}$ ("p16"), and expression of β-gaiactosidase. Senescence begins with damage or stress (such as overstimulation by growth factors) of cells. The damage or stress negatively impacts mitochondrial DNA in the cells to cause them to produce free radicals which react with sugars in the cell to form methyl glyoxal (MG). MG in turn reacts with proteins or lipids to generate advanced glycation end products (AGEs). In the case of the protein component lysine, MG reacts to form carboxymethyllysine, which is an AGE. AGEs also form from non-enzymatic reaction of sugars in the blood with external cell proteins.

[0002] Damage or stress to mitochondrial DNA also sets off a DNA damage response which induces the cell to produce cell cycle blocking proteins. These blocking proteins prevent the cell from dividing. Continued damage or stress causes mTOR production, which in turn activates protein synthesis and inactivates protein breakdown. Further stimulation of the cells leads to programmed cell death (apoptosis).

[0003] p16 is a protein involved in regulation of the cell cycle, by inhibiting the S phase. It can be activated during ageing or in response to various stresses, such as DNA damage, oxidative stress or exposure to drugs. p16 is typically considered a tumor suppressor protein, causing a cell to become senescent in response to DNA damage and irreversibly preventing the cell from entering a hyperproliferative state. However, there has been some ambiguity in this regard, as some tumors show overexpression of p16, while other show downregulated expression. Evidence suggests that overexpression of p16 in some tumors results from a defective retinoblastoma protein ("Rb"). p16 acts on Rb to inhibit the S phase, and Rb downregulates p16, creating negative feedback. Defective Rb fails to both inhibit the S phase and downregulate p16, thus resulting in overexpression of p16 in hyperproliferating cells. Romagosa, C. et al., p16Ink4a overexpression in cancer: a tumor suppressor gene associated with senescence and high-grade tumors, Oncogene, Vol. 30, 2087-2097 (2011).

[0004] Senescent cells are known to fuel the growth of cancer cells. Senescent cells are associated with secretion of many factors involved in intercellular signaling, including pro-inflammatory factors; secretion of these factors has been termed the senescence-associated secretory phenotype, or SASP. One study showed that senescent mesenchymal stem cells promote proliferation and migration of breast cancer cells by the secretion of IL-6 (Di, G-h. et al. IL-6 Secreted from Senescent Mesenchymal Stem Cells Promotes Proliferation and migration of Breast Cancer Cells, PLOS One, Vol. 9, 11, e113572 (2014)). Another study showed that senescent human fibroblasts increase the growth of tumors by the secretion of matrix metalloproteinase (Liu, D. et al. Senescent Human Fibroblasts Increase the Early Growth of Xenograft Tumors via Matrix Metalloproteinase Secretion, Cancer Res, Vol. 67, 3117-3126 (2007)).

[0005] Senescent cells secrete reactive oxygen species ("ROS") as part of the SASP. ROS is believed to play an important role in maintaining senescence of cells. The secretion of ROS creates a bystander effect, where senescent cells induce senescence in neighboring cells: ROS create the very cellular damage known to activate p16 expression, leading to senescence (Nelson, G., A senescent cell bystander effect: senescence-induced senescence, Aging Cell, Vo. 11, 345-349 (2012)). The p16/Rb pathway leads to the induction of ROS, which in turn activates the protein kinase C delta creating a positive feedback loop that further enhance ROS, helping maintain the irreversible cell cycle arrest; it has even been suggested that exposing cancer cells to ROS might be effective to treat cancer by inducing cell phase arrest in hyperproliferating cells (Rayess, H. et al., Cellular senescence and tumor suppressor gene p16, Int J Cancer, Vol. 130, 1715-1725 (2012)).

[0006] Advanced glycation end-products (AGEs; also referred to as AGE-modified proteins, or glycation end-products) arise from a non-enzymatic reaction of sugars with protein side-chains (Ando, K. et al., Membrane Proteins of Human Erythrocytes Are Modified by Advanced Glycation End Products during Aging in the Circulation, Biochem Biophys Res Commun., Vol. 258, 123, 125 (1999)). This process begins with a reversible reaction between the reducing sugar and the amino group to form a Schiff base, which proceeds to form a covalently-bonded Amadori rearrangement product. Once formed, the Amadori product undergoes further rearrangement to produce AGEs. Hyperglycemia, caused by diabetes mellitus (DM), and oxidative stress promote this post-translational modification of membrane proteins (Lindsey JB, et al., "Receptor For Advanced Glycation End-Products (RAGE) and soluble RAGE (sRAGE): Cardiovascular Implications," Diabetes Vascular Disease Research, Vol. 6(1), 7-14, (2009)). AGEs have been associated with several pathological conditions including diabetic complications, inflammation, retinopathy, nephropathy, atherosclerosis, stroke, endothelial cell dysfunction, and neurodegenerative disorders (Bierhaus A, "AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept," Cardiovasc Res, Vol. 37(3), 586-600 (1998)).

[0007] AGE-modified proteins are also a marker of senescent cells. This association between glycation end-product and senescence is well known in the art. See, for example, Gruber, L. (WO 2009/143411, 26 Nov. 2009), Ando, K. et al. (Membrane Proteins of Human Erythrocytes Are Modified by Advanced Glycation End Products during Aging in the Circulation, Biochem Biophys Res Commun., Vol. 258, 123, 125 (1999)), Ahmed, E.K. et al. ("Protein Modification and Replicative Senescence of WI-38 Human Embryonic Fibroblasts" Aging Cells, vol. 9, 252, 260 (2010)), Vlassara, H. et al. (Advanced Glycosylation Endproducts on Erythrocyte Cell Surface Induce Receptor-Mediated Phagocytosis by Macrophages, J. Exp. Med., Vol. 166, 539, 545 (1987)) and Vlassara et al. ("High-affinity-receptor-mediated Uptake and Degradation of Glucose-modified Proteins: A Potential Mechanism for the Removal of Senescent Macromolecules" Proc. Natl. Acad. Sci. USAI, Vol. 82, 5588, 5591 (1985)). Furthermore, Ahmed, E.K. *et al.* indicates that glycation end-products are "one of the major causes of spontaneous damage to cellular and extracellular proteins" (Ahmed, E.K. *et al.*, see above, page 353). Accordingly, the accumulation of glycation end-products is associated with senescence. Since the formation of glycation end-products is associate with oxidation, the accumulation of glycation end-products may be a result of the formation of ROS in the senescent cells (Fu, M.-X., et al., The Advanced Glycation End Product, NE-(Carboxymethyl)lysine, Is a Product of both Lipid Peroxidation and Glycoxidation

Reactions, J. Biol. Chem., Vol. 271, 9982-9986 (1996)).

[0008] Van Heijst J. W. J. *et al.* (2005) mention the detection of N^E-(carboxymethyl)lysine (CML) and argpyrimidine in human cancer tissues (van Heijst J. W. J. et al., Advanced glycation end products in human cancer tissues: detection of NE-(carboxymethyl)lysine and argpyrimidine. Ann. N. Y. Acad. Sci. Vol 1043, 725-733 (2005)).

SUMMARY

[0009] The invention is defined according to the claims. Thus, the invention provides a composition comprising an anti-AGE antibody for use in treating metastatic cancer, and/or preventing cancer metastasis in a subject, wherein the anti-AGE antibody binds a carboxymethyllysine-modified protein.

[0010] In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

[0011] In some embodiments, the subject is selected from the group consisting of humans, mice, rats, goats, sheep, cows, horses, dogs and cats. In some embodiments, the subject is a human.

[0012] In some embodiments, the anti-AGE antibody is non-immunogenic to a species selected from the group consisting of humans, cats, dogs, horses, camels, alpaca, cattle, sheep, and goats.

[0013] In some embodiments, the subject has metastatic cancer. In some embodiments, the subject does not have metastatic cancer.

[0014] In some embodiments, the composition is in unit dosage form.

[0015] In some embodiments, (a) the subject is a human; (b) the anti-AGE antibody is non-immunogenic to a species selected from the group consisting of humans, cats, dogs, horses, camels, alpaca, cattle, sheep, and goats; (c) subject has metastatic cancer; and (d) the composition is in unit dosage form.

[0016] In some embodiments, the composition is in multidosage form. In some embodiments, the composition is sterile.

[0017] In some embodiments, the anti-AGE antibody binds a metastatic cancer cell expressing an AGE modification. In some embodiments, the anti-AGE antibody binds a circulating cell expressing an AGE modification.

[0018] In some embodiments, the subject is pregnant. In some embodiments, the subject has been previously diagnosed with cancer cachexia. In some embodiments, the subject has a compromised immune system.

[0019] In some embodiments, the metastatic cancer is metastatic breast cancer.

[0020] Disclosed herein is a method of treating cancer, killing metastatic cancer cells, killing potentially-malignant neoplasm cells and/or preventing cancer metastasis comprising administering to a subject a composition comprising an anti-AGE antibody.

[0021] Disclosed herein is a method of treating cancer, killing metastatic cancer cells, killing potentially-malignant neoplasm cells and/or preventing cancer metastasis comprising administering a composition comprising a first anti-AGE antibody and a second anti-AGE antibody. The second anti-AGE antibody is different from the first anti-AGE antibody.

[0022] Disclosed herein is a method of treating a subject with cancer, killing metastatic cancer cells, killing potentially-malignant neoplasm cells and/or preventing cancer metastasis comprising a first administering of an anti-AGE antibody; followed by testing the subject for effectiveness of the first administration at treating the cancer, killing metastatic cancer cells, killing potentially-malignant neoplasm cells and/or preventing cancer metastasis; followed by a second administering of the anti-AGE antibody.

[0023] Disclosed herein is use of an anti-AGE antibody for the manufacture of a medicament for treating cancer, killing metastatic cancer cells, killing potentially-malignant neoplasm cells and/or preventing cancer metastasis.

[0024] Disclosed herein is a composition comprising an anti-AGE antibody for use in treating cancer, killing metastatic cancer cells, killing potentially-malignant neoplasm cells and/or preventing cancer metastasis.

[0025] Disclosed herein is a composition for treating cancer, killing metastatic cancer cells, killing potentially-malignant neoplasm cells and/or preventing cancer metastasis comprising a first anti-AGE antibody, a second anti-AGE antibody and a pharmaceutically acceptable carrier. The first anti-AGE antibody is different from the second anti-AGE antibody.

[0026] Disclosed herein is a method of diagnosing metastatic cancer comprising detecting an immune complex comprising an anti-AGE antibody bound to a cell expressing an AGE modification.

[0027] Disclosed herein is an immune complex comprising an anti-AGE antibody bound to a metastatic cancer cell. The metastatic cancer cell expresses an AGE modification.

[0028] Disclosed herein is a kit for diagnosing metastatic cancer comprising an anti-AGE antibody, a control sample and, optionally, a reagent that binds to the anti-AGE antibody.

DEFINITIONS

[0029] The term "peptide" means a molecule composed of 2-50 amino acids.

[0030] The term "protein" means a molecule composed of more than 50 amino acids.

[0031] The terms "advanced glycation end-product," "AGE," "AGE-modified protein or peptide," "glycation end-product" and "AGE antigen" refer to modified proteins or peptides that are formed as the result of the reaction of sugars with protein side chains that further rearrange and form irreversible cross-links. This process begins with a reversible reaction between a reducing sugar and an amino group to form a Schiff base, which proceeds to form a covalently-bonded Amadori rearrangement product. Once formed, the Amadori product undergoes further rearrangement to produce AGEs. AGE-modified proteins and antibodies to AGE-modified proteins are described in U.S. 5,702,704 to Bucala ("Bucala") and U.S. 6,380,165 to Al-Abed et al. ("Al-Abed"). Glycated proteins or peptides that have not undergone the necessary rearrangement to form AGEs, such as N-deoxyfructosyllysine found on glycated albumin, are not AGEs. AGEs may be identified by the presence of AGE modifications (also referred to as AGE epitopes or AGE moieties) such as 2-(2-furoyl)-4(5)-(2-furanyl)-1H-imidazole ("FFI"); 5-hydroxymethyl-1-alkylpyrrole-2-carbaldehyde ("Pyrraline"); 1-alkyl-2-formyl-3,4-diglycosyl pyrrole ("AFGP"), a non-fluorescent model AGE; carboxymethyllysine; and pentosidine. ALI, another AGE, is described in Al-Abed.

[0032] "An antibody that binds to an AGE-modified protein on a cell", "anti-AGE antibody" or "AGE antibody" means an antibody or other protein that binds to an AGE-modified protein or peptide and includes a constant region of an antibody, where the protein or peptide which has been AGE-modified is a protein or peptide normally found bound on the surface of a cell, preferably a mammalian cell, more preferably a human, cat, dog, horse, camelid (for example, camel or alpaca), cattle, sheep, or goat cell. "An antibody that binds to an AGE-modified protein on a cell", "anti-AGE antibody" or "AGE antibody" does not include an antibody or other protein which binds with the same specificity and selectivity to both the AGE-modified protein or peptide, and the same non-AGE-modified protein or peptide (that is, the presence of the AGE modification does not increase binding). AGE-modified albumin is not an AGE-modified protein on a cell, because albumin is not a protein normally found bound on the surface of cells. "An antibody that binds to an AGE-modified protein on a cell", "anti-AGE antibody" or "AGE antibody" only includes those antibodies which lead to removal, destruction, or death of the cell. Also included are antibodies which are conjugated, for example to a toxin, drug, or other chemical or particle. Preferably, the antibodies are monoclonal antibodies, but polyclonal antibodies are also permissible.

[0033] The term "senescent cell" means a cell which is in a state of proliferative arrest and expresses one or more biomarkers of senescence, such as activation of $p16^{Ink4a}$ or expression of senescence-associated β-galactosidase.

[0034] The term "variant" means a nucleotide, protein or amino acid sequence different from the specifically identified sequences, wherein one or more nucleotides, proteins or amino acid residues is deleted, substituted or added. Variants may be naturally-occurring allelic variants, or non-naturally-occurring variants. Variants of the identified sequences may retain some or all of the functional characteristics of the identified sequences.

[0035] The term "percent (%) sequence identity" is defined as the percentage of amino acid residues in a candidate sequence that are identical to the amino acid residues in a reference

polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Preferably, % sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program is publicly available from Genentech, Inc. (South San Francisco, CA), or may be compiled from the source code, which has been filed with user documentation in the U.S. Copyright Office and is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0036] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. Where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained using the ALIGN-2 computer program.

[0037] The term "immune complex" means the combination of an antibody bound to an antigen. An immune complex may also be referred to as an "antibody-antigen complex."

BRIEF DESCRIPTION OF THE DRAWING

[0038]

FIG. 1 is a graph of the response versus time in an antibody binding experiment.

FIG. 2 illustrates a kit for diagnosing cancer metastases.

FIG. 3 illustrates a graph of the normalized tumor volume over the course of an *in vivo* study investigating the effect of an anti-AGE antibody on tumor growth, metastatic potential and cachexia.

FIG. 4 illustrates a graph of the normalized body weight of the mice over the course of an *in vivo* study investigating the effect of an anti-AGE antibody on tumor growth, metastatic potential and cachexia.

DETAILED DESCRIPTION

[0039] Recent research in *C. elegans* suggests that cells which are actively proliferating are not invasive, and that invasive cells such as metastasizing cancer cells are not proliferating and must be in cell-cycle arrest (Matus et al., Invasive Cell Fate Requires G1 Cell-Cycle arrest and Histone Deacetylase-Mediated Changes in Gene Expression, Developmental Cell, Vol. 35, 162-174 (2015)). Other researchers have found that formation of ROS can induce cancer cells to metastasize (Porporato, P. E., et al. A Mitochondrial Switch Promotes Tumor Metastasis, Cell Reports, Vol. 8, 754-766 (2014)).

[0040] Cell phase arrest and the production of ROS gives metastasizing cancer cells many characteristics of senescent cells, which would be expected to include the presence of AGE-modified proteins on the cell surface. AGE-modified proteins therefore provide an antigen which can be targeted using antibodies, to seek out and destroy metastasizing cancer cells. Administration of anti-AGE antibodies would kill metastasizing cancer cells, thereby treating cancer. Administration of anti-AGE antibodies would prevent metastasis in a cancer patient and could be used to prevent the speared of cancer, in a prophylactic manner.

[0041] Potentially-malignant neoplasms, such as seborrheic keratosis, actinic keratosis and carcinoma *in situ,* have many characteristics of senescent cells, such as expression of p16, which would be expected to include the presence of AGE-modified proteins on the cell surface. AGE-modified proteins therefore provide an antigen which can be targeted using antibodies, to seek out and destroy potentially-malignant neoplasm cells. Administration of anti-AGE antibodies would kill potentially-malignant neoplasm cells, thereby preventing cancer. Administration of anti-AGE antibodies would prevent cancer in a patient, in a prophylactic manner.

[0042] An antibody that binds to an AGE-modified protein on a cell ("anti-AGE antibody" or "AGE antibody") is known in the art. Examples include those described in U.S. 5,702,704 (Bucala) and U.S. 6,380,165 (Al-Abed et al.). Examples include an antibody that binds to one or more AGE-modified proteins having an AGE modification such as FFI, pyrraline, AFGP, ALI, carboxymethyllysine, carboxyethyllysine and pentosidine, and mixtures of such antibodies. Anti-AGE antibodies for use according to the invention bind carboxymethyllysine-modified proteins. Preferably, the antibody is non-immunogenic to the animal in which it will be used, such as non-immunogenic to humans; companion animals including cats, dogs and horses; and commercially important animals, such camels (or alpaca), cattle (bovine), sheep, and goats. More preferably, the antibody has the same species constant region as antibodies of the animal to reduce the immune response against the antibody, such as being humanized (for humans), felinized (for cats), caninized (for dogs), equuinized (for horses), camelized (for camels or alpaca), bovinized (for cattle), ovinized (for sheep), or caperized (for goats). Most preferably, the antibody is identical to that of the animal in which it will be used (except for the variable region), such as a human antibody, a cat antibody, a dog antibody, a horse antibody, a camel antibody, a bovine antibody, a sheep antibody or a goat antibody. Details of the constant regions and other parts of antibodies for these animals are described below. Preferably, the antibody is a monoclonal antibody, but polyclonal antibodies are also permissible.

[0043] Anti-AGE antibodies for use according to the invention include those which bind to proteins or peptides that exhibit a carboxymethyllysine modification. Particularly preferred anti-AGE antibodies according to the disclosure include those which bind to proteins or peptides that exhibit a carboxyethyllysine AGE modification. Carboxymethyllysine (also known as N(epsilon)-(carboxymethyl)lysine, N(6)-carboxymethyllysine, or 2-Amino-6-(carboxymethylamino)hexanoic acid) and carboxyethyllysine (also known as N-epsilon-(carboxyethyl)lysine) are found on proteins or peptides and lipids as a result of oxidative stress and chemical glycation. CML- and CEL-modified proteins or peptides are recognized by the receptor RAGE which is expressed on a variety of cells. CML and CEL have been well-studied and CML- and CEL-related products are commercially available. For example, Cell Biolabs, Inc. sells CML-BSA antigens, CML polyclonal antibodies, CML immunoblot kits, and CML competitive ELISA kits (www.cellbiolabs.com/cml-assays) as well as CEL-BSA antigens and CEL competitive ELISA kits (www.cellbiolabs.com/cel-n-epsilon-carboxyethyl-lysine-assays-and-reagents). A particularly preferred antibody includes the variable region of the commercially available mouse anti-glycation end-product antibody raised against carboxymethyl lysine conjugated with keyhole limpet hemocyanin, the carboxymethyl lysine MAb (Clone 318003) available from R&D Systems, Inc. (Minneapolis, MN; catalog no. MAB3247), modified to have a human constant region (or the constant region of the animal into which it will be administered). Commercially-available antibodies, such as the carboxymethyl lysine antibody corresponding to catalog no. MAB3247 from R&D Systems, Inc., may be intended for diagnostic purposes and may contain material that is not suited for use in animals or humans. Preferably, commercially-available antibodies are purified and/or isolated prior to use in animals or humans to remove toxins or other potentially-harmful material.

[0044] The anti-AGE antibody has low rate of dissociation from the antibody-antigen complex, or k_d (also referred to as k_{back} or off-rate), preferably at most 9×10^{-3}, 8×10^{3}, 7×10^{-3} or 6×10^{-3} (sec^{-1}). The anti-AGE antibody has a high affinity for the AGE-modified protein of a cell, which may be expressed as a low dissociation constant K_D of at most 9×10^{-6}, 8×10^{-6}, 7×10^{-6}, 6×10^{-6}, 5×10^{-6}, 4×10^{-6} or 3×10^{-6} (M). Preferably, the binding properties of the anti-AGE antibody are similar to, the same as, or superior to the carboxymethyl lysine MAb (Clone 318003) available from R&D Systems, Inc. (Minneapolis, MN; catalog no. MAB3247), illustrated in FIG. 1.

[0045] The anti-AGE antibody may destroy AGE-modified cells through antibody-dependent cell-mediated cytotoxicity (ADCC). ADCC is a mechanism of cell-mediated immune defense in which an effector cell of the immune system actively lyses a target cell whose membrane-surface antigens have been bound by specific antibodies. ADCC may be mediated by natural killer (NK) cells, macrophages, neutrophils or eosinophils. The effector cells bind to the Fc portion of the bound antibody. Administration of NK cells, such as NK92 cells (a cell line available from NantKwest, Culver City, CA), together with, or subsequent to, administration of anti-AGE antibodies, can enhance the compliment activity and therefore the effectiveness of the anti-AGE antibodies to kill metastasizing cancer cells. The anti-AGE antibody may also destroy AGE-modified cells through complement-dependent cytotoxicity (CDC). In CDC, the complement cascade of the immune system is triggered by an antibody binding to a target antigen.

[0046] The anti-AGE antibody may be conjugated to an agent that causes the destruction of AGE-

modified cells. Such agents may be a toxin, a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

[0047] A toxin, such as pore-forming toxins (PFT) (Aroian R. et al., "Pore-Forming Toxins and Cellular Non-Immune Defenses (CNIDs)," Current Opinion in Microbiology, 10:57-61 (2007)), conjugated to an anti-AGE antibody may be injected into a patient to selectively target and remove AGE-modified cells. The anti-AGE antibody recognizes and binds to AGE-modified cells. Then, the toxin causes pore formation at the cell surface and subsequent cell removal through osmotic lysis.

[0048] Magnetic nanoparticles conjugated to the anti-AGE antibody may be injected into a patient to target and remove AGE-modified cells. The magnetic nanoparticles can be heated by applying a magnetic field in order to selectively remove the AGE-modified cells.

[0049] As an alternative, magnetic spin-vortex discs, which are magnetized only when a magnetic field is applied to avoid self-aggregation that can block blood vessels, begin to spin when a magnetic field is applied, causing membrane disruption of target cells. Magnetic spin-vortex discs, conjugated to anti-AGE antibodies specifically target AGE-modified cell types, without removing other cells.

[0050] Antibodies typically comprise two heavy chains and two light chains of polypeptides joined to form a "Y" shaped molecule. The constant region determines the mechanism used to target the antigen. The amino acid sequence in the tips of the "Y" (the variable region) varies among different antibodies. This variation gives the antibody its specificity for binding antigen. The variable region, which includes the ends of the light and heavy chains, is further subdivided into hypervariable (HV - also sometimes referred to as complementarity determining regions, or CDRs) and framework (FR) regions. When antibodies are prepared recombinantly, it is also possible to have a single antibody with variable regions (or complementary determining regions) that bind to two different antigens, with each tip of the "Y" being specific to one of the antigens; these are referred to as bi-specific antibodies.

[0051] A humanized anti-AGE antibody for use according to the present invention may have the human constant region sequence of amino acids shown in SEQ ID NO: 22. The heavy chain complementarity determining regions of the humanized anti-AGE antibody may have one or more of the protein sequences shown in SEQ ID NO: 23 (CDR1H), SEQ ID NO: 24 (CDR2H) and SEQ ID NO: 25 (CDR3H). The light chain complementarity determining regions of the humanized anti-AGE antibody may have one or more of the protein sequences shown in SEQ ID NO: 26 (CDR1L), SEQ ID NO: 27 (CDR2L) and SEQ ID NO: 28 (CDR3L).

[0052] The heavy chain of human (*Homo sapiens*) antibody immunoglobulin G1 may have or may include the protein sequence of SEQ ID NO: 1. The variable domain of the heavy chain may have or may include the protein sequence of SEQ ID NO: 2. The complementarity determining regions of the variable domain of the heavy chain (SEQ ID NO: 2) are shown in SEQ ID NO: 41, SEQ ID NO: 42 and SEQ ID NO: 43. The kappa light chain of human (*Homo sapiens*) antibody immunoglobulin G1 may have or may include the protein sequence of SEQ ID NO: 3. The variable domain of the kappa light chain may have or may include the protein sequence of SEQ ID NO: 4. Optionally, the arginine (Arg or R) residue at position 128 of SEQ ID NO: 4 may be omitted. The

complementarity determining regions of the variable domain of the light chain (SEQ ID NO: 4) are shown in SEQ ID NO: 44, SEQ ID NO: 45 and SEQ ID NO: 46. The variable regions may be codon-optimized, synthesized and cloned into expression vectors containing human immunoglobulin G1 constant regions. In addition, the variable regions may be used in the humanization of non-human antibodies.

[0053] The antibody heavy chain may be encoded by the DNA sequence of SEQ ID NO: 12, a murine anti-AGE immunoglobulin G2b heavy chain. The protein sequence of the murine anti-AGE immunoglobulin G2b heavy chain encoded by SEQ ID NO: 12 is shown in SEQ ID NO: 16. The variable region of the murine antibody is shown in SEQ ID NO: 20, which corresponds to positions 25-142 of SEQ ID NO: 16. The antibody heavy chain may alternatively be encoded by the DNA sequence of SEQ ID NO: 13, a chimeric anti-AGE human immunoglobulin G1 heavy chain. The protein sequence of the chimeric anti-AGE human immunoglobulin G1 heavy chain encoded by SEQ ID NO: 13 is shown in SEQ ID NO: 17. The chimeric anti-AGE human immunoglobulin includes the murine variable region of SEQ ID NO: 20 in positions 25-142. The antibody light chain may be encoded by the DNA sequence of SEQ ID NO: 14, a murine anti-AGE kappa light chain. The protein sequence of the murine anti-AGE kappa light chain encoded by SEQ ID NO: 14 is shown in SEQ ID NO: 18. The variable region of the murine antibody is shown in SEQ ID NO: 21, which corresponds to positions 21-132 of SEQ ID NO: 18. The antibody light chain may alternatively be encoded by the DNA sequence of SEQ ID NO: 15, a chimeric anti-AGE human kappa light chain. The protein sequence of the chimeric anti-AGE human kappa light chain encoded by SEQ ID NO: 15 is shown in SEQ ID NO: 19. The chimeric anti-AGE human immunoglobulin includes the murine variable region of SEQ ID NO: 21 in positions 21-132.

[0054] A humanized anti-AGE antibody for use according to the present invention may have or may include one or more humanized heavy chains or humanized light chains. A humanized heavy chain may be encoded by the DNA sequence of SEQ ID NO: 30, 32 or 34. The protein sequences of the humanized heavy chains encoded by SEQ ID NOs: 30, 32 and 34 are shown in SEQ ID NOs: 29, 31 and 33, respectively. A humanized light chain may be encoded by the DNA sequence of SEQ ID NO: 36, 38 or 40. The protein sequences of the humanized light chains encoded by SEQ ID NOs: 36, 38 and 40 are shown in SEQ ID NOs: 35, 37 and 39, respectively. Preferably, the humanized anti-AGE antibody maximizes the amount of human sequence while retaining the original antibody specificity. A complete humanized antibody may be constructed that contains a heavy chain having a protein sequence chosen from SEQ ID NOs: 29, 31 and 33 and a light chain having a protein sequence chosen from SEQ ID NOs: 35, 37 and 39.

[0055] Particularly preferred anti-AGE antibodies may be obtained by humanizing murine monoclonal anti-AGE antibodies. Murine monoclonal anti-AGE antibodies have the heavy chain protein sequence shown in SEQ ID NO: 47 (the protein sequence of the variable domain is shown in SEQ ID NO: 52) and the light chain protein sequence shown in SEQ ID NO: 57 (the protein sequence of the variable domain is shown in SEQ ID NO: 62). A preferred humanized heavy chain may have the protein sequence shown in SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50 or SEQ ID NO: 51 (the protein sequences of the variable domains of the humanized heavy chains are shown in SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55 and SEQ ID NO: 56, respectively). A preferred humanized light chain may have the protein sequence shown in SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60 or SEQ ID NO: 61 (the protein sequences of the variable domains of the

humanized light chains are shown in SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively). Preferably, a humanized anti-AGE monoclonal antibody is composed a heavy chain having a protein sequence selected from the group consisting of SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50 and SEQ ID NO: 51 and a light chain having a protein sequence selected from the group consisting of SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60 and SEQ ID NO: 61. Humanized monoclonal anti-AGE antibodies composed of these protein sequences may have better binding and/or improved activation of the immune system, resulting in greater efficacy.

[0056] The protein sequence of an antibody from a non-human species may be modified to include the variable domain of the heavy chain having the sequence shown in SEQ ID NO: 2 or the kappa light chain having the sequence shown in SEQ ID NO: 4. The non-human species may be a companion animal, such as the domestic cat or domestic dog, or livestock, such as cattle, the horse or the camel. Preferably, the non-human species is not the mouse. The heavy chain of the horse (*Equus caballus*) antibody immunoglobulin gamma 4 may have or may include the protein sequence of SEQ ID NO: 5 (EMBL/GenBank accession number AY445518). The heavy chain of the horse (*Equus caballus*) antibody immunoglobulin delta may have or may include the protein sequence of SEQ ID NO: 6 (EMBL/GenBank accession number AY631942). The heavy chain of the dog (*Canis familiaris*) antibody immunoglobulin A may have or may include the protein sequence of SEQ ID NO: 7 (GenBank accession number L36871). The heavy chain of the dog (*Canis familiaris*) antibody immunoglobulin E may have or may include the protein sequence of SEQ ID NO: 8 (GenBank accession number L36872). The heavy chain of the cat (*Felis catus*) antibody immunoglobulin G2 may have or may include the protein sequence of SEQ ID NO: 9 (DDBJ/EMBL/GenBank accession number KF811175).

[0057] Animals of the camelid family, such as camels (*Camelus dromedarius* and *Camelus bactrianus*), llamas (*Lama glama*, *Lama pacos* and *Lama vicugna*), alpacas (*Vicugna pacos*) and guanacos (*Lama guanicoe*), have a unique antibody that is not found in other mammals. In addition to conventional immunoglobulin G antibodies composed of heavy and light chain tetramers, camelids also have heavy chain immunoglobulin G antibodies that do not contain light chains and exist as heavy chain dimers. These antibodies are known as heavy chain antibodies, HCAbs, single-domain antibodies or sdAbs, and the variable domain of a camelid heavy chain antibody is known as the VHH. The camelid heavy chain antibodies lack the heavy chain CH1 domain and have a hinge region that is not found in other species. The variable region of the Arabian camel (*Camelus dromedarius*) single-domain antibody may have or may include the protein sequence of SEQ ID NO: 10 (GenBank accession number AJ245148). The variable region of the heavy chain of the Arabian camel (*Camelus dromedarius*) tetrameric immunoglobulin may have or may include the protein sequence of SEQ ID NO: 11 (GenBank accession number AJ245184).

[0058] In addition to camelids, heavy chain antibodies are also found in cartilaginous fishes, such as sharks, skates and rays. This type of antibody is known as an immunoglobulin new antigen receptor or IgNAR, and the variable domain of an IgNAR is known as the VNAR. The IgNAR exists as two identical heavy chain dimers composed of one variable domain and five constant domains each. Like camelids, there is no light chain.

[0059] The protein sequences of additional non-human species may be readily found in online

databases, such as the International ImMunoGeneTics Information System (www.imgt.org), the European Bioinformatics Institute (www.ebi.ac.uk), the DNA Databank of Japan (ddbj.nig.ac.jp/arsa) or the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov).

[0060] An anti-AGE antibody or a variant thereof may include a heavy chain variable region having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 20, including post-translational modifications thereof. A variable region having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity may contain substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-AGE antibody including that sequence retains the ability to bind to AGE. The substitutions, insertions, or deletions may occur in regions outside the variable region.

[0061] An anti-AGE antibody or a variant thereof may include a light chain variable region having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 21, including post-translational modifications thereof. A variable region having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity may contain substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-AGE antibody including that sequence retains the ability to bind to AGE. The substitutions, insertions, or deletions may occur in regions outside the variable region.

[0062] Alternatively, the antibody may have the complementarity determining regions of commercially available mouse anti-glycation end-product antibody raised against carboxymethyl lysine conjugated with keyhole limpet hemocyanin (CML-KLH), the carboxymethyl lysine MAb (Clone 318003) available from R&D Systems, Inc. (Minneapolis, MN; catalog no. MAB3247).

[0063] The antibody may have or may include constant regions which permit destruction of targeted cells by a subject's immune system.

[0064] Mixtures of antibodies that bind to more than one type AGE of AGE-modified proteins may also be used.

[0065] Bi-specific antibodies, which are anti-AGE antibodies directed to two different epitopes, may also be used. Such antibodies will have a variable region (or complementary determining region) from those of one anti-AGE antibody, and a variable region (or complementary determining region) from a different antibody.

[0066] Antibody fragments may be used in place of whole antibodies. For example, immunoglobulin G may be broken down into smaller fragments by digestion with enzymes. Papain digestion cleaves the N-terminal side of inter-heavy chain disulfide bridges to produce Fab fragments. Fab fragments include the light chain and one of the two N-terminal domains of the heavy chain (also known as the Fd fragment). Pepsin digestion cleaves the C-terminal side of the inter-heavy chain disulfide bridges to produce $F(ab')_2$ fragments. $F(ab')_2$ fragments include both light chains and the two N-terminal domains linked by disulfide bridges. Pepsin digestion may also form the Fv (fragment variable) and Fc (fragment crystallizable) fragments. The Fv fragment

contains the two N-terminal variable domains. The Fc fragment contains the domains which interact with immunoglobulin receptors on cells and with the initial elements of the complement cascade. Pepsin may also cleave immunoglobulin G before the third constant domain of the heavy chain (C_H3) to produce a large fragment F(abc) and a small fragment pFc'. Antibody fragments may alternatively be produced recombinantly.

[0067] If additional antibodies are desired, they can be produced using well-known methods. For example, polyclonal antibodies (pAbs) can be raised in a mammalian host by one or more injections of an immunogen, and if desired, an adjuvant. Typically, the immunogen (and adjuvant) is injected in a mammal by a subcutaneous or intraperitoneal injection. The immunogen may be an AGE-modified protein of a cell, such as AGE-antithrombin III, AGE-calmodulin, AGE-insulin, AGE-ceruloplasmin, AGE-collagen, AGE-cathepsin B, AGE-albumin such as AGE-bovine serum albumin (AGE-BSA), AGE-human serum albumin and ovalbumin, AGE-crystallin, AGE-plasminogen activator, AGE-endothelial plasma membrane protein, AGE-aldehyde reductase, AGE-transferrin, AGE-fibrin, AGE-copper/zinc SOD, AGE-apo B, AGE-fibronectin, AGE-pancreatic ribose, AGE-apo A-I and II, AGE-hemoglobin, AGE-Na^+/K^+-ATPase, AGE-plasminogen, AGE-myelin, AGE-lysozyme, AGE-immunoglobulin, AGE-red cell Glu transport protein, AGE-β-N-acetyl hexominase, AGE-apo E, AGE-red cell membrane protein, AGE-aldose reductase, AGE-ferritin, AGE-red cell spectrin, AGE-alcohol dehydrogenase, AGE-haptoglobin, AGE-tubulin, AGE-thyroid hormone, AGE-fibrinogen, AGE-β_2-microglobulin, AGE-sorbitol dehydrogenase, AGE-α_1-antitrypsin, AGE-carbonate dehydratase, AGE-RNAse, AGE-low density lipoprotein, AGE-hexokinase, AGE-apo C-I, AGE-RNAse, AGE-hemoglobin such as AGE-human hemoglobin, AGE-albumin such as AGE-bovine serum albumin (AGE-BSA) and AGE-human serum albumin, AGE-low density lipoprotein (AGE-LDL) and AGE-collagen IV. AGE-modified cells, such as AGE-modified erythrocytes, whole, lysed, or partially digested, may also be used as AGE antigens. Examples of adjuvants include Freund's complete, monophosphoryl Lipid A synthetic-trehalose dicorynomycolate, aluminum hydroxide (alum), heat shock proteins HSP 70 or HSP96, squalene emulsion containing monophosphoryl lipid A, a2-macroglobulin and surface active substances, including oil emulsions, pleuronic polyols, polyanions and dinitrophenol. To improve the immune response, an immunogen may be conjugated to a polypeptide that is immunogenic in the host, such as keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, cholera toxin, labile enterotoxin, silica particles or soybean trypsin inhibitor. A preferred immunogen conjugate is AGE-KLH. Alternatively, pAbs may be made in chickens, producing IgY molecules.

[0068] Monoclonal antibodies (mAbs) may also be made by immunizing a host or lymphocytes from a host, harvesting the mAb-secreting (or potentially secreting) lymphocytes, fusing those lymphocytes to immortalized cells (for example, myeloma cells), and selecting those cells that secrete the desired mAb. Other techniques may be used, such as the EBV-hybridoma technique. Techniques for the generation of chimeric antibodies by splicing genes encoding the variable domains of antibodies to genes of the constant domains of human (or other animal) immunoglobulin result in "chimeric antibodies" that are substantially human (humanized) or substantially "ized" to another animal (such as cat, dog, horse, camel or alpaca, cattle, sheep, or goat) at the amino acid level. If desired, the mAbs may be purified from the culture medium or ascites fluid by conventional procedures, such as protein A-sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, ammonium sulfate precipitation or affinity

chromatography. Additionally, human monoclonal antibodies can be generated by immunization of transgenic mice containing a third copy IgG human trans-loci and silenced endogenous mouse Ig loci or using human-transgenic mice. Production of humanized monoclonal antibodies and fragments thereof can also be generated through phage display technologies.

[0069] A "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Preferred examples of such carriers or diluents include water, saline, Ringer's solutions and dextrose solution. Supplementary active compounds can also be incorporated into the compositions. Solutions and suspensions used for parenteral administration can include a sterile diluent, such as water for injection, saline solution, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0070] Pharmaceutical compositions suitable for injection include sterile aqueous solutions or dispersions for the extemporaneous preparation of sterile injectable solutions or dispersion. Various excipients may be included in pharmaceutical compositions of antibodies suitable for injection. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, CREMOPHOR EL® (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid so as to be administered using a syringe. Such compositions should be stable during manufacture and storage and must be preserved against contamination from microorganisms such as bacteria and fungi. Various antibacterial and anti-fungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, and thimerosal, can contain microorganism contamination. Isotonic agents such as sugars, polyalcohols, such as manitol, sorbitol, and sodium chloride can be included in the composition. Compositions that can delay absorption include agents such as aluminum monostearate and gelatin. Sterile injectable solutions can be prepared by incorporating antibodies, and optionally other therapeutic components, in the required amount in an appropriate solvent with one or a combination of ingredients as required, followed by sterilization. Methods of preparation of sterile solids for the preparation of sterile injectable solutions include vacuum drying and freeze-drying to yield a solid.

[0071] For administration by inhalation, the antibodies may be delivered as an aerosol spray from a nebulizer or a pressurized container that contains a suitable propellant, for example, a gas such as carbon dioxide. Antibodies may also be delivered via inhalation as a dry powder, for example using the iSPERSE™ inhaled drug deliver platform (PULMATRIX, Lexington, Mass.). The use of anti-AGE antibodies which are chicken antibodies (IgY) may be non-immunogenic in a variety of animals, including humans, when administered by inhalation.

[0072] Topical application may be effective for cancers and potentially-malignant neoplasms present in the skin, for example melanomas, seborrheic keratosis and actinic keratosis. Compositions for topical administration may be in the form of creams or lotions.

[0073] An appropriate dosage level of each type of antibody will generally be about 0.01 to 500 mg per kg patient body weight. Preferably, the dosage level will be about 0.1 to about 250 mg/kg; more preferably about 0.5 to about 100 mg/kg. A suitable dosage level may be about 0.01 to 250 mg/kg, about 0.05 to 100 mg/kg, or about 0.1 to 50 mg/kg. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg. Although each type of antibody may be administered on a regimen of 1 to 4 times per day, such as once or twice per day, antibodies typically have a long half-life *in vivo.* Accordingly, each type of antibody may be administered once a day, once a week, once every two or three weeks, once a month, or once every 60 to 90 days.

[0074] A subject that receives administration of an anti-AGE antibody may be tested to determine if it has been effective to treat the cancer, by examining the patient for the spread of the cancer to different parts of the body, particularly in lymph nodes. Any suitable diagnostic test may be used, such as a biopsy, endoscopy, blood test or diagnostic imaging test such as an X-ray or CT scan. The diagnostic test may also include anti-AGE antibodies for detection. Administration of antibody and subsequent testing may be repeated until the desired therapeutic result is achieved. Similarly, a subject may be tested to determine if a potentially-malignant neoplasm has been effectively treated by a reduction in size, or disappearance, of the neoplasm.

[0075] Unit dosage forms can be created to facilitate administration and dosage uniformity. Unit dosage form refers to physically discrete units suited as single dosages for the subject to be treated, containing a therapeutically effective quantity of one or more types of antibodies in association with the required pharmaceutical carrier. Preferably, the unit dosage form is in a sealed container and is sterile.

[0076] Any mammal that could develop metastatic cancer may be treated by the methods herein described. Humans are a preferred mammal for treatment. Other mammals that may be treated include mice, rats, goats, sheep, cows, horses and companion animals, such as dogs or cats. A subject in need of treatment may be identified by the diagnosis of a cancer. Cancers which are particularly subject to metastasis include lung cancer, melanoma, colon cancer, renal cell carcinoma, prostate cancer, cancer of the cervix, bladder cancer, rectal cancer, esophageal cancer, liver cancer, mouth and throat cancer, multiple myeloma, ovarian cancer, and stomach cancer. Treatment may be of patients experiencing metastatic cancer. Treatment may also be administered to patients who have cancer, but prior to any identified metastasis, in order to prevent metastasis. Similarly, any mammal that could develop potentially-malignant neoplasms may be treated by the methods herein described. Humans are a preferred mammal for treatment. Other mammals that may be treated include mice, rats, goats, sheep, cows, horses and companion animals, such as dogs or cats. A subject in need of treatment may be identified by the diagnosis of a potentially-malignant neoplasm.

[0077] A particularly preferred treatment group includes subjects who are unable to receive conventional cancer treatments such as surgery, radiation therapy or chemotherapy. A patient with metastatic cancer or at risk for cancer metastasis may not be able to undergo certain cancer treatments due to other diagnoses, physical conditions or complications. For example, pregnant women cannot receive radiation therapy due to a risk of harm to the fetus. Aged or weakened patients, such as those experiencing cancer cachexia, may not be good candidates for surgery

due to a risk of not surviving an invasive procedure. Patients who already have a compromised immune system or a chronic infection may not be able to receive chemotherapy since many chemotherapy drugs harm the immune system.

[0078] The anti-AGE antibodies may be used in cellular purification processes, such as immunopanning and immunoadsorption. Purification processes are useful in isolating desirable or unwanted cells from tissue cultures, cell cultures or blood. Cellular purification may be used in transplantations, such as a bone marrow transplant, or transfusions, such as a blood transfusion. Cellular purification is especially useful in autologous stem cell transplantation during chemotherapy to remove metastasizing malignant cells and concentrate beneficial stem cells. Immunopanning or immunoadsorption using an anti-AGE antibody may isolate metastasizing cancer, from a tissue culture, cell culture or blood sample.

[0079] The anti-AGE antibodies may also be used to diagnose cancer metastases. An immune complex (also known as an antibody-antigen complex) including an anti-AGE antibody bound to a metastatic cancer cell expressing AGE-modified proteins is a unique analyte that may be predictive or indicative of metastatic cancer. The specific binding of anti-AGE antibodies to metastasizing cancer cells may allow for the detection of cancer metastases at subclinical levels. Diagnostic anti-AGE antibodies may be used to detect circulating metastatic cancer cells that pose a risk of metastasizing in a new location. Alternatively, diagnostic anti-AGE antibodies may be used to test cells obtained from a specific location for the presence of metastatic cancer cells. A biopsy may involve collecting cells from a specific part of the body that is a known risk for accumulation of metastatic cancer cells, such as the lymph nodes, lungs, liver, brain or bones, or from a part of the body where metastasis is suspected due to other symptoms, such as a suspicious lump. Anti-AGE antibodies may be used in any diagnostic method that employs antibodies for detection of an analyte of interest. For example, an immune complex may be detected using a suitable imaging technique after attaching a label to the antibodies, such as a fluorescent label or radiolabel; using cytological techniques such as immunofluorescence, flow cytometry or fluorescence-activated cell sorting (FACS); using biochemical techniques such as immunoassays, especially enzyme-linked immunosorbent arrays (ELISA), Western blotting or immunoprecipitation; or using cellular purification techniques such as immunopanning.

[0080] FIG. 2 illustrates a kit 200 for diagnosing cancer metastases. The kit may include an anti-AGE antibody 210, a control 220 and, optionally, a reagent 230 for detecting the anti-AGE antibody. The anti-AGE antibody, the control and the optional reagent may be supplied in any suitable container, such as bottles, ampules, envelopes, test tubes, vials, flasks or syringes. The anti-AGE antibody and/or the reagent may optionally be labelled, such as with a fluorescent label, radiolabel or a gold particle. The control may be normal serum from an animal in which a secondary antibody was made, a solution containing a known amount of an AGE-modified protein or peptide or fixed or preserved cells that exhibit and AGE modification. Examples of reagents for detecting the anti-AGE antibody include secondary antibodies, such as an anti-human polyclonal antibody made in donkey and labelled with rhodamine. The kit may optionally be housed in a container 240. The kit may optionally include printed instructions 250. Preferably, the contents of the kit are sterile and ready for use.

[0081] The kit may optionally include a container for housing the kit ingredients. The container

may be formed of a rigid, durable material, such as plastic, or may be flexible, such as a bag or soft-sided box.

[0082] The kit may optionally include instructions for use. The instructions may be provided as printed instructions or in electronic format, such as on a universal serial bus (USB) drive, on a secure digital (SD) card, or hosted over the internet and accessible through a quick response (QR) code.

[0083] Kits may optionally contain additional diagnostic materials or equipment such as buffers, fixatives, blocking solutions, protease inhibitors, substrates for analysis such as microscope slides and/or cover slips, microtiter plates and cell extraction reagents such as detergents and detergent solutions.

[0084] The one-letter amino acid sequence that corresponds to SEQ ID NO: 1 is shown below:

```
          10         20         30         40         50
MNLLLILTFV AAAVAQVQLL QPGAELVKPG ASVKLACKAS GYLFTTYWMH

          60         70         80         90
WLKQRPGQGL EWIGEISPTN GRAYYNARFK SEATLTVDKS
         100        110        120        130
SNTAYMQLSS LTSEASAVYY CARAYGNYEF AYWGQGTLVT
         140        150        160        170
VSVASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV
         180        190        200        210        220
TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH
         230        240        250        260
KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP
         270        280        290        300
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV
         310        320        330        340
HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
         350        360        370        380        390
NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
         400        410        420        430
SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK
         440        450        460
SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK
```

[0085] Positions 16-133 of the above amino acid sequence correspond to SEQ ID NO: 2. Positions 46-50 of the above amino acid sequence correspond to SEQ ID NO: 41. Positions 65-81 of the above amino acid sequence correspond to SEQ ID NO: 42. Positions 114-122 of the above amino acid sequence correspond to SEQ ID NO: 43.

[0086] The one-letter amino acid sequence that corresponds to SEQ ID NO: 3 is shown below:

```
          10         20         30         40         50
MNLLLILTFV AAAVADVVMT QTPLSLPVSL GDQASISCRS RQSLVNSNGN

          60         70         80         90        100
TFLQWYLQKP GQSPKLLIYK VSLRFSGVPD RFSGSGSGTD FTLKISRVEA
         110        120        130        140        150
EDLGLYFCSQ STHVPPTFGG GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA
         160        170        180        190
SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD
         200        210        220        230
STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
```

[0087] Positions 16-128 of the above amino acid sequence correspond to SEQ ID NO: 4. Optionally, the arginine (Arg or R) residue at position 128 of SEQ ID NO: 4 may be omitted. Positions 39-54 of the above amino acid sequence correspond to SEQ ID NO: 44. Positions 70-76 of the above amino acid sequence correspond to SEQ ID NO: 45. Positions 109-117 of the above amino acid sequence correspond to SEQ ID NO: 46.

[0088] The DNA sequence that corresponds to SEQ ID NO: 12 is shown below:

```
ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGCCTGGC
CTTCGAGCTGAGCTACGGCCAGGTGCAGCTGCTGCAGCCAGGTGCCGAGCTC
GTGAAACCTGGCGCCTCTGTGAAGCTGGCCTGCAAGGCTTCCGGCTACCTGTT
CACCACCTACTGGATGCACTGGCTGAAGCAGAGGCCAGGCCAGGGCCTGGAA
TGGATCGGCGAGATCTCCCCCACCAACGGCAGAGCCTACTACAACGCCCGGTT
CAAGTCCGAGGCCACCCTGACCGTGGACAAGTCCTCCAACACCGCCTACATGC
AGCTGTCCTCCCTGACCTCTGAGGCCTCCGCCGTGTACTACTGCGCCAGAGCT
TACGGCAACTACGAGTTCGCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTC
TGTGGCTAAGACCACCCCTCCCTCCGTGTACCCTCTGGCTCCTGGCTGTGGCG
ACACCACCGGATCCTCTGTGACCCTGGGCTGCCTCGTGAAGGGCTACTTCCCT
GAGTCCGTGACCGTGACCTGGAACTCCGGCTCCCTGTCCTCCTCCGTGCACAC
CTTTCCAGCCCTGCTGCAGTCCGGCCTGTACACCATGTCCTCCAGCGTGACAG
TGCCCTCCTCCACCTGGCCTTCCCAGACCGTGACATGCTCTGTGGCCCACCCT
GCCTCTTCCACCACCGTGGACAAGAAGCTGGAACCCTCCGGCCCCATCTCCAC
CATCAACCCTTGCCCTCCCTGCAAAGAATGCCACAAGTGCCCTGCCCCCAACC

TGGAAGGCGGCCCTTCCGTGTTCATCTTCCCACCCAACATCAAGGACGTGCTG
ATGATCTCCCTGACCCCCAAAGTGACCTGCGTGGTGGTGGACGTGTCCGAGGA
CGACCCTGACGTGCAGATCAGTTGGTTCGTGAACAACGTGGAAGTGCACACCG
CCCAGACCCAGACACACAGAGAGGACTACAACAGCACCATCAGAGTGGTGTCT
ACCCTGCCCATCCAGCACCAGGACTGGATGTCCGGCAAAGAATTCAAGTGCAA
AGTGAACAACAAGGACCTGCCCAGCCCCATCGAGCGGACCATCTCCAAGATCA
AGGGCCTCGTGCGGGCTCCCCAGGTGTACATTCTGCCTCCACCAGCCGAGCA
GCTGTCCCGGAAGGATGTGTCTCTGACATGTCTGGTCGTGGGCTTCAACCCCG
```

GCGACATCTCCGTGGAATGGACCTCCAACGGCCACACCGAGGAAAACTACAAG
GACACCGCCCCTGTGCTGGACTCCGACGGCTCCTACTTCATCTACTCCAAGCT
GAACATGAAGACCTCCAAGTGGGAAAAGACCGACTCCTTCTCCTGCAACGTGC
GGCACGAGGGCCTGAAGAACTACTACCTGAAGAAAACCATCTCCCGGTCCCCC
GGCTAG

[0089] The DNA sequence that corresponds to SEQ ID NO: 13 is shown below:
ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGCCTGGC
CTTCGAGCTGAGCTACGGCCAGGTGCAGCTGCTGCAGCCAGGTGCCGAGCTC
GTGAAACCTGGCGCCTCTGTGAAGCTGGCCTGCAAGGCTTCCGGCTACCTGTT
CACCACCTACTGGATGCACTGGCTGAAGCAGAGGCCAGGCCAGGGCCTGGAA
TGGATCGGCGAGATCTCCCCCACCAACGGCAGAGCCTACTACAACGCCCGGTT
CAAGTCCGAGGCCACCCTGACCGTGGACAAGTCCTCCAACACCGCCTACATGC
AGCTGTCCTCCCTGACCTCTGAGGCCTCCGCCGTGTACTACTGCGCCAGAGCT
TACGGCAACTACGAGTTCGCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTC
TGTGGCTAGCACCAAGGGCCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAG
AGCACCAGCGGCGGAACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCC
CCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGAGTGCA
CACCTTCCCTGCCGTGCTGCAGAGCAGCGGCCTGTACTCCCTGAGCAGCGTG
GTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAA
CCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAGCCTAAGAGCTGC
GACAAGACCCACACCTGCCCTCCCTGCCCCGCCCCCGAGCTGCTGGGCGGAC
CCAGCGTGTTCCTGTTCCCCTCCCAAGCCCAAGGACACCCTGATGATCAGCCGC
ACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCCGAGG

TGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAG
CCTCGGGAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCG
TGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAA
CAAGGCCCTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAG
CCCCGGGAGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCTGACCA
AGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACATC
GCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCC
CTCCCGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
GACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACG
AGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCCGGATA
G

[0090] The DNA sequence that corresponds to SEQ ID NO: 14 is shown below:
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCT
CCACCGGAGACGTCGTGATGACCCAGACCCCTCTGTCCCTGCCTGTGTCTCTG
GGCGACCAGGCCTCCATCTCCTGCCGGTCTAGACAGTCCCTCGTGAACTCCAA
CGGCAACACCTTCCTGCAGTGGTATCTGCAGAAGCCCGGCCAGTCCCCCAAGC
TGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACAGATTTTCC

TGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACAGATTTTCC
GGCTCTGGCTCTGGCACCGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGA
GGACCTGGGCCTGTACTTCTGCAGCCAGTCCACCCACGTGCCCCCTACATTTG
GCGGAGGCACCAAGCTGGAAATCAAACGGGCAGATGCTGCACCAACTGTATCC
ATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGC
TTCTTGAACAACTTCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGGC
AGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGATCAGGACAGCAAAGA
CAGCACCTACAGCATGAGCAGCACCCTCACGTTGACCAAGGACGAGTATGAAC
GACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCACCCATTG
TCAAGAGCTTCAACAGGAATGAGTGTTGA

[0091] The DNA sequence that corresponds to SEQ ID NO: 15 is shown below:
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCT
CCACCGGAGACGTCGTGATGACCCAGACCCCTCTGTCCCTGCCTGTGTCTCTG

GGCGACCAGGCCTCCATCTCCTGCCGGTCTAGACAGTCCCTCGTGAACTCCAA
CGGCAACACCTTCCTGCAGTGGTATCTGCAGAAGCCCGGCCAGTCCCCCAAGC
TGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACAGATTTTCC
GGCTCTGGCTCTGGCACCGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGA
GGACCTGGGCCTGTACTTCTGCAGCCAGTCCACCCACGTGCCCCCTACATTTG
GCGGAGGCACCAAGCTGGAAATCAAGCGGACCGTGGCCGCCCCCAGCGTGTT
CATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGT
GCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGA
CAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCC
AAGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTA
CGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGC
CCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA

[0092] The one-letter amino acid sequence that corresponds to SEQ ID NO: 16 is shown below:
MDPKGSLSWRILLFLSLAFELSYGQVQLLQPGAELVKPGASVKLACKASGYLFTTY
WMHWLKQRPGQGLEWIGEISPTNGRAYYNARFKSEATLTVDKSSNTAYMQLSSLT
SEASAVYYCARAYGNYEFAYWGQGTLVTVSVAKTTPPSVYPLAPGCGDTTGSSVT
LGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQT
VTCSVAHPASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFIFPPNIK
DVLMISLTPKVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTIRVVS
TLPIQHQDWMSGKEFKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLSRK
DVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYFIYSKLNMKTSKW
EKTDSFSCNVRHEGLKNYYLKKTISRSPG*

[0093] The alanine residue at position 123 of the above amino acid sequence may optionally be replaced with a serine residue. The tyrosine residue at position 124 of the above amino acid sequence may optionally be replaced with a phenylalanine residue. Positions 25-142 of the above

amino acid sequence correspond to SEQ ID NO: 20. SEQ ID NO: 20 may optionally include the substitutions at positions 123 and 124. SEQ ID NO: 20 may optionally contain one additional lysine residue after the terminal valine residue.

[0094] The one-letter amino acid sequence that corresponds to SEQ ID NO: 17 is shown below:
MDPKGSLSWRILLFLSLAFELSYGQVQLLQPGAELVKPGASVKLACKASGYLFTTY
WMHWLKQRPGQGLEWIGEISPTNGRAYYNARFKSEATLTVDKSSNTAYMQLSSLT
SEASAVYYCARAYGNYEFAYWGQGTLVTVSVASTKGPSVFPLAPSSKSTSGGTAA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPG*

[0095] The one-letter amino acid sequence that corresponds to SEQ ID NO: 18 is shown below:
METDTLLLWVLLLWVPGSTGDVVMTQTPLSLPVSLGDQASISCRSRQSLVNSNGN
TFLQWYLQKPGQSPKLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGLYF
CSQSTHVPPTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDI
NVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHK
TSTSPIVKSFNRNEC*

[0096] Positions 21-132 of the above amino acid sequence correspond to SEQ ID NO: 21.

[0097] The one-letter amino acid sequence that corresponds to SEQ ID NO: 19 is shown below:
METDTLLLWVLLLWVPGSTGDVVMTQTPLSLPVSLGDQASISCRSRQSLVNSNGN
TFLQWYLQKPGQSPKLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGLYF
CSQSTHVPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC*

[0098] The one-letter amino acid sequence that corresponds to SEQ ID NO: 22 is shown below:

```
          10         20         30         40         50
ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV
          60         70         80         90         100
HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER
          110        120        130        140        150
KCCVECPPCP APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP
          160        170        180        190
EVQFNWYVDG VEVHNAKTKP REEQFNSTFR VVSVLTVVHQ
          200        210        220        230        240
DWLNGKEYKC KVSNKGLPAP IEKTISKTKG QPREPQVYTL PPSREEMTKN
```

250 260 270 280 290
QVSLTCLVKG FYPSDISVEW ESNGQPENNY KTTPPMLDSD GSFFLYSKLT
300 310 320
VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK

[0099] The one-letter amino acid sequence that corresponds to SEQ ID NO: 23 is SYTMGVS.

[0100] The one-letter amino acid sequence that corresponds to SEQ ID NO: 24 is TISSGGGSTYYPDSVKG.

[0101] The one-letter amino acid sequence that corresponds to SEQ ID NO: 25 is QGGWLPPFAX, where X may be any naturally occurring amino acid.

[0102] The one-letter amino acid sequence that corresponds to SEQ ID NO: 26 is RASKSVSTSSRGYSYMH.

[0103] The one-letter amino acid sequence that corresponds to SEQ ID NO: 27 is LVSNLES.

[0104] The one-letter amino acid sequence that corresponds to SEQ ID NO: 28 is QHIRELTRS.

[0105] The one-letter amino acid sequence that corresponds to SEQ ID NO: 29 is
MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVSCKASGYLFTTY
WMHWVRQAPGQGLEWMGEISPTNGRAYYNQKFQGRVTMTVDKSTNTVYMELSS
LRSEDTAVYYCARAYGNYFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPG.

[0106] The DNA sequence that corresponds to SEQ ID NO: 30 is
ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGCCTGGC
CTTCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTG
AAGAAACCTGGCGCCTCCGTGAGGTGTCCTGCAAGGCTTCCGGCTACCTGTTC
ACCACCTACTGGATGCACTGGGTGCGACAGGCCCCTGGACAGGGCCTGGAAT
GGATGGGCGAGATCTCCCCTACCAACGGCAGAGCCTACTACAACAGAAATTCC
AGGGCAGAGTGACCATGACCGTGGACAAGTCCACCAACACCGTGTACATGGAA
CTGTCCTCCCTGCGGAGCGAGGACACCGCCGTGTACTACTGCGCTAGAGCCTA
CGGCAACTACGATTCGCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTCCTC
TGCTAGCACCAAGGGCCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAGAGC
ACCAGCGGCGGAACCGCCGCCCTGGGCTGCCTGGGAAGGACTACTTCCCCGA
GCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGAGTGCACACC

TTCCCTGCCGTGCTGCAGAGCAGCGGCCTGTACTCCCTGAGCAGCGTGGTGA
CCGTGCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACA
AGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAGCCTAAGAGCTGCGACAA
GACCCACACCTGCCCTCCCTGCCCCGCCCCGAGCTGCTGGGCGGACCCAGCG
TGTTCCTGTTCCCTCCCAAGCCCAAGGACACCCTGATGATCAGCCGCACCCCC
GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCCGAGGTGAGTT
CAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGG

GAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCGTGCTGC
ACCAGGACTGGCTGAACGGCAGGAGTACAAGTGCAAGGTGAGCAACAAGGCC
CTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGG
AGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCTGACAAGAACCAG
GTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACATCGCCGTGGA
GTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCCGTG
CTGGACAGCGACGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCC
CGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGC
ACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCGGATAGTAA.

[0107] The one-letter amino acid sequence that corresponds to SEQ ID NO: 31 is
MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVSCKASGYLFTTY
WMHWVRQAPGQGLEWMGEISPTNGRAYYNAKFQGRVTMTVDKSTNTAYMELSS
LRSEDTAVYYCARAYGNYFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPG.

[0108] The DNA sequence that corresponds to SEQ ID NO: 32 is
ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGCCTGGC
CTTCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTG
AAGAAACCTGGCGCCTCCGTGAGGTGTCCTGCAAGGCTTCCGGCTACCTGTTC
ACCACCTACTGGATGCACTGGGTGCGACAGGCCCCTGGACAGGGCCTGGAAT
GGATGGGCGAGATCTCCCCTACCAACGGCAGAGCCTACTACAACCAAAATTCC
AGGGCAGAGTGACCATGACCGTGGACAAGTCCACCAACACCGCTTACATGGAA
CTGTCCTCCCTGCGGAGCGAGGACACCGCCGTGTACTACTGCGCTAGAGCCTA
CGGCAACTACGATTCGCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTCCTC
TGCTAGCACCAAGGGCCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAGAGC
ACCAGCGGCGGAACCGCCGCCCTGGGCTGCCTGGGAAGGACTACTTCCCCGA
GCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGAGTGCACACC

TTCCCTGCCGTGCTGCAGAGCAGCGGCCTGTACTCCCTGAGCAGCGTGGTGA

CCGTGCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACA
AGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAGCCTAAGAGCTGCGACAA
GACCCACACCTGCCCTCCCTGCCCCGCCCCGAGCTGCTGGGCGGACCCAGCG
TGTTCCTGTTCCCTCCCAAGCCCAAGGACACCCTGATGATCAGCCGCACCCCC
GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCCGAGGTGAGTT
CAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGG
GAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCGTGCTGC
ACCAGGACTGGCTGAACGGCAGGAGTACAAGTGCAAGGTGAGCAACAAGGCC
CTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGG
AGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCTGACAAGAACCAG
GTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACATCGCCGTGGA
GTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCCGTG
CTGGACAGCGACGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCC
CGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGC
ACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCGGATAGTAA.

[0109] The one-letter amino acid sequence that corresponds to SEQ ID NO: 33 is
MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVSCKASGYLFTTY
WMHWVRQAPGQGLEWMGEISPTNGRAYYNAKFQGRVTMTVDKSINTAYMELSRL
RSDDTAVYYCARAYGNYFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPG.

[0110] The DNA sequence that corresponds to SEQ ID NO: 34 is
ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGCCTGGC
CTTCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTG
AAGAAACCTGGCGCCTCCGTGAGGTGTCCTGCAAGGCTTCCGGCTACCTGTTC
ACCACCTACTGGATGCACTGGGTGCGACAGGCCCCTGGACAGGGCCTGGAAT

GGATGGGCGAGATCTCCCCTACCAACGGCAGAGCCTACTACAACCAAAATTCC
AGGGCAGAGTGACCATGACCGTGGACAAGTCCATCAACACCGCTTACATGGAA
CTGTCCAGACTGCGGAGCGATGACACCGCCGTGTACTACTGCGCTAGAGCCTA
CGGCAACTACGATTCGCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTCCTC
TGCTAGCACCAAGGGCCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAGAGC
ACCAGCGGCGGAACCGCCGCCCTGGGCTGCCTGGGAAGGACTACTTCCCCGA
GCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGAGTGCACACC
TTCCCTGCCGTGCTGCAGAGCAGCGGCCTGTACTCCCTGAGCAGCGTGGTGA
CCGTGCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACA
AGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAGCCTAAGAGCTGCGACAA

AGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAGCCTAAGAGCTGCGACAA
GACCCACACCTGCCCTCCCTGCCCCGCCCCGAGCTGCTGGGCGGACCCAGCG
TGTTCCTGTTCCCTCCCAAGCCCAAGGACACCCTGATGATCAGCCGCACCCCC
GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCCGAGGTGAGTT
CAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGG
GAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCGTGCTGC
ACCAGGACTGGCTGAACGGCAGGAGTACAAGTGCAAGGTGAGCAACAAGGCC
CTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGG
AGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCTGACAAGAACCAG
GTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACATCGCCGTGGA
GTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCCGTG
CTGGACAGCGACGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCC
CGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGC
ACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCGGATAGTAA.

[0111] The one-letter amino acid sequence that corresponds to SEQ ID NO: 35 is
METDTLLLWVLLLWVPGSTGDVVMTQSPLSLPVTLGQPASISCRSSQSLVNSNGNT
FLQWYQQRPGQSPRLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYY
CSQSTHVPPTFGGGTVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC.

[0112] The DNA sequence that corresponds to SEQ ID NO: 36 is
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCT

CCACCGGAGACGTCGTGATGACCCAGTCCCCTCTGTCCCTGCCTGTGACCCTG
GGACAGCCTGCCTCCATCTCCTCAGATCCTCCCAGTCCCTCGTGAACTCCAAC
GGCAACACCTTCCTGCAGTGGTATCAGCAGCGGCCTGGCCAGAGCCCCAGAC
TGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACGATTTTCCG
GCTCTGGCTCTGGCACCGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGAG
GACGTGGGCGTGTACTACTGCTCCCAGAGCACCCACGTGCCCCCTACATTTGG
CGGAGGCACCAAGTGGAAATCAAGCGGACCGTGGCCGCCCCCAGCGTGTTCA
TCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTG
CCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGGCAGTGGAAGGTGGACA
ACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAA
GGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTAC
GAGAAGACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCC
CGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA.

[0113] The one-letter amino acid sequence that corresponds to SEQ ID NO: 37 is
METDTLLLWVLLLWVPGSTGDVVMTQSPLSLPVTLGQPASISCRSRQSLVNSNGN
TFLQWYQQRPGQSPRLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVY
YCSQSTHVPPTFGGGTVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA

TCSQSTHVPPTFGQGTLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC.

[0114] The DNA sequence that corresponds to SEQ ID NO: 38 is
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCT
CCACCGGAGACGTCGTGATGACCCAGTCCCCTCTGTCCCTGCCTGTGACCCTG
GGACAGCCTGCCTCCATCTCCTCAGATCCAGGCAGTCCCTCGTGAACTCCAAC
GGCAACACCTTCCTGCAGTGGTATCAGCAGCGGCCTGGCCAGAGCCCCAGAC
TGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACGATTTTCCG
GCTCTGGCTCTGGCACCGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGAG
GACGTGGGCGTGTACTACTGCTCCCAGAGCACCCACGTGCCCCCTACATTTGG
CGGAGGCACCAAGTGGAAATCAAGCGGACCGTGGCCGCCCCCAGCGTGTTCA
TCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTG
CCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGGCAGTGGAAGGTGGACA
ACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAA

GGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTAC
GAGAAGACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCC
CGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA.

[0115] The one-letter amino acid sequence that corresponds to SEQ ID NO: 39 is
METDTLLLWVLLLWVPGSTGDVVMTQSPLSSPVTLGQPASISCRSSQSLVNSNGN
TFLQWYHQRPGQPPRLLIYKVSLRFSGVPDRFSGSGAGKDFTLKISRVEAEDVGVY
YCSQSTHVPPTFGQGTLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC.

[0116] The DNA sequence that corresponds to SEQ ID NO: 40 is
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCT
CCACCGGAGACGTCGTGATGACCCAGTCCCCTCTGTCCAGTCCTGTGACCCTG
GGACAGCCTGCCTCCATCTCCTCAGATCCTCCCAGTCCCTCGTGAACTCCAAC
GGCAACACCTTCCTGCAGTGGTATCACCAGCGGCCTGGCCAGCCTCCCAGACT
GCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACGATTTTCCGG
CTCTGGCGCTGGCAAGGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGAG
GACGTGGGCGTGTACTACTGCTCCCAGAGCACCCACGTGCCCCCTACATTTGG
CCAGGGCACCAACTGGAAATCAAGCGGACCGTGGCCGCCCCCAGCGTGTTCA
TCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTG
CCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGGCAGTGGAAGGTGGACA
ACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAA
GGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTAC
GAGAAGACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCC
CGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA

CGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA.

[0117] The one-letter amino acid sequence that corresponds to SEQ ID NO: 47 is
MGWTLVFLFLLSVTAGVHSQVQLLQPGAELVKPGASVKLACKASGYLFTTYWMHW
LKQRPGQGLEWIGEISPTNGRAYYNARFKSEATLTVDKSSNTAYMQLSSLTSEASA
VYYCARSFGNYEFAYWQGTLVTVSVASTKGPSVFPLAPSSKSTSGGTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVT

CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK.

[0118] The one-letter amino acid sequence that corresponds to SEQ ID NO: 48 is
MGWTLVFLFLLSVTAGVHSEVQLLESGAEAKKPGASVKLSCKASGYLFTTYWMHW
VHQAPGQRLEWMGEISPTNGRAYYNARFKSRVTITVDKSASTAYMELSSLRSEDT
AVYYCARSFGNYEFAYWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPGK.

[0119] The one-letter amino acid sequence that corresponds to SEQ ID NO: 49 is
MGWTLVFLFLLSVTAGVHSQVQLVQSGAEVKKPGASVKVSCKASGYLFTTYWMH
WVRQAPGQRLEWIGEISPTNGRAYYNARFKSRVTITRDTSASTAYMELSSLRSEDT
AVYYCARSFGNYEFAYWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPGK.

[0120] The one-letter amino acid sequence that corresponds to SEQ ID NO: 50 is
MGWTLVFLFLLSVTAGVHSQVQLVQSGAEVKKPGSSVKVSCKASGYLFTTYWMH
WVRQAPGQGLEWMGEISPTNGRAYYNARFKSRVTITADKSTSTAYMELSSLRSED
TAVYYCARSFGNYEFAYWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPE

VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK.

[0121] The one-letter amino acid sequence that corresponds to SEQ ID NO: 51 is
MGWTLVFLFLLSVTAGVHSQVQLVQSGAEVKKPGASVKVSCEASGYLFTTYWMH
WVRQAPGQGLEWMGEISPTNGRAYYNARFKSRVTITRDTSINTAYMELSRLRSDD
TAVYYCARSFGNYEFAYWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK.

[0122] The one-letter amino acid sequence that corresponds to SEQ ID NO: 52 is
QVQLLQPGAELVKPGASVKLACKASGYLFTTYWMHWLKQRPGQGLEWIGEISPTN
GRAYYNARFKSEATLTVDKSSNTAYMQLSSLTSEASAVYYCARSFGNYEFAYWGQ
GTLVTVSV.

[0123] The one-letter amino acid sequence that corresponds to SEQ ID NO: 53 is
EVQLLESGAEAKKPGASVKLSCKASGYLFTTYWMHWVHQAPGQRLEWMGEISPT
NGRAYYNARFKSRVTITVDKSASTAYMELSSLRSEDTAVYYCARSFGNYEFAYWG
QGTLVTVSS.

[0124] The one-letter amino acid sequence that corresponds to SEQ ID NO: 54 is
QVQLVQSGAEVKKPGASVKVSCKASGYLFTTYWMHWVRQAPGQRLEWIGEISPT
NGRAYYNARFKSRVTITRDTSASTAYMELSSLRSEDTAVYYCARSFGNYEFAYWG
QGTLVTVSS.

[0125] The one-letter amino acid sequence that corresponds to SEQ ID NO: 55 is
QVQLVQSGAEVKKPGSSVKVSCKASGYLFTTYWMHWVRQAPGQGLEWMGEISP
TNGRAYYNARFKSRVTITADKSTSTAYMELSSLRSEDTAVYYCARSFGNYEFAYW
GQGTLVTVSS.

[0126] The one-letter amino acid sequence that corresponds to SEQ ID NO: 56 is
QVQLVQSGAEVKKPGASVKVSCEASGYLFTTYWMHWVRQAPGQGLEWMGEISP
TNGRAYYNARFKSRVTITRDTSINTAYMELSRLRSDDTAVYYCARSFGNYEFAYWG

QGTLVTVSS.

[0127] The one-letter amino acid sequence that corresponds to SEQ ID NO: 57 is MVSSAQFLGLLLLCFQGTRCDVVMTQTPLSLPVSLGDQASISCRSRQSLVNSNGNT FLQWYLQKPGQSPKLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGLYF CSQSTHVPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC.

[0128] The one-letter amino acid sequence that corresponds to SEQ ID NO: 58 is MVSSAQFLGLLLLCFQGTRCDIVMTQTPLSLPVTLGQPASISCRSRQSLVNSNGNT FLQWLQQRPGQPPRLLIYKVSLRFSGVPDRFSGSGAGTDFTLTISRVEAEDVGIYF CSQSTHVPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC.

[0129] The one-letter amino acid sequence that corresponds to SEQ ID NO: 59 is MVSSAQFLGLLLLCFQGTRCDIVMTQTPLSLSVTPGQPASISCRSRQSLVNSNGNT FLQWYLQKPGQSPQLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEPEDVGVYY CSQSTHVPPTFGGGTKVEVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC.

[0130] The one-letter amino acid sequence that corresponds to SEQ ID NO: 60 is MVSSAQFLGLLLLCFQGTRCDVVMTQSPLSLPVTLGQPASISCRSRQSLVNSNGNT FLQWFQQRPGQSPRRLIYKVSLRFSGVPDRFSGSGSDTDFTLRISRVEAEDVGLYY CSQSTHVPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC.

[0131] The one-letter amino acid sequence that corresponds to SEQ ID NO: 61 is MVSSAQFLGLLLLCFQGTRCDIVMTQTPLSLSVTPGQPASISCRSRQSLVNSNGNT FLQWLLQKPGQPPQLLIYKVSLRFSGVPNRFSGSGSGTDFTLKISRVEAEDVGLYY CSQSTHVPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC.

[0132] The one-letter amino acid sequence that corresponds to SEQ ID NO: 62 is DVVMTQTPLSLPVSLGDQASISCRSRQSLVNSNGNTFLQWYLQKPGQSPKLLIYKV SLRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGLYFCSQSTHVPPTFGGGTKLEIK.

[0133] The one-letter amino acid sequence that corresponds to SEQ ID NO: 63 is DIVMTQTPLSLPVTLGQPASISCRSRQSLVNSNGNTFLQWLQQRPGQPPRLLIYKV SLRFSGVPDRFSGSGAGTDFTLTISRVEAEDVGIYFCSQSTHVPPTFGQGTKVEIK.

[0134] The one-letter amino acid sequence that corresponds to SEQ ID NO: 64 is DIVMTQTPLSLSVTPGQPASISCRSRQSLVNSNGNTFLQWYLQKPGQSPQLLIYKV SLRFSGVPDRFSGSGSGTDFTLKISRVEPEDVGVYYCSQSTHVPPTFGGGTKVEV K.

[0135] The one-letter amino acid sequence that corresponds to SEQ ID NO: 65 is DVVMTQSPLSLPVTLGQPASISCRSRQSLVNSNGNTFLQWFQQRPGQSPRRLIYK VSLRFSGVPDRFSGSGSDTDFTLRISRVEAEDVGLYYCSQSTHVPPTFGQGTKLEI K.

[0136] The one-letter amino acid sequence that corresponds to SEQ ID NO: 66 is DIVMTQTPLSLSVTPGQPASISCRSRQSLVNSNGNTFLQWLLQKPGQPPQLLIYKV SLRFSGVPNRFSGSGSGTDFTLKISRVEAEDVGLYYCSQSTHVPPTFGGGTKVEIK.

EXAMPLES

[0137] Example 1: *In vivo* study of the administration of anti-glycation end-product antibody. This example show that the anti-AGE antibody can target cell have AGE-modified proteins on the cell surface. Although the cells considered in this study are senescent cells, they may be considered a model of metastasizing cancer cells.

[0138] To examine the effects of an anti-glycation end-product antibody, the antibody was administered to the aged CD1 (ICR) mouse (Charles River Laboratories), twice daily by intravenous injection, once a week, for three weeks (Days 1, 8 and 15), followed by a 10 week treatment-free period. The test antibody was a commercially available mouse anti-glycation end-product antibody raised against carboxymethyl lysine conjugated with keyhole limpet hemocyanin, the carboxymethyl lysine MAb (Clone 318003) available from R&D Systems, Inc. (Minneapolis, MN; catalog no. MAB3247). A control reference of physiological saline was used in the control animals.

[0139] Mice referred to as "young" were 8 weeks old, while mice referred to as "old" were 88 weeks (±2 days) old. No adverse events were noted from the administration of the antibody. The different groups of animals used in the study are shown in Table 1.

Table 1: The different groups of animals used in the study

Group No.	Test Material	Mice	Dose Level (µg/gm/BID/ week)	Number of Animals	
				Main Study	Treatment-Free
				Females	Females
1	Saline	young	0	20	-
2	Saline	old	0	20	20
3	Antibody	old	2.5	20	20
4	None	old	0	20	pre
5	Antibody	old	5.0	20	20
- = Not Applicable, Pre = Subset of animals euthanized prior to treatment start for collection of adipose tissue.					

[0140] $P16^{INK4a}$ mRNA, a marker for senescent cells, was quantified in adipose tissue of the groups by Real Time-qPCR. The results are shown in Table 2. In the table ΔΔCt = ΔCt mean control Group (2) - ΔCt mean experimental Group (1 or 3 or 5); Fold Expression= $2^{-\Delta\Delta Ct}$.

Table 2: $P16^{INK4a}$ mRNA quantified in adipose tissue

Calculation (unadjusted to Group 4: 5.59)	Group 2 vs Group 1		Group 2 vs Group 3		Group 2 vs Group 5	
	Group 2	Group 1	Group 2	Group 3	Group	Group 5
Mean ΔCt	5.79	7.14	5.79	6.09	5.79	7.39
ΔΔCt	-1.35		-0.30		-1.60	
Fold Expression	**2.55**		**1.23**		**3.03**	

[0141] The table above indicates that untreated old mice (Control Group 2) express 2.55-fold more $p16^{Ink4a}$ mRNA than the untreated young mice (Control Group 1), as expected. This was observed when comparing Group 2 untreated old mice euthanized at end of recovery Day 85 to Group 1 untreated young mice euthanized at end of treatment Day 22. When results from Group 2 untreated old mice were compared to results from Group 3 treated old mice euthanized Day 85, it was observed that $p16^{Ink4a}$ mRNA was 1.23-fold higher in Group 2 than in Group 3. Therefore, the level of $p16^{Ink4a}$ mRNA expression was lower when the old mice were treated with 2.5 µg/gram/BID/week of antibody.

[0142] When results from Group 2 (Control) untreated old mice were compared to results from Group 5 (5 µg/gram) treated old mice euthanized Day 22, it was observed that $p16^{Ink4a}$ mRNA was 3.03-fold higher in Group 2 (controls) than in Group 5 (5 µg/gram). This comparison indicated that the Group 5 animals had lower levels of $p16^{Ink4a}$ mRNA expression when they were treated with 5.0 µg/gram/BID/week, providing $p16^{Ink4a}$ mRNA expression levels comparable to that of the young untreated mice (i.e. Group 1). Unlike Group 3 (2.5 µg/gram) mice that were euthanized at

end of recovery Day 85, Group 5 mice were euthanized at end of treatment Day 22.

[0143] These results indicate the antibody administration resulted in the killing of senescent cells.

[0144] The mass of the gastrocnemius muscle was also measured, to determine the effect of antibody administration on sarcopenia. The results are provided in Table 3. The results indicate that administration of the antibody increased muscle mass as compared to controls, but only at the higher dosage of 5.0 µg/gm/BID/ week.

Table 3: Effect of antibody administration on mass of the gastrocnemius muscle

Group	Summary Information	Absolute weight of Gastrocnemius Muscle	Weight relative to body mass of Gastrocnemius Muscle
1	Mean	0.3291	1.1037
	SD	0.0412	0.1473
	N	20	20
2	Mean	0.3304	0.7671
	SD	0.0371	0.1246
	N	20	20
3	Mean	0.3410	0.7706
	SD	0.0439	0.0971
	N	19	19
5	Mean	0.4074	0.9480
	SD	0.0508	0.2049
	N	9	9

[0145] These results demonstrate that administration of antibodies that bind to AGEs of a cell resulted in a reduction of cells expressing $p16^{Ink4a}$, a biomarker of senescence. The data show that reducing senescent cells leads directly to an increase in muscle mass in aged mice. These results indicate that the loss of muscle mass, a classic sign of sarcopenia, can be treated by administration of antibodies that bind to AGEs of a cell. The results suggest that administration of the antibodies would be effective in treating cancer metastases by removing senescent cells.

Example 2: Affinity and kinetics of test antibody

[0146] The affinity and kinetics of the test antibody used in Example 1 were analyzed using Na,Na-bis(carboxymethyl)-L-lysine trifluoroacetate salt (Sigma-Aldrich, St. Louis, MO) as a model substrate for an AGE-modified protein of a cell. Label-free interaction analysis was carried out on a BIACORE™ T200 (GE Healthcare, Pittsburgh, PA), using a Series S sensor chip CM5 (GE

Healthcare, Pittsburgh, PA), with Fc1 set as blank, and Fc2 immodilized with the test antibody (molecular weigh of 150,000 Da). The running buffer was a HBS-EP buffer (10 mM HEPES, 150 mM NaCl, 3 mM EDTA and 0.05% P-20, pH of 7.4), at a temperature of 25 °C. Software was BIACORE™ T200 evaluation software, version 2.0. A double reference (Fc2-1 and only buffer injection), was used in the analysis, and the data was fitted to a Langmuir 1:1 binding model.

Table 4: Experimental set-up of affinity and kinetics analysis

Association and dissociation	
Flow path	Fc1 and Fc2
Flow rate (µl/min.)	30
Association time (s)	300
Dissociation time (s)	300
Sample concentration (µM)	20 - 5 - 1.25 (x2) - 0.3125 - 0.078 - 0

[0147] A graph of the response versus time is illustrated in FIG. 1. The following values were determined from the analysis: k_a (1/Ms) = 1.857 x 10^3; k_d (1/s) = 6.781 x 10^{-3}; K_D (M) = 3.651 x 10^{-6}; R_{max} (RU) = 19.52; and Chi^2 = 0.114. Because the Chi^2 value of the fitting is less than 10% of R_{max}, the fit is reliable.

Example 3: Construction and production of murine anti-AGE IgG2b antibody and chimeric anti-AGE IgG1 antibody

[0148] Murine and chimeric human anti-AGE antibodies were prepared. The DNA sequence of murine anti-AGE antibody IgG2b heavy chain is shown in SEQ ID NO: 12. The DNA sequence of chimeric human anti-AGE antibody IgG1 heavy chain is shown in SEQ ID NO: 13. The DNA sequence of murine anti-AGE antibody kappa light chain is shown in SEQ ID NO: 14. The DNA sequence of chimeric human anti-AGE antibody kappa light chain is shown in SEQ ID NO: 15. The gene sequences were synthesized and cloned into high expression mammalian vectors. The sequences were codon optimized. Completed constructs were sequence confirmed before proceeding to transfection.

[0149] HEK293 cells were seeded in a shake flask one day before transfection, and were grown using serum-free chemically defined media. The DNA expression constructs were transiently transfected into 0.03 liters of suspension HEK293 cells. After 20 hours, cells were sampled to obtain the viabilities and viable cell counts, and titers were measured (Octet QKe, ForteBio). Additional readings were taken throughout the transient transfection production runs. The cultures were harvested on day 5, and an additional sample for each was measured for cell density, viability and titer.

[0150] The conditioned media for murine and chimeric anti-AGE antibodies were harvested and clarified from the transient transfection production runs by centrifugation and filtration. The supernatants were run over a Protein A column and eluted with a low pH buffer. Filtration using a

0.2 µm membrane filter was performed before aliquoting. After purification and filtration, the protein concentrations were calculated from the OD280 and the extinction coefficient. A summary of yields and aliquots is shown in Table 5:

Table 5: Yields and Aliquots

Protein	Concentration (mg/mL)	Volume (mL)	No. of vials	Total Yield (mg)
Murine anti-AGE	0.08	1.00	3	0.24
Chimeric anti-AGE	0.23	1.00	3	0.69

[0151] Antibody purity was evaluated by capillary electrophoresis sodium-dodecyl sulfate (CE-SDS) analysis using LabChip® GXII (PerkinElmer).

Example 4: Binding of murine (parental) and chimeric anti-AGE antibodies

[0152] The binding of the murine (parental) and chimeric anti-AGE antibodies described in Example 3 was investigated by a direct binding ELISA. An anti-carboxymethyl lysine (CML) antibody (R&D Systems, MAB3247) was used as a control. CML was conjugated to KLH (CML-KLH) and both CML and CML-KLH were coated overnight onto an ELISA plate. HRP-goat anti-mouse Fc was used to detect the control and murine (parental) anti-AGE antibodies. HRP-goat anti-human Fc was used to detect the chimeric anti-AGE antibody.

[0153] The antigens were diluted to 1 µg/mL in 1x phosphate buffer at pH 6.5. A 96-well microtiter ELISA plate was coated with 100 µL/well of the diluted antigen and let sit at 4°C overnight. The plate was blocked with 1x PBS, 2.5% BSA and allowed to sit for 1-2 hours the next morning at room temperature. The antibody samples were prepared in serial dilutions with 1x PBS, 1% BSA with the starting concentration of 50 pg/mL. Secondary antibodies were diluted 1:5,000. 100 µL of the antibody dilutions was applied to each well. The plate was incubated at room temperature for 0.5-1 hour on a microplate shaker. The plate was washed 3 times with 1x PBS. 100 µL/well diluted HRP-conjugated goat anti-human Fc secondary antibody was applied to the wells. The plate was incubated for 1 hour on a microplate shaker. The plate was then washed 3 times with 1x PBS. 100 µL HRP substrate TMB was added to each well to develop the plate. After 3-5 minutes elapsed, the reaction was terminated by adding 100 µL of 1N HCl. A second direct binding ELISA was performed with only CML coating. The absorbance at OD450 was read using a microplate reader.

[0154] The OD450 absorbance raw data for the CML and CML-KLH ELISA is shown in the plate map below. 48 of the 96 wells in the well plate were used. Blank wells in the plate map indicate unused wells.

Plate map of CML and CML-KLH ELISA:

Conc. (ug/mL)	1	2	3	4	5	6	7
50	0.462	0.092	0.42		1.199	0.142	1.852

Conc. (ug/mL)	1	2	3	4	5	6	7
16.67	0.312	0.067	0.185		0.31	0.13	0.383
5.56	0.165	0.063	0.123		0.19	0.115	0.425
1.85	0.092	0.063	0.088		0.146	0.099	0.414
0.62	0.083	0.072	0.066		0.108	0.085	0.248
0.21	0.075	0.066	0.09		0.096	0.096	0.12
0.07	0.086	0.086	0.082		0.098	0.096	0.098
0	0.09	0.085	0.12		0.111	0.083	0.582
	R&D Positive Control	Parental Anti-AGE	Chimeric Anti-AGE		R&D Positive Control	Parental Anti-AGE	Chimeric Anti-AGE
	CML-KLH Coat				CML Coat		

[0155] The OD450 absorbance raw data for the CML-only ELISA is shown in the plate map below. 24 of the 96 wells in the well plate were used. Blank wells in the plate map indicate unused wells.
Plate map of CML-only ELISA:

Conc. (ug/mL)	1	2	3	4	5	6	7
50	1.913	0.165	0.992				
16.66667	1.113	0.226	0.541				
5.555556	0.549	0.166	0.356				
1.851852	0.199	0.078	0.248				
0.617284	0.128	0.103	0.159				
0.205761	0.116	0.056	0.097				
0.068587	0.073	0.055	0.071				
0	0.053	0.057	0.06				
	R&D Positive Control	Parental Anti-AGE	Chimeric Anti-AGE				

[0156] The control and chimeric anti-AGE antibodies showed binding to both CML and CML-KLH. The murine (parental) anti-AGE antibody showed very weak to no binding to either CML or CML-KLH. Data from repeated ELISA confirms binding of the control and chimeric anti-AGE to CML. All buffer control showed negative signal.

Example 5: Humanized antibodies

[0157] Humanized antibodies were designed by creating multiple hybrid sequences that fuse

select parts of the parental (mouse) antibody sequence with the human framework sequences. Acceptor frameworks were identified based on the overall sequence identity across the framework, matching interface position, similarly classed CDR canonical positions, and presence of N-glycosylation sites that would have to be removed. Three humanized light chains and three humanized heavy chains were designed based on two different heavy and light chain human acceptor frameworks. The amino acid sequences of the heavy chains are shown in SEQ ID NO: 29, 31 and 33, which are encoded by the DNA sequences shown in SEQ ID NO: 30, 32 and 34, respectively. The amino acid sequences of the light chains are shown in SEQ ID NO: 35, 37 and 39, which are encoded by the DNA sequences shown in SEQ ID NO: 36, 38 and 40, respectively. The humanized sequences were methodically analyzed by eye and computer modeling to isolate the sequences that would most likely retain antigen binding. The goal was to maximize the amount of human sequence in the final humanized antibodies while retaining the original antibody specificity. The light and heavy humanized chains could be combined to create nine variant fully humanized antibodies.

[0158] The three heavy chains and three light chains were analyzed to determine their humanness. Antibody humanness scores were calculated according to the method described in Gao, S. H., et al., "Monoclonal antibody humanness score and its applications", BMC Biotechnology, 13:55 (July 5, 2013). The humanness score represents how human-like an antibody variable region sequence looks. For heavy chains a score of 79 or above is indicative of looking human-like; for light chains a score of 86 or above is indicative of looking human-like. The humanness of the three heavy chains, three light chains, a parental (mouse) heavy chain and a parental (mouse) light chain are shown below in Table 6:

Table 6: Antibody humanness

Antibody	Humanness (Framework + CDR)
Parental (mouse) heavy chain	63.60
Heavy chain 1 (SEQ ID NO: 29)	82.20
Heavy chain 2 (SEQ ID NO: 31)	80.76
Heavy chain 3 (SEQ ID NO: 33)	81.10
Parental (mouse) light chain	77.87
Light chain 1 (SEQ ID NO: 35)	86.74
Light chain 2 (SEQ ID NO: 37)	86.04
Light chain 3 (SEQ IN NO: 39)	83.57

[0159] Full-length antibody genes were constructed by first synthesizing the variable region sequences. The sequences were optimized for expression in mammalian cells. These variable region sequences were then cloned into expression vectors that already contain human Fc domains; for the heavy chain, the IgG1 was used.

[0160] Small scale production of humanized antibodies was carried out by transfecting plasmids for the heavy and light chains into suspension HEK293 cells using chemically defined media in the absence of serum. Whole antibodies in the conditioned media were purified using MabSelect SuRe Protein A medium (GE Healthcare).

[0161] Nine humanized antibodies were produced from each combination of the three heavy chains having the amino acid sequences shown in SEQ ID NO: 29, 31 and 33 and three light chains having the amino acid sequences shown in SEQ ID NO: 35, 37 and 39. A comparative chimeric parental antibody was also prepared. The antibodies and their respective titers are shown below in Table 7:

Table 7: Antibody titers

Antibody	Titer (mg/L)
Chimeric parental	23.00
SEQ ID NO: 29 + SEQ ID NO: 35	24.67
SEQ ID NO: 29 + SEQ ID NO: 37	41.67
SEQ ID NO: 29 + SEQ ID NO: 39	29.67
SEQ ID NO: 31 + SEQ ID NO: 35	26.00
SEQ ID NO:31 + SEQ ID NO: 37	27.33
SEQ ID NO: 31 + SEQ ID NO: 39	35.33
SEQ ID NO: 33 + SEQ ID NO: 35	44.00
SEQ ID NO: 33 + SEQ ID NO: 37	30.33
SEQ ID NO: 33 + SEQ ID NO: 39	37.33

[0162] The binding of the humanized antibodies may be evaluated, for example, by dose-dependent binding ELISA or cell-based binding assay.

Example 6 (prophetic): killing of metastatic cancer cells, and treating metastatic cancer

[0163] Aggregates of human ovarian cancer cells (Creative BioArray, Shirley, NY) are inoculated i.p. into two groups (A and B) of T and B cell -deficient prkdcscid (SCID) mice, specifically NSG mice available from Jackson Laboratories (Farmington, CT). Group A is a control group injected intravenously with physiological saline and Group B is injected intravenously with 5 µg per gram per mouse of any of the anti-AGE monoclonal antibodies described.

[0164] 80 days post inoculation with cancer cells, mice from both Groups A and B undergo gross and histological examination. The antibody-treated group B mice have significantly fewer metastatic foci than Group A control mice.

Example 6: *In vivo* study of the administration of a carboxymethyl lysine monoclonal antibody

[0165] The effect of a carboxymethyl lysine antibody on tumor growth, metastatic potential and cachexia was investigated. *In vivo* studies were carried out in mice using a murine breast cancer

tumor model. Female BALB/c mice (BALB/cAnNCrl, Charles River) were eleven weeks old on Day 1 of the study.

[0166] 4T1 murine breast tumor cells (ATCC CRL-2539) were cultured in RPMI 1640 medium containing 10% fetal bovine serum, 2 mM glutamine, 25 µg/mL gentamicin, 100 units/mL penicillin G Na and 100 µg/mL streptomycin sulfate. Tumor cells were maintained in tissue culture flasks in a humidified incubator at 37 °C in an atmosphere of 5% CO_2 and 95% air.

[0167] The cultured breast cancer cells were then implanted in the mice. 4T1 cells were harvested during log phase growth and re-suspended in phosphate buffered saline (PBS) at a concentration of 1 x 10^6 cells/mL on the day of implant. Tumors were initiated by subcutaneously implanting 1 x 10^5 4T1 cells (0.1 mL suspension) into the right flank of each test animal. Tumors were monitored as their volumes approached a target range of 80-120 mm^3. Tumor volume was determined using the formula: tumor volume = $(\text{tumor width})^2(\text{tumor length})/2$. Tumor weight was approximated using the assumption that 1 mm^3 of tumor volume has a weight of 1 mg. Thirteen days after implantation, designated as Day 1 of the study, mice were sorted into four groups (n=15/group) with individual tumor volumes ranging from 108 to 126 mm^3 and a group mean tumor volume of 112 mm^3. The four treatment groups are shown in Table 8 below:

Table 8: Treatment groups

Group	Description	Agent	Dosing (µg/g)
1	Control	phosphate buffered saline (PBS)	N/A
2	Low-dose	carboxymethyl lysine monoclonal antibody	5
3	High-dose	carboxymethyl lysine monoclonal antibody	10
4	Observation only	None	N/A

[0168] An anti-carboxymethyl lysine monoclonal antibody was used as a therapeutic agent. 250 mg of carboxymethyl lysine monoclonal antibody was obtained from R&D Systems (Minneapolis, MN). Dosing solutions of the carboxymethyl lysine monoclonal antibody were prepared at 1 and 0.5 mg/mL in a vehicle (PBS) to provide the active dosages of 10 and 5 µg/g, respectively, in a dosing volume of 10 mL/kg. Dosing solutions were stored at 4 °C protected from light.

[0169] All treatments were administered intravenously (i.v.) twice daily for 21 days, except on Day 1 of the study where the mice were administered one dose. On Day 19 of the study, i.v. dosing was changed to intraperitoneal (i.p.) dosing for those animals that could not be dosed i.v. due to tail vein degradation. The dosing volume was 0.200 mL per 20 grams of body weight (10 mL/kg), and was scaled to the body weight of each individual animal.

[0170] The study continued for 23 days. Tumors were measured using calipers twice per week. Animals were weighed daily on Days 1-5, then twice per week until the completion of the study. Mice were also observed for any side effects. Acceptable toxicity was defined as a group mean

body weight loss of less than 20% during the study and not more than 10% treatment-related deaths. Treatment efficacy was determined using data from the final day of the study (Day 23).

[0171] The ability of the anti-carboxymethyl lysine antibody to inhibit tumor growth was determined by comparing the median tumor volume (MTV) for Groups 1-3. Tumor volume was measured as described above. Percent tumor growth inhibition (%TGI) was defined as the difference between the MTV of the control group (Group 1) and the MTV of the drug-treated group, expressed as a percentage of the MTV of the control group. %TGI may be calculated according to the formula: $\%TGI = (1-MTV_{treated}/MTV_{control}) \times 100$. FIG. 3 illustrates a graph of the normalized tumor volume over the course of an *in vivo* study investigating the effect of an anti-AGE antibody on tumor growth, metastatic potential and cachexia.

[0172] The ability of the anti-carboxymethyl lysine antibody to inhibit cancer metastasis was determined by comparing lung cancer foci for Groups 1-3. Percent inhibition (%Inhibition) was defined as the difference between the mean count of metastatic foci of the control group and the mean count of metastatic foci of a drug-treated group, expressed as a percentage of the mean count of metastatic foci of the control group. %Inhibition may be calculated according to the following formula:
$\%Inhibition = (1-\text{Mean Count of } Foci_{treated}/\text{Mean Count of } Foci_{control}) \times 100$.

[0173] The ability of the anti-carboxymethyl lysine antibody to inhibit cachexia was determined by comparing the weights of the lungs and gastrocnemius muscles for Groups 1-3. Tissue weights were also normalized to 100 g body weight. FIG. 4 illustrates a graph of the normalized body weight of the mice over the course of an *in vivo* study investigating the effect of an anti-AGE antibody on tumor growth, metastatic potential and cachexia.

[0174] Treatment efficacy was also evaluated by the incidence and magnitude of regression responses observed during the study. Treatment may cause partial regression (PR) or complete regression (CR) of the tumor in an animal. In a PR response, the tumor volume was 50% or less of its Day 1 volume for three consecutive measurements during the course of the study, and equal to or greater than 13.5 mm^3 for one or more of these three measurements. In a CR response, the tumor volume was less than 13.5 mm^3 for three consecutive measurements during the course of the study.

[0175] Statistical analysis was carried out using Prism (GraphPad) for Windows 6.07. Statistical analyses of the differences between Day 23 mean tumor volumes (MTVs) of two groups were accomplished using the Mann-Whitney U test. Comparisons of metastatic foci were assessed by ANOVA-Dunnett. Normalized tissue weights were compared by ANOVA. Two-tailed statistical analyses were conducted at significance level $P = 0.05$. Results were classified as statistically significant or not statistically significant.

[0176] The results of the study are shown below in Table 9:
Table 9: Results

Group	MTV (mm^3)	%TGI	Lung foci	%Inhibition	PR	CR	Gastroc. weight/normalized (mg)	Lung weight/normalized (mg)
1	1800	N/A	70.4	N/A	0	0	353.4/19.68	2799.4/292.98
2	1568	13%	60.3	14%	0	0	330.4/21.62	2388.9/179.75
3	1688	6%	49.0	30%	0	0	398.6/24.91	2191.6/214.90

[0177] All treatment regimens were acceptably tolerated with no treatment-related deaths. The only animal deaths were non-treatment-related deaths due to metastasis. The %TGI trended towards significance ($P > 0.05$, Mann-Whitney) for the 5 µg/g (Group 2) and 10 µg/g treatment group (Group 3). The %Inhibition trended towards significance ($P > 0.05$, ANOVA-Dunnett) for the 5 µg/g treatment group. The %Inhibition was statistically significant ($P \leq 0.01$, ANOVA-Dunnett) for the 10 µg/g treatment group. The ability of the carboxymethyl lysine antibody to treat cachexia trended towards significance ($P > 0.05$, ANOVA) based on a comparison of the organ weights of the lung and gastrocnemius between treatment groups and the control group. The results indicate that administration of an anti-carboxymethyl lysine monoclonal antibody is able to reduce cancer metastases.

Example 7: Diagnosis of metastatic cancer (prophetic)

[0178] A patient with breast cancer exhibits enlarged lymph nodes. An oncologist suspects that the breast cancer has metastasized to her lymph nodes. The oncologist obtains a blood sample as well as a biopsy from one of her enlarged lymph nodes. Cells from the blood sample and the biopsy are tested for the presence of AGE-modified cancer cells using a kit containing a fluorescent-labelled anti-AGE antibody and a control. The diagnostic test indicates the presence of circulating AGE-modified cancer cells in the patient's blood as well as the presence of metastatic breast cancer cells in the lymph nodes. A second staining of the cells for cell-surface nucleolin, a well-known cancer marker, as described in U.S. Pat. No. 7,541,150 to Miller et al. confirms the presence of cancerous cells.

REFERENCES

[0179]

1. 1. International Application Pub. No. WO 2009/143411 to Gruber (26 Nov. 2009).
2. 2. U.S. Patent No. 5,702,704 to Bucala (issued December 30, 1997).
3. 3. U.S. Patent No. 6,380,165 to Al-Abed et al. (issued April 30, 2002).
4. 4. U.S. Patent No. 6,387,373 to Wright et al. (issued May 14, 2002).
5. 5. U.S. Patent No. 4,217,344 to Vanlerberghe et al. (issued August 12, 1980).
6. 6. U.S. Patent No. 4,917,951 to Wallach (issued April 17, 1990).
7. 7. U.S. Patent No. 4,911,928 to Wallach (issued March 27, 1990).
8. 8. U.S. Patent Application Publication Pub. No. US 2010/226932 to Smith et al. (September

9, 2010).

9. 9. Ando K, et al., "Membrane Proteins of Human Erythrocytes Are Modified by Advanced Glycation End Products During Aging in the Circulation," Biochemical and Biophysical Research Communications, Vol. 258, 123-27 (1999).
10. 10. Lindsey JB, et al., "Receptor For Advanced Glycation End-Products (RAGE) and soluble RAGE (sRAGE): Cardiovascular Implications," Diabetes Vascular Disease Research, Vol. 6(1), 7-14, (2009).
11. 11. Bierhaus A, "AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept," Cardiovasc Res, Vol. 37(3), 586-600 (1998).
12. 12. Meuter A., et al. "Markers of cellular senescence are elevated in murine blastocysts cultured in vitro: molecular consequences of culture in atmospheric oxygen" J Assist Reprod Genet. 2014 Aug 10. [Epub ahead of print].
13. 13. Baker, D.J. et al., "Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders", Nature, vol. 479, pp. 232-236, (2011).
14. 14. Jana Hadrabová, et al. "Chicken immunoglobulins for prophylaxis: Effect of inhaled antibodies on inflammatory parameters in rat airways" Journal of Applied Biomedicine (in press; Available online 5 May 2014).
15. 15. Vlassara, H. et al., "High-affinity-receptor-mediated Uptake and Degradation of Glucose-modified Proteins: A Potential Mechanism for the Removal of Senescent Macromolecules", Proc. Natl. Acad. Sci. USA, Vol. 82, 5588, 5591 (1985).
16. 16. Roll, P. et al., "Anti-CD20 Therapy in Patients with Rheumatoid Arthritis", Arthritis & Rheumatism, Vol. 58, No. 6, 1566-1575 (2008).
17. 17. Kajstura, J. et al., "Myocite Turnover in the Aging Human Heart", Circ. Res., Vol. 107(11), 1374-86, (2010).
18. 18. de Groot, K. et al., "Vascular Endothelial Damage and Repair in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis", Arthritis and Rheumatism, Vol. 56(11), 3847, 3847 (2007).
19. 19. Manesso, E. et al., "Dynamics of β-Cell Turnover: Evidence for β-Cell Turnover and Regeneration from Sources of β-Cells other than β-cell Replication in the HIP Rat", Am. J. Physiol. Endocrinol. Metab., Vol. 297, E323, E324 (2009).
20. 20. Kirstein, M. et al., "Receptor-specific Induction of Insulin-like Growth Factor I in Human Monocytes by Advanced Glycosylation End Product-modified Proteins", J. Clin. Invest., Vol. 90, 439, 439-440 (1992).
21. 21. Murphy, J. F., "Trends in cancer immunotherapy", Clinical Medical Insights: Oncology, Vol. 14(4), 67-80 (2010).
22. 22. Virella, G. et al., "Autoimmune Response to Advanced Glycosylation End-Products of Human LDL", Journal of Lipid Research, Vol. 44, 487-493 (2003).
23. 23. Ameli, S. et al., "Effect of Immunization With Homologous LDL and Oxidized LDL on Early Atherosclerosis in Hypercholesterolemic Rabbits", Arteriosclerosis, Thrombosis, and Vascular Biology, Vol. 16, 1074 (1996).
24. 24. "Sarcopenia", available online at en.wikipedia.org/wiki/Sarcopenia (November 14, 2014).
25. 25. "What is sarcopenia?", available online at www.iofbonehealth.org/what-sarcopenia (2014).
26. 26. Blahd, W., "Sarcopenia with aging", available online at www.webmd.com/healthy-aging/sarcopenia-with-aging (August 3, 2014).
27. 27. "Keyhole limpet hemocyanin", available online at

en.wikipedia.org/wiki/Keyhole_limpet_hemocyanin (April 18, 2014).

28. 28. "CML-BSA Product Data Sheet", available online at www.cellbiolabs.com/sites/default/files/STA-314-cml-bsa.pdf (2010).
29. 29. "CML (N-epsilon-(Carboxymethyl)Lysine) Assays and Reagents", available online at www.cellbiolabs.com/cml-assays (Accessed on December 15, 2014).
30. 30. Cruz-Jentoft, A. J. et al., "Sarcopenia: European consensus on definition and diagnosis", Age and Ageing, Vol. 39, pp. 412-423 (April 13, 2010).
31. 31. Rolland, Y. et al., "Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives", J. Nutr. Health Aging, Vol. 12(7), pp. 433-450 (2008).
32. 32. Mera, K. et al., "An autoantibody against Nε-(carboxyethyl)lysine (CEL): Possible involvement in the removal of CEL-modified proteins by macrophages", Biochemical and Biophysical Research Communications, Vol. 407, pp. 420-425 (March 12, 2011).
33. 33. Reddy, S. et al., "Nε-(carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteins", Biochemistry, Vol. 34, pp. 10872-10878 (August 1, 1995).
34. 34. Naylor, R. M. et al., "Senescent cells: a novel therapeutic target for aging and age-related diseases", Clinical Pharmacology & Therapeutics, Vol. 93(1), pp.105-116 (December 5, 2012).
35. 35. Katcher, H. L., "Studies that shed new light on aging", Biochemistry (Moscow), Vol. 78(9), pp. 1061-1070 (2013).
36. 36. Ahmed, E. K. et al., "Protein Modification and Replicative Senescence of WI-38 Human Embryonic Fibroblasts", Aging Cells, Vol. 9, 252, 260 (2010).
37. 37. Vlassara, H. et al., "Advanced Glycosylation Endproducts on Erythrocyte Cell Surface Induce Receptor-Mediated Phagocytosis by Macrophages", J. Exp. Med., Vol. 166, 539, 545 (1987).
38. 38. Fielding, R. A., et al., "Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences", Journal of the American Medical Directors Association, Vol. 12(4), pp. 249-256 (May 2011).
39. 39. Maass, D. R. et al., "Alpaca (Lama pacos) as a convenient source of recombinant camelid heavy chain antibodies (VHHs)", Journal of Immunological Methods, Vol. 324, No. 1-2, pp. 13-25 (July 31, 2007).
40. 40. Strietzel, C.J. et al., "In vitro functional characterization of feline IgGs", Veterinary Immunology and Immunopathology, Vol. 158, pp. 214-223 (2014).
41. 41. Patel, M. et al., "Sequence of the dog immunoglobulin alpha and epsilon constant region genes", Immunogenetics, Vol. 41, pp. 282-286 (1995).
42. 42. Wagner, B. et al., "The complete map of the Ig heavy chain constant gene region reveals evidence for seven IgG isotypes and for IgD in the horse", The Journal of Immunology, Vol. 173, pp. 3230-3242 (2004).
43. 43. Hamers-Casterman, C. et al., "Naturally occurring antibodies devoid of light chains", Nature, Vol. 363, pp. 446-448 (June 3, 1993).
44. 44. De Genst, E. et al., "Antibody repertoire development in camelids", Developmental & Comparative Immunology, Vol. 30, pp. 187-198 (available online July 11, 2005).
45. 45. Griffin, L.M. et al., "Analysis of heavy and light chain sequences of conventional camelid antibodies from Camelus dromedarius and Camelus bactrianus species", Journal of Immunological Methods, Vol. 405, pp. 35-46 (available online January 18, 2014).
46. 46. Nguyen, V.K. et al., "Camel heavy-chain antibodies: diverse germline VHH and specific

mechanisms enlarge the antigen-binding repertoire", The European Molecular Biology Organization Journal, Vol. 19, No, 5, pp. 921-930 (2000).

47. 47. Muyldermans, S. et al., "Sequence and structure of VH domain from naturally occurring camel heavy chain immunoglobulins lacking light chains", Protein Engineering, Vol. 7, No. 9, pp. 1129-1135 (1994).

Sequence Listing

[0180]

<110> Lewis S. Gruber

<120> METHOD AND COMPOSITION FOR TREATING CANCER, KILLING METASTATIC CANCER CELLS AND PREVENTING CANCER METASTASIS

<130> SIW01-013-WO

<160> 66

<210> 1
<211> 463
<212> PRT
<213> Artificial sequence

<220>
<223> Modified Homo sapiens immunoglobulin G1 heavy chain

<400> 1

```
Met Asn Leu Leu Leu Ile Leu Thr Phe Val Ala Ala Ala Val Ala Gln
1               5                   10                  15

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

Val Lys Leu Ala Cys Lys Ala Ser Gly Tyr Leu Phe Thr Thr Tyr Trp
        35                  40                  45

Met His Trp Leu Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
    50                  55                  60

Glu Ile Ser Pro Thr Asn Gly Arg Ala Tyr Tyr Asn Ala Arg Phe Lys
65                  70                  75                  80

Ser Glu Ala Thr Leu Thr Val Asp Lys Ser Ser Asn Thr Ala Tyr Met
                85                  90                  95

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

Arg Ala Tyr Gly Asn Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
```

```
        115                 120                 125

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

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
145                 150                 155                 160

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

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

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

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
    210                 215                 220

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

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His Glu Asp Pro Glu
        275                 280                 285

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    290                 295                 300

Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 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 Val 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> 2

<211> 118

<212> PRT

<213> Mus musculus

<400> 2

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

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

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

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

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

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

Ala Arg Ala Tyr Gly Asn Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Val
        115
```

<210> 3

<211> 234

<212> PRT

<213> Artificial sequence

<220>

<223> Modified Homo sapiens immunoglobulin G1 kappa light chain

<400> 3

```
Met Asn Leu Leu Leu Ile Leu Thr Phe Val Ala Ala Ala Val Ala Asp

1               5                   10                  15

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

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

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

Lys Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe Ser Gly Val Pro Asp
65                  70                  75                  80

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

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

His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu 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> 4

<211> 113

<212> PRT

<213> Mus musculus

<400> 4

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

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

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

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

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

```
Ser Arg Val Glu Ala Glu Asp Leu Gly Leu Tyr Phe Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg
```

<210> 5

<211> 327

<212> PRT

<213> Equus caballus

<400> 5

```
Ala Ser Thr Thr Ala Pro Lys Val Phe Pro Leu Ala Ser His Ser Ala
1               5                   10                  15

Ala Thr Ser Gly Ser Thr Val Ala Leu Gly Cys Leu Val Ser Ser Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ser Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Leu Lys Ser Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys
                85                  90                  95

Lys Ile Val Ile Lys Glu Cys Asn Gly Gly Cys Pro Ala Glu Cys Leu
            100                 105                 110

Gln Val Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val
        115                 120                 125

Leu Met Ile Ser Arg Thr Pro Thr Val Thr Cys Val Val Val Asp Val
    130                 135                 140

Gly His Asp Phe Pro Asp Val Gln Phe Asn Trp Tyr Val Asp Gly Val
145                 150                 155                 160

Glu Thr His Thr Ala Thr Thr Glu Pro Lys Gln Glu Gln Phe Asn Ser
                165                 170                 175

Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gln His Lys Asp Trp Leu
            180                 185                 190

Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Ala Leu Pro Ala
        195                 200                 205

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

Gln Val Tyr Val Leu Ala Pro His Arg Asp Glu Leu Ser Lys Asn Lys
225                 230                 235                 240
```

225 230 235 240

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

Ile Glu Trp Lys Ser Asn Gly Gln Pro Glu Pro Glu Thr Lys Tyr Ser
260 265 270

Thr Thr Pro Ala Gln Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Ser
275 280 285

Lys Leu Thr Val Glu Thr Asn Arg Trp Gln Gln Gly Thr Thr Phe Thr
290 295 300

Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Glu Lys Ser
305 310 315 320

Val Ser Lys Ser Pro Gly Lys
325

<210> 6

<211> 415

<212> PRT

<213> Equus caballus

<400> 6

Ser Leu Glu Asp Thr Ala Val Ile Pro Leu Phe Ser Glu Cys Lys Ala
1 5 10 15

Pro Lys Glu Asp Asp Val Val Ser Leu Ala Cys Leu Val Lys Gly Tyr
20 25 30

Phe Pro Glu Pro Val Gln Val Thr Trp Glu Pro Glu Met Gln Asn Gln
35 40 45

Lys Pro Trp Thr Phe Pro Ala Met Lys Lys Gly Gln Glu Tyr Ile His
50 55 60

Val Phe Ser Leu Thr Thr Trp Trp Lys Pro Gly Ser His Ser Cys Thr
65 70 75 80

Val His His Lys Ala Ser Ser Phe Arg Lys Lys Met Thr Phe Gln Glu
85 90 95

Pro Ala Ser Trp Ala Pro Gln Arg Thr Ser Ala Leu Pro Val Thr Ser
100 105 110

Lys Glu Pro Thr Pro Ala Pro Thr Thr Leu Arg Lys Ser Glu Pro Ser
115 120 125

Thr Arg His Thr Gln Pro Glu Thr Gln Lys Pro Arg Ile Pro Val Asp
130 135 140

Thr Pro Leu Lys Glu Cys Gln Ser His Thr His Pro Pro Ser Ile Tyr
145 150 155 160

Leu Leu His Pro Pro Leu Gln Gly Leu Trp Leu Lys Gly Glu Ala Thr
165 170 175

```
Phe Thr Cys Leu Val Val Gly Asp Asp Leu Lys Asp Ala His Leu Ser
            180                 185                 190

Trp Glu Leu Ser Glu Arg Ser Asn Gly Met Phe Val Glu Ser Gly Pro
        195                 200                 205

Leu Glu Lys His Thr Asn Gly Ser Gln Ser Arg Ser Ser Arg Leu Ala
    210                 215                 220

Leu Pro Arg Ser Ser Trp Ala Met Gly Thr Ser Val Thr Cys Lys Leu
225                 230                 235                 240

Ser Tyr Pro Asn Leu Leu Ser Ser Met Glu Val Val Gly Leu Lys Glu
                245                 250                 255

His Ala Ala Ser Ala Pro Arg Ser Leu Thr Val His Ala Leu Thr Thr
            260                 265                 270

Pro Gly Leu Asn Ala Ser Pro Gly Ala Thr Ser Trp Leu Gln Cys Lys
        275                 280                 285

Val Ser Gly Phe Ser Pro Pro Glu Ile Val Leu Thr Trp Leu Glu Gly
    290                 295                 300

Gln Arg Glu Val Asp Pro Ser Trp Phe Ala Thr Ala Arg Pro Thr Ala
305                 310                 315                 320

Gln Pro Gly Asn Thr Thr Phe Gln Thr Trp Ser Ile Leu Leu Val Pro
                325                 330                 335

Thr Ile Pro Gly Pro Pro Thr Ala Thr Tyr Thr Cys Val Val Gly His
            340                 345                 350

Glu Ala Ser Arg Gln Leu Leu Asn Thr Ser Trp Ser Leu Asp Thr Gly
        355                 360                 365

Gly Leu Ala Met Thr Pro Glu Ser Lys Asp Glu Asn Ser Asp Asp Tyr
    370                 375                 380

Ala Asp Leu Asp Asp Ala Gly Ser Leu Trp Leu Thr Phe Met Ala Leu
385                 390                 395                 400

Phe Leu Ile Thr Leu Leu Tyr Ser Gly Phe Val Thr Phe Ile Lys
                405                 410                 415
```

<210> 7

<211> 334

<212> PRT

<213> Canis familiaris

<400> 7

```
Ser Lys Thr Ser Pro Ser Val Phe Pro Leu Ser Leu Cys His Gln Glu
1               5                   10                  15

Ser Glu Gly Tyr Val Val Ile Gly Cys Leu Val Gln Gly Phe Phe Pro

            20                  25                  30
```

```
            20                  25                  30

Pro Glu Pro Val Asn Val Thr Trp Asn Ala Gly Lys Asp Ser Thr Ser
        35                  40                  45

Val Lys Asn Phe Pro Pro Met Lys Ala Ala Thr Gly Ser Leu Tyr Thr
    50                  55                  60

Met Ser Ser Gln Leu Thr Leu Pro Ala Ala Gln Cys Pro Asp Asp Ser
65                  70                  75                  80

Ser Val Lys Cys Gln Val Gln His Ala Ser Ser Pro Ser Lys Ala Val
                85                  90                  95

Ser Val Pro Cys Lys Asp Asn Ser His Pro Cys His Pro Cys Pro Ser
            100                 105                 110

Cys Asn Glu Pro Arg Leu Ser Leu Gln Lys Pro Ala Leu Glu Asp Leu
        115                 120                 125

Leu Leu Gly Ser Asn Ala Ser Leu Thr Cys Thr Leu Ser Gly Leu Lys
    130                 135                 140

Asp Pro Lys Gly Ala Thr Phe Thr Trp Asn Pro Ser Lys Gly Lys Glu
145                 150                 155                 160

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

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

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

Ser Ile Thr Lys Thr Thr Glu His Ile Pro Pro Gln Val His Leu Leu
    210                 215                 220

Pro Pro Pro Ser Glu Glu Leu Ala Leu Asn Glu Leu Val Thr Leu Thr
225                 230                 235                 240

Cys Leu Val Arg Gly Phe Lys Pro Lys Asp Val Leu Val Arg Trp Leu
                245                 250                 255

Gln Gly Thr Gln Glu Leu Pro Gln Glu Lys Tyr Leu Thr Trp Glu Pro
            260                 265                 270

Leu Lys Glu Pro Asp Gln Thr Asn Met Phe Ala Val Thr Ser Met Leu
        275                 280                 285

Arg Val Thr Ala Glu Asp Trp Lys Gln Gly Glu Lys Phe Ser Cys Met
    290                 295                 300

Val Gly His Glu Ala Leu Pro Met Ser Phe Thr Gln Lys Thr Ile Asp
305                 310                 315                 320

Arg Leu Ala Gly Lys Pro Thr His Val Asn Val Ser Val Val
                325                 330
```

<210> 8

<211> 426

<212> PRT

<213> Canis familiaris

<400> 8

```
Thr Ser Gln Asp Leu Ser Val Phe Pro Leu Ala Ser Cys Cys Lys Asp
1               5                  10                  15

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

Leu Pro Met Ser Thr Thr Val Thr Trp Asp Thr Gly Ser Leu Asn Lys
        35                  40                  45

Asn Val Thr Thr Phe Pro Thr Thr Phe His Glu Thr Tyr Gly Leu His
    50                  55                  60

Ser Ile Val Ser Gln Val Thr Ala Ser Gly Lys Trp Ala Lys Gln Arg
65                  70                  75                  80

Phe Thr Cys Ser Val Ala His Ala Glu Ser Thr Ala Ile Asn Lys Thr
                85                  90                  95

Phe Ser Ala Cys Ala Leu Asn Phe Ile Pro Pro Thr Val Lys Leu Phe
            100                 105                 110

His Ser Ser Cys Asn Pro Val Gly Asp Thr His Thr Thr Ile Gln Leu
        115                 120                 125

Leu Cys Leu Ile Ser Gly Tyr Val Pro Gly Asp Met Glu Val Ile Trp
    130                 135                 140

Leu Val Asp Gly Gln Lys Ala Thr Asn Ile Phe Pro Tyr Thr Ala Pro
145                 150                 155                 160

Gly Thr Lys Glu Gly Asn Val Thr Ser Thr His Ser Glu Leu Asn Ile
                165                 170                 175

Thr Gln Gly Glu Trp Val Ser Gln Lys Thr Tyr Thr Cys Gln Val Thr
            180                 185                 190

Tyr Gln Gly Phe Thr Phe Lys Asp Glu Ala Arg Lys Cys Ser Glu Ser
        195                 200                 205

Asp Pro Arg Gly Val Thr Ser Tyr Leu Ser Pro Pro Ser Pro Leu Asp
    210                 215                 220

Leu Tyr Val His Lys Ala Pro Lys Ile Thr Cys Leu Val Val Asp Leu
225                 230                 235                 240

Ala Thr Met Glu Gly Met Asn Leu Thr Trp Tyr Arg Glu Ser Lys Glu
                245                 250                 255

Pro Val Asn Pro Gly Pro Leu Asn Lys Lys Asp His Phe Asn Gly Thr
            260                 265                 270

Ile Thr Val Thr Ser Thr Leu Pro Val Asn Thr Asn Asp Trp Ile Glu
```

```
                                                                  Asp Asp
        275                 280                 285

Gly Glu Thr Tyr Tyr Cys Arg Val Thr His Pro His Leu Pro Lys Asp
    290                 295                 300

Ile Val Arg Ser Ile Ala Lys Ala Pro Gly Lys Arg Ala Pro Pro Asp
305                 310                 315                 320

Val Tyr Leu Phe Leu Pro Pro Glu Glu Glu Gln Gly Thr Lys Asp Arg
                325                 330                 335

Val Thr Leu Thr Cys Leu Ile Gln Asn Phe Phe Pro Ala Asp Ile Ser
            340                 345                 350

Val Gln Trp Leu Arg Asn Asp Ser Pro Ile Gln Thr Asp Gln Tyr Thr
        355                 360                 365

Thr Thr Gly Pro His Lys Val Ser Gly Ser Arg Pro Ala Phe Phe Ile
    370                 375                 380

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

Phe Thr Cys Gln Val Val His Glu Ala Leu Ser Gly Ser Arg Ile Leu
                405                 410                 415

Gln Lys Trp Val Ser Lys Thr Pro Gly Lys
            420                 425
```

<210> 9

<211> 335

<212> PRT

<213> Felis catus

<400> 9

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

Thr Thr Ser Gly Ala Thr Val Ala Leu Ala Cys Leu Val Leu Gly Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ser Val Leu Gln Ala Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Met Val Thr Val Pro Ser Ser Arg Trp Leu Ser Asp Thr
65                  70                  75                  80

Phe Thr Cys Asn Val Ala His Arg Pro Ser Ser Thr Lys Val Asp Lys
                85                  90                  95

Thr Val Pro Lys Thr Ala Ser Thr Ile Glu Ser Lys Thr Gly Glu Gly
            100                 105                 110

Pro Lys Cys Pro Val Pro Glu Ile Pro Gly Ala Pro Ser Val Phe Ile
        115                 120                 125
```

```
Phe Pro Pro Lys Pro Lys Asp Thr Leu Ser Ile Ser Arg Thr Pro Glu
    130                 135                 140

Val Thr Cys Leu Val Val Asp Leu Gly Pro Asp Asp Ser Asn Val Gln
145                 150                 155                 160

Ile Thr Trp Phe Val Asp Asn Thr Glu Met His Thr Ala Lys Thr Arg
                165                 170                 175

Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
            180                 185                 190

Pro Ile Leu His Gln Asp Trp Leu Lys Gly Lys Glu Phe Lys Cys Lys

        195                 200                 205

Val Asn Ser Lys Ser Leu Pro Ser Ala Met Glu Arg Thr Ile Ser Lys
    210                 215                 220

Ala Lys Gly Gln Pro His Glu Pro Gln Val Tyr Val Leu Pro Pro Thr
225                 230                 235                 240

Gln Glu Glu Leu Ser Glu Asn Lys Val Ser Val Thr Cys Leu Ile Lys
                245                 250                 255

Gly Phe His Pro Pro Asp Ile Ala Val Glu Trp Glu Ile Thr Gly Gln
            260                 265                 270

Pro Glu Pro Glu Asn Asn Tyr Gln Thr Thr Pro Pro Gln Leu Asp Ser
        275                 280                 285

Asp Gly Thr Tyr Phe Leu Tyr Ser Arg Leu Ser Val Asp Arg Ser His
    290                 295                 300

Trp Gln Arg Gly Asn Thr Tyr Thr Cys Ser Val Ser His Glu Ala Leu
305                 310                 315                 320

His Ser His His Thr Gln Lys Ser Leu Thr Gln Ser Pro Gly Lys
                325                 330                 335
```

<210> 10

<211> 96

<212> PRT

<213> Camelus dromedarius

<400> 10

```
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

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Arg Glu Arg Glu Gly Val
        35                  40                  45
```

```
Ala Ala Ile Asn Ser Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
```

<210> 11

<211> 96

<212> PRT

<213> Camelus dromedarius

<400> 11

```
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 Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Thr Ile Asn Ser Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Met Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
```

<210> 12

<211> 1434

<212> DNA

<213> Artificial sequence

<220>

<223> Murine anti-AGE IgG2b heavy chain

<400> 12

```
atggacccca agggcagcct gagctggaga atcctgctgt tcctgagcct ggccttcgag     60

ctgagctacg gccaggtgca gctgctgcag ccaggtgccg agctcgtgaa acctggcgcc    120

tctgtgaagc tggcctgcaa ggcttccggc tacctgttca ccacctactg gatgcactgg    180

ctgaagcaga ggccaggcca gggcctggaa tggatcggcg agatctcccc caccaacggc    240

agagcctact acaacgcccg gttcaagtcc gaggccaccc tgaccgtgga caagtcctcc    300

aacaccgcct acatgcagct gtcctccctg acctctgagg cctccgccgt gtactactgc    360

gccagagctt acggcaacta cgagttcgcc tactggggcc agggcaccct cgtgacagtg    420
```

```
tctgtggcta agaccacccc tccctccgtg taccctctgg ctcctggctg tggcgacacc    480

accggatcct ctgtgaccct gggctgcctc gtgaagggct acttccctga gtccgtgacc    540

gtgacctgga actccggctc cctgtcctcc tccgtgcaca cctttccagc cctgctgcag    600

tccggcctgt acaccatgtc ctccagcgtg acagtgccct cctccacctg gccttcccag    660

accgtgacat gctctgtggc ccaccctgcc tcttccacca ccgtggacaa gaagctggaa    720

ccctccggcc ccatctccac catcaaccct tgccctccct gcaaagaatg ccacaagtgc    780

cctgccccca acctggaagg cggcccttcc gtgttcatct tcccacccaa catcaaggac    840

gtgctgatga tctccctgac ccccaaagtg acctgcgtgg tggtggacgt gtccgaggac    900

gaccctgacg tgcagatcag ttggttcgtg aacaacgtgg aagtgcacac cgcccagacc    960

cagacacaca gagaggacta caacagcacc atcagagtgg tgtctaccct gcccatccag   1020

caccaggact ggatgtccgg caaagaattc aagtgcaaag tgaacaacaa ggacctgccc   1080

agccccatcg agcggaccat ctccaagatc aagggcctcg tgcgggctcc ccaggtgtac   1140

attctgcctc caccagccga gcagctgtcc cggaaggatg tgtctctgac atgtctggtc   1200

gtgggcttca accccggcga catctccgtg gaatggacct ccaacggcca caccgaggaa   1260

aactacaagg acaccgcccc tgtgctggac tccgacggct cctacttcat ctactccaag   1320

ctgaacatga agacctccaa gtgggaaaag accgactcct tctcctgcaa cgtgcggcac   1380

gagggcctga agaactacta cctgaagaaa accatctccc ggtcccccgg ctag         1434
```

<210> 13
<211> 1416
<212> DNA
<213> Artificial sequence

<220>
<223> Chimeric anti-AGE human IgG1 antibody heavy chain

<400> 13

```
atggacccca agggcagcct gagctggaga atcctgctgt tcctgagcct ggccttcgag     60

ctgagctacg gccaggtgca gctgctgcag ccaggtgccg agctcgtgaa acctggcgcc    120

tctgtgaagc tggcctgcaa ggcttccggc tacctgttca ccacctactg gatgcactgg    180

ctgaagcaga ggccaggcca gggcctggaa tggatcggcg agatctcccc caccaacggc    240
```

```
agagcctact acaacgcccg gttcaagtcc gaggccaccc tgaccgtgga caagtcctcc    300

aacaccgcct acatgcagct gtcctccctg acctctgagg cctccgccgt gtactactgc    360

gccagagctt acggcaacta cgagttcgcc tactggggcc agggcaccct cgtgacagtg    420

tctgtggcta gcaccaaggg ccccagcgtg ttccctctgg ccccagcag caagagcacc    480

agcggcggaa ccgccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc    540

gtgtcctgga acagcggcgc tctgaccagc ggagtgcaca ccttccctgc cgtgctgcag    600

agcagcggcc tgtactccct gagcagcgtg gtgaccgtgc ccagcagcag cctgggcacc    660

cagacctaca tctgcaacgt gaaccacaag ccctccaaca ccaaggtgga caagaaggtg    720

gagcctaaga gctgcgacaa gacccacacc tgccctccct gccccgcccc cgagctgctg    780

ggcggaccca gcgtgttcct gttccctccc aagcccaagg acaccctgat gatcagccgc    840

acccccgagg tgacctgcgt ggtggtggac gtgagccacg aggaccccga ggtgaagttc    900

aactggtacg tggacggcgt ggaggtgcac aacgccaaga ccaagcctcg ggaggagcag    960

tacaactcca cctaccgcgt ggtgagcgtg ctgaccgtgc tgcaccagga ctggctgaac   1020

ggcaaggagt acaagtgcaa ggtgagcaac aaggccctgc ccgctcccat cgagaagacc   1080

atcagcaagg ccaagggcca gccccgggag cctcaggtgt acaccctgcc ccccagccgc   1140

gacgagctga ccaagaacca ggtgagcctg acctgcctgg tgaagggctt ctacccctcc   1200

gacatcgccg tggagtggga gagcaacggc cagcctgaga acaactacaa gaccacccct   1260

cccgtgctgg acagcgacgg cagcttcttc ctgtacagca agctgaccgt ggacaagtcc   1320

cggtggcagc agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac   1380

tacacccaga agagcctgag cctgagcccc ggatag                             1416
```

<210> 14
<211> 720
<212> DNA
<213> Artificial sequence

<220>
<223> Murine anti-AGE Kappa light chain

<400> 14

```
atggagaccg acaccctgct gctctgggtg ctgctgctct gggtgcccgg ctccaccgga      60
```

gacgtcgtga tgacccagac ccctctgtcc ctgcctgtgt ctctgggcga ccaggcctcc 120

atctcctgcc ggtctagaca gtccctcgtg aactccaacg gcaacacctt cctgcagtgg 180

tatctgcaga agcccggcca gtcccccaag ctgctgatct acaaggtgtc cctgcggttc 240

tccggcgtgc ccgacagatt ttccggctct ggctctggca ccgacttcac cctgaagatc 300

tcccgggtgg aagccgagga cctgggcctg tacttctgca gccagtccac ccacgtgccc 360

cctacatttg gcggaggcac caagctggaa atcaaacggg cagatgctgc accaactgta 420

tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480

ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 540

caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600

agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660

gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgttga 720

<210> 15
<211> 720
<212> DNA
<213> Artificial sequence

<220>
<223> Chimeric anti-AGE human kappa light chain

<400> 15
atggagaccg acaccctgct gctctgggtg ctgctgctct gggtgcccgg ctccaccgga 60

gacgtcgtga tgacccagac ccctctgtcc ctgcctgtgt ctctgggcga ccaggcctcc 120

atctcctgcc ggtctagaca gtccctcgtg aactccaacg gcaacacctt cctgcagtgg 180

tatctgcaga agcccggcca gtcccccaag ctgctgatct acaaggtgtc cctgcggttc 240

tccggcgtgc ccgacagatt ttccggctct ggctctggca ccgacttcac cctgaagatc 300

tcccgggtgg aagccgagga cctgggcctg tacttctgca gccagtccac ccacgtgccc 360

cctacatttg gcggaggcac caagctggaa atcaagcgga ccgtggccgc ccccagcgtg 420

ttcatcttcc ctcccagcga cgagcagctg aagtctggca ccgccagcgt ggtgtgcctg 480

ctgaacaact tctaccccg cgaggccaag gtgcagtgga aggtggacaa cgccctgcag 540

agcggcaaca gccaggagag cgtgaccgag caggactcca aggacagcac ctacagcctg 600

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 660

gtgacccacc agggactgtc tagccccgtg accaagagct tcaaccgggg cgagtgctaa 720

<210> 16

<211> 477

<212> PRT

<213> Artificial sequence

<220>

<223> Murine anti-AGE IgG2b heavy chain

<400> 16

```
Met Asp Pro Lys Gly Ser Leu Ser Trp Arg Ile Leu Leu Phe Leu Ser
1               5                  10                  15

Leu Ala Phe Glu Leu Ser Tyr Gly Gln Val Gln Leu Leu Gln Pro Gly
            20                  25                  30

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

Ser Gly Tyr Leu Phe Thr Thr Tyr Trp Met His Trp Leu Lys Gln Arg
    50                  55                  60

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

Arg Ala Tyr Tyr Asn Ala Arg Phe Lys Ser Glu Ala Thr Leu Thr Val
                85                  90                  95

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

Glu Ala Ser Ala Val Tyr Tyr Cys Ala Arg Ala Tyr Gly Asn Tyr Glu
        115                 120                 125

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

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

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

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

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

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Gln Thr Val Thr Cys
    210                 215                 220

Ser Val Ala His Pro Ala Ser Ser Thr Thr Val Asp Lys Lys Leu Glu
225                 230                 235                 240

Pro Ser Glu Pro Ile Ser Thr Ile Asn Pro Cys Pro Pro Cys Lys Glu
```

```
Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Cys Pro Pro Cys Lys Glu
                245                 250                 255

Cys His Lys Cys Pro Ala Pro Asn Leu Glu Gly Gly Pro Ser Val Phe
            260                 265                 270

Ile Phe Pro Pro Asn Ile Lys Asp Val Leu Met Ile Ser Leu Thr Pro
        275                 280                 285

Lys Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val
    290                 295                 300

Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr
305                 310                 315                 320

Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Ile Arg Val Val Ser Thr
                325                 330                 335

Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys
            340                 345                 350

Lys Val Asn Asn Lys Asp Leu Pro Ser Pro Ile Glu Arg Thr Ile Ser
        355                 360                 365

Lys Ile Lys Gly Leu Val Arg Ala Pro Gln Val Tyr Ile Leu Pro Pro
    370                 375                 380

Pro Ala Glu Gln Leu Ser Arg Lys Asp Val Ser Leu Thr Cys Leu Val
385                 390                 395                 400

Val Gly Phe Asn Pro Gly Asp Ile Ser Val Glu Trp Thr Ser Asn Gly
                405                 410                 415

His Thr Glu Glu Asn Tyr Lys Asp Thr Ala Pro Val Leu Asp Ser Asp
            420                 425                 430

Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Met Lys Thr Ser Lys Trp
        435                 440                 445

Glu Lys Thr Asp Ser Phe Ser Cys Asn Val Arg His Glu Gly Leu Lys
    450                 455                 460

Asn Tyr Tyr Leu Lys Lys Thr Ile Ser Arg Ser Pro Gly
465                 470                 475
```

<210> 17

<211> 471

<212> PRT

<213> Artificial sequence

<220>

<223> Chimeric anti-AGE human IgG1 heavy chain

<400> 17

```
Met Asp Pro Lys Gly Ser Leu Ser Trp Arg Ile Leu Leu Phe Leu Ser
1               5                   10                  15

Leu Ala Phe Glu Leu Ser Tyr Gly Gln Val Gln Leu Leu Gln Pro Gly
            20                  25                  30
```

```
            20                  25                  30

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

Ser Gly Tyr Leu Phe Thr Thr Tyr Trp Met His Trp Leu Lys Gln Arg
    50                  55                  60

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

Arg Ala Tyr Tyr Asn Ala Arg Phe Lys Ser Glu Ala Thr Leu Thr Val
                85                  90                  95

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

Glu Ala Ser Ala Val Tyr Tyr Cys Ala Arg Ala Tyr Gly Asn Tyr Glu
        115                 120                 125

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

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

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

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

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

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220

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

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

            260                 265                 270

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305                 310                 315                 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
```

```
                325                 330                 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            340                 345                 350

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    370                 375                 380

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

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

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        435                 440                 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460

Ser Leu Ser Leu Ser Pro Gly
465                 470
```

<210> 18

<211> 239

<212> PRT

<213> Artificial sequence

<220>

<223> Murine anti-AGE kappa light chain

<400> 18

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

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

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

Leu Val Asn Ser Asn Gly Asn Thr Phe Leu Gln Trp Tyr Leu Gln Lys
    50                  55                  60

Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

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

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Leu Tyr Phe
```

```
          100                 105                 110

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

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

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

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

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

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

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

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

<210> 19

<211> 239

<212> PRT

<213> Artificial sequence

<220>

<223> Chimeric anti-AGE human kappa light chain

<400> 19

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

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

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

Leu Val Asn Ser Asn Gly Asn Thr Phe Leu Gln Trp Tyr Leu Gln Lys
    50                  55                  60

Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

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

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

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys
```

```
Cys Ser Gln Ser Thr His Val Pro Phe Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

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

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

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

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

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

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

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

<210> 20

<211> 118

<212> PRT

<213> Artificial sequence

<220>

<223> Murine anti-AGE IgG2b heavy chain (variable region)

<400> 20

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

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

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

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

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

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

Ala Arg Ala Tyr Gly Asn Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Val
        115
```

<210> 21

<211> 112

<212> PRT

<213> Artificial sequence

<220>

<223> Murine anti-AGE kappa light chain (variable region)

<400> 21

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

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

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

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

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

Ser Arg Val Glu Ala Glu Asp Leu Gly Leu Tyr Phe Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 22

<211> 326

<212> PRT

<213> Artificial sequence

<220>

<223> Human constant region

<400> 22

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

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
```

```
Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
        115                 120                 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
        195                 200                 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
    210                 215                 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225                 230                 235                 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                245                 250                 255

Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            260                 265                 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        275                 280                 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    290                 295                 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305                 310                 315                 320

Ser Leu Ser Pro Gly Lys
                325
```

<210> 23

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> CDR1H (heavy chain)

<400> 23

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

<210> 24
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> CDR2H (heavy chain)

<400> 24
Thr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
1 5 10 15

Gly

<210> 25
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> CDR3H (heavy chain)

<220>
<221> misc_feature
<222> (10)..(10)
<223> Xaa can be any naturally occurring amino acid

<400> 25
Gln Gly Gly Trp Leu Pro Pro Phe Ala Xaa
1 5 10

<210> 26
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> CDR1L (light chain)

<400> 26
Arg Ala Ser Lys Ser Val Ser Thr Ser Ser Arg Gly Tyr Ser Tyr Met
1 5 10 15

His

<210> 27
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> CDR2L (light chain)

<400> 27

```
Leu Val Ser Asn Leu Glu Ser
1               5
```

<210> 28

<211> 9

<212> PRT

<213> Artificial sequence

<220>

<223> CDR3L (light chain)

<400> 28

```
Gln His Ile Arg Glu Leu Thr Arg Ser
1               5
```

<210> 29

<211> 468

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized heavy chain

<400> 29

```
Met Asp Pro Lys Gly Ser Leu Ser Trp Arg Ile Leu Leu Phe Leu Ser
1               5                   10                  15


Leu Ala Phe Glu Leu Ser Tyr Gly Gln Val Gln Leu Val Gln Ser Gly
            20                  25                  30


Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala
        35                  40                  45


Ser Gly Tyr Leu Phe Thr Thr Tyr Trp Met His Trp Val Arg Gln Ala
    50                  55                  60


Pro Gly Gln Gly Leu Glu Trp Met Gly Glu Ile Ser Pro Thr Asn Gly
65                  70                  75                  80


Arg Ala Tyr Tyr Asn Gln Lys Phe Gln Gly Arg Val Thr Met Thr Val

                85                  90                  95


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


Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Tyr Gly Asn Tyr Phe
        115                 120                 125


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


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

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

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

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

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    210                 215                 220

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

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro 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 Lys Asn Gln
    370                 375                 380

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            420                 425                 430

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
        435                 440                 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    450                 455                 460
```

Leu Ser Pro Gly
465

<210> 30
<211> 1408
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized heavy chain

<400> 30
atggacccca agggcagcct gagctggaga atcctgctgt tcctgagcct ggccttcgag 60

ctgagctacg gccaggtgca gctggtgcag tctggcgccg aagtgaagaa acctggcgcc 120

tccgtgaggt gtcctgcaag gcttccggct acctgttcac cacctactgg atgcactggg 180

tgcgacaggc ccctggacag ggcctggaat ggatgggcga gatctcccct accaacggca 240

gagcctacta caacagaaat tccagggcag agtgaccatg accgtggaca agtccaccaa 300

caccgtgtac atggaactgt cctccctgcg gagcgaggac accgccgtgt actactgcgc 360

tagagcctac ggcaactacg attcgcctac tggggccagg gcaccctcgt gacagtgtcc 420

tctgctagca ccaagggccc cagcgtgttc cctctggccc ccagcagcaa gagcaccagc 480

ggcggaaccg ccgccctggg ctgcctggga aggactactt ccccgagccc gtgaccgtgt 540

cctggaacag cggcgctctg accagcggag tgcacacctt ccctgccgtg ctgcagagca 600

gcggcctgta ctccctgagc agcgtggtga ccgtgccagc agcagcctgg gcacccagac 660

ctacatctgc aacgtgaacc acaagccctc caacaccaag gtggacaaga aggtggagcc 720

taagagctgc gacaagaccc acacctgccc tccctgcccc gccccgagct gctgggcgga 780

cccagcgtgt tcctgttccc tcccaagccc aaggacaccc tgatgatcag ccgcaccccc 840

gaggtgacct gcgtggtggt ggacgtgagc cacgaggacc ccgaggtgag ttcaactggt 900

acgtggacgg cgtggaggtg cacaacgcca agaccaagcc tcgggaggag cagtacaact 960

ccacctaccg cgtggtgagc gtgctgaccg tgctgcacca ggactggctg aacggcagga 1020

gtacaagtgc aaggtgagca acaaggccct gcccgctccc atcgagaaga ccatcagcaa 1080

ggccaagggc cagccccggg agcctcaggt gtacaccctg ccccccagcc gcgacgagct 1140

gacaagaacc aggtgagcct gacctgcctg gtgaagggct tctacccctc cgacatcgcc 1200

gtggagtggg agagcaacgg ccagcctgag aacaactaca agaccacccc tcccgtgctg 1260

gacagcgacg cagcttcttc ctgtacagca agctgaccgt ggacaagtcc cggtggcagc 1320

agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac tacacccaga 1380

agagcctgag cctgagcccg gatagtaa 1408

<210> 31
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized heavy chain

<400> 31

```
Met Asp Pro Lys Gly Ser Leu Ser Trp Arg Ile Leu Leu Phe Leu Ser
1               5                  10                  15

Leu Ala Phe Glu Leu Ser Tyr Gly Gln Val Gln Leu Val Gln Ser Gly
            20                  25                  30

Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala
        35                  40                  45

Ser Gly Tyr Leu Phe Thr Thr Tyr Trp Met His Trp Val Arg Gln Ala
    50                  55                  60

Pro Gly Gln Gly Leu Glu Trp Met Gly Glu Ile Ser Pro Thr Asn Gly
65                  70                  75                  80

Arg Ala Tyr Tyr Asn Ala Lys Phe Gln Gly Arg Val Thr Met Thr Val

                85                  90                  95

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

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Tyr Gly Asn Tyr Phe
        115                 120                 125

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

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

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

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

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

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    210                 215                 220

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

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro 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
```

```
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 Lys Asn Gln
    370                 375                 380

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            420                 425                 430

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
        435                 440                 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    450                 455                 460

Leu Ser Pro Gly
465
```

<210> 32

<211> 1408

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized heavy chain

<400> 32

```
atggacccca agggcagcct gagctggaga atcctgctgt tcctgagcct ggccttcgag       60

ctgagctacg gccaggtgca gctggtgcag tctggcgccg aagtgaagaa acctggcgcc      120

tccgtgaggt gtcctgcaag gcttccggct acctgttcac cacctactgg atgcactggg      180

tgcgacaggc ccctggacag ggcctggaat ggatgggcga gatctccccc accaacggca      240

gagcctacta caaccaaaat tccagggcag agtgaccatg accgtggaca agtccaccaa      300

caccgcttac atggaactgt cctccctgcg gagcgaggac accgccgtgt actactgcgc      360

tagagcctac ggcaactacg attcgcctac tggggccagg gcaccctcgt gacagtgtcc      420

tctgctagca ccaagggccc cagcgtgttc cctctggccc ccagcagcaa gagcaccagc      480

ggcggaaccg ccgccctggg ctgcctggga aggactactt ccccgagccc gtgaccgtgt      540
```

-- -- - - --- - --- -- - - - - - -

cctggaacag cggcgctctg accagcggag tgcacacctt ccctgccgtg ctgcagagca 600

gcggcctgta ctccctgagc agcgtggtga ccgtgccagc agcagcctgg gcacccagac 660

ctacatctgc aacgtgaacc acaagccctc caacaccaag gtggacaaga aggtggagcc 720

taagagctgc gacaagaccc acacctgccc tccctgcccc gccccgagct gctgggcgga 780

cccagcgtgt tcctgttccc tcccaagccc aaggacaccc tgatgatcag ccgcaccccc 840

gaggtgacct gcgtggtggt ggacgtgagc cacgaggacc ccgaggtgag ttcaactggt 900

acgtggacgg cgtggaggtg cacaacgcca agaccaagcc tcgggaggag cagtacaact 960

ccacctaccg cgtggtgagc gtgctgaccg tgctgcacca ggactggctg aacggcagga 1020

gtacaagtgc aaggtgagca acaaggccct gcccgctccc atcgagaaga ccatcagcaa 1080

ggccaagggc cagccccggg agcctcaggt gtacaccctg ccccccagcc gcgacgagct 1140

gacaagaacc aggtgagcct gacctgcctg gtgaagggct tctacccctc cgacatcgcc 1200

gtggagtggg agagcaacgg ccagcctgag aacaactaca agaccacccc tcccgtgctg 1260

gacagcgacg cagcttcttc ctgtacagca agctgaccgt ggacaagtcc cggtggcagc 1320

agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac tacacccaga 1380

agagcctgag cctgagcccg gatagtaa 1408

<210> 33

<211> 468

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized heavy chain

<400> 33

Met Asp Pro Lys Gly Ser Leu Ser Trp Arg Ile Leu Leu Phe Leu Ser
1 5 10 15

Leu Ala Phe Glu Leu Ser Tyr Gly Gln Val Gln Leu Val Gln Ser Gly
20 25 30

Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala
35 40 45

Ser Gly Tyr Leu Phe Thr Thr Tyr Trp Met His Trp Val Arg Gln Ala
50 55 60

Pro Gly Gln Gly Leu Glu Trp Met Gly Glu Ile Ser Pro Thr Asn Gly
65 70 75 80

Arg Ala Tyr Tyr Asn Ala Lys Phe Gln Gly Arg Val Thr Met Thr Val

85 90 95

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

Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Tyr Gly Asn Tyr Phe

```
        115                 120                 125

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

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

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

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

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

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    210                 215                 220

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

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro 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 Lys Asn Gln
    370                 375                 380

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            420                 425                 430
```

```
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
        435                 440                 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    450                 455                 460

Leu Ser Pro Gly
465
```

<210> 34

<211> 1408

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized heavy chain

<400> 34

```
atggacccca agggcagcct gagctggaga atcctgctgt tcctgagcct ggccttcgag       60

ctgagctacg gccaggtgca gctggtgcag tctggcgccg aagtgaagaa acctggcgcc      120

tccgtgaggt gtcctgcaag gcttccggct acctgttcac cacctactgg atgcactggg      180

tgcgacaggc ccctggacag ggcctggaat ggatgggcga gatctcccct accaacggca      240

gagcctacta caaccaaaat tccagggcag agtgaccatg accgtggaca agtccatcaa      300

caccgcttac atggaactgt ccagactgcg gagcgatgac accgccgtgt actactgcgc      360

tagagcctac ggcaactacg attcgcctac tggggccagg gcaccctcgt gacagtgtcc      420

tctgctagca ccaagggccc cagcgtgttc cctctggccc ccagcagcaa gagcaccagc      480

ggcggaaccg ccgccctggg ctgcctggga aggactactt ccccgagccc gtgaccgtgt      540

cctggaacag cggcgctctg accagcggag tgcacacctt ccctgccgtg ctgcagagca      600

gcggcctgta ctccctgagc agcgtggtga ccgtgccagc agcagcctgg gcacccagac      660

ctacatctgc aacgtgaacc acaagccctc caacaccaag gtggacaaga aggtggagcc      720

taagagctgc gacaagaccc acacctgccc tccctgcccc gccccgagct gctgggcgga      780

cccagcgtgt tcctgttccc tcccaagccc aaggacaccc tgatgatcag ccgcaccccc      840

gaggtgacct gcgtggtggt ggacgtgagc cacgaggacc ccgaggtgag ttcaactggt      900

acgtggacgg cgtggaggtg cacaacgcca agaccaagcc tcgggaggag cagtacaact      960

ccacctaccg cgtggtgagc gtgctgaccg tgctgcacca ggactggctg aacggcagga     1020

gtacaagtgc aaggtgagca acaaggccct gcccgctccc atcgagaaga ccatcagcaa     1080

ggccaagggc cagccccggg agcctcaggt gtacaccctg ccccccagcc gcgacgagct     1140

gacaagaacc aggtgagcct gacctgcctg gtgaagggct tctacccctc cgacatcgcc     1200

gtggagtggg agagcaacgg ccagcctgag aacaactaca agaccacccc tcccgtgctg     1260

gacagcgacg cagcttcttc ctgtacagca agctgaccgt ggacaagtcc cggtggcagc     1320

agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac tacacccaga     1380

agagcctgag cctgagcccg gatagtaa                                        1408
```

<210> 35

<211> 238

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized light chain

<400> 35

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

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

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

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

Pro Gly Gln Ser Pro Arg Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe

                85                  90                  95

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

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Val
        115                 120                 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
                165                 170                 175

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

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

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
    210                 215                 220

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

<210> 36

<211> 715

<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized light chain

<400> 36
atggagaccg acaccctgct gctctgggtg ctgctgctct gggtgcccgg ctccaccgga 60

gacgtcgtga tgacccagtc ccctctgtcc ctgcctgtga ccctgggaca gcctgcctcc 120

atctcctcag atcctcccag tccctcgtga actccaacgg caacaccttc ctgcagtggt 180

atcagcagcg gcctggccag agccccagac tgctgatcta caaggtgtcc ctgcggttct 240

ccggcgtgcc cgacgatttt ccggctctgg ctctggcacc gacttcaccc tgaagatctc 300

ccgggtggaa gccgaggacg tgggcgtgta ctactgctcc cagagcaccc acgtgccccc 360

tacatttggc ggaggcacca agtggaaatc aagcggaccg tggccgcccc cagcgtgttc 420

atcttccctc ccagcgacga gcagctgaag tctggcaccg ccagcgtggt gtgcctgctg 480

aacaacttct accccccgcga ggccaagggc agtggaaggt ggacaacgcc ctgcagagcg 540

gcaacagcca ggagagcgtg accgagcagg actccaagga cagcacctac agcctgagca 600

gcaccctgac cctgagcaag gccgactacg agaagacaag gtgtacgcct gcgaggtgac 660

ccaccaggga ctgtctagcc ccgtgaccaa gagcttcaac cggggcgagt gctaa 715

<210> 37
<211> 238
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized light chain

<400> 37
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

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

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

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

Pro Gly Gln Ser Pro Arg Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65 70 75 80

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

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

```
Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Val
        115                 120                 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
                165                 170                 175

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

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

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
    210                 215                 220

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

<210> 38

<211> 715

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized light chain

<400> 38

```
atggagaccg acaccctgct gctctgggtg ctgctgctct gggtgcccgg ctccaccgga       60

gacgtcgtga tgacccagtc ccctctgtcc ctgcctgtga ccctgggaca gcctgcctcc      120

atctcctcag atccaggcag tccctcgtga actccaacgg caacaccttc ctgcagtggt      180

atcagcagcg gcctggccag agccccagac tgctgatcta caaggtgtcc ctgcggttct      240

ccggcgtgcc cgacgatttt ccggctctgg ctctggcacc gacttcaccc tgaagatctc      300

ccgggtggaa gccgaggacg tgggcgtgta ctactgctcc cagagcaccc acgtgccccc      360

tacatttggc ggaggcacca agtggaaatc aagcggaccg tggccgcccc cagcgtgttc      420

atcttccctc ccagcgacga gcagctgaag tctggcaccg ccagcgtggt gtgcctgctg      480

aacaacttct accccccgcga ggccaagggc agtggaaggt ggacaacgcc ctgcagagcg      540

gcaacagcca ggagagcgtg accgagcagg actccaagga cagcacctac agcctgagca      600

gcaccctgac cctgagcaag gccgactacg agaagacaag gtgtacgcct gcgaggtgac      660

ccaccaggga ctgtctagcc ccgtgaccaa gagcttcaac cggggcgagt gctaa            715
```

<210> 39

<211> 238

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized light chain

<400> 39

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

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

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

Leu Val Asn Ser Asn Gly Asn Thr Phe Leu Gln Trp Tyr His Gln Arg
    50                  55                  60

Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly Lys Asp Phe
                85                  90                  95

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

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Leu
        115                 120                 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
                165                 170                 175

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

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

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
    210                 215                 220

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

<210> 40

<211> 715

<212> DNA

<213> Artificial Sequence

<220>

<223> Humanized light chain

<400> 40

atggagaccg acaccctgct gctctgggtg ctgctgctct gggtgcccgg ctccaccgga 60

gacgtcgtga tgacccagtc ccctctgtcc agtcctgtga ccctgggaca gcctgcctcc 120

atctcctcag atcctcccag tccctcgtga actccaacgg caacaccttc ctgcagtggt 180

atcaccagcg gcctggccag cctcccagac tgctgatcta caaggtgtcc ctgcggttct 240

ccggcgtgcc cgacgatttt ccggctctgg cgctggcaag gacttcaccc tgaagatctc 300

ccgggtggaa gccgaggacg tgggcgtgta ctactgctcc cagagcaccc acgtgccccc 360

tacatttggc cagggcacca actggaaatc aagcggaccg tggccgcccc cagcgtgttc 420

atcttccctc ccagcgacga gcagctgaag tctggcaccg ccagcgtggt gtgcctgctg 480

aacaacttct acccccgcga ggccaagggc agtggaaggt ggacaacgcc ctgcagagcg 540

gcaacagcca ggagagcgtg accgagcagg actccaagga cagcacctac agcctgagca 600

gcaccctgac cctgagcaag gccgactacg agaagacaag gtgtacgcct gcgaggtgac 660

ccaccaggga ctgtctagcc ccgtgaccaa gagcttcaac cggggcgagt gctaa 715

<210> 41

<211> 5

<212> PRT

<213> Mus musculus

<400> 41

Thr Tyr Trp Met His
1 5

<210> 42

<211> 17

<212> PRT

<213> Mus musculus

<400> 42

Glu Ile Ser Pro Thr Asn Gly Arg Ala Tyr Tyr Asn Ala Arg Phe Lys
1 5 10 15

Ser

<210> 43

<211> 9

<212> PRT

<213> Mus musculus

<400> 43

Ala Tyr Gly Asn Tyr Glu Phe Ala Tyr
1 5

<210> 44

<211> 16

<212> PRT

<213> Mus musculus

<400> 44
Arg Ser Arg Gln Ser Leu Val Asn Ser Asn Gly Asn Thr Phe Leu Gln
1 5 10 15

<210> 45
<211> 7
<212> PRT
<213> Mus musculus

<400> 45
Lys Val Ser Leu Arg Phe Ser
1 5

<210> 46
<211> 9
<212> PRT
<213> Mus musculus

<400> 46
Ser Gln Ser Thr His Val Pro Pro Thr
1 5

<210> 47
<211> 467
<212> PRT
<213> Mus musculus

<400> 47
Met Gly Trp Thr Leu Val Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
1 5 10 15

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

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

Thr Thr Tyr Trp Met His Trp Leu Lys Gln Arg Pro Gly Gln Gly Leu
50 55 60

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

Ala Arg Phe Lys Ser Glu Ala Thr Leu Thr Val Asp Lys Ser Ser Asn
85 90 95

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

Tyr Tyr Cys Ala Arg Ser Phe Gly Asn Tyr Glu Phe Ala Tyr Trp Gly
115 120 125

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly 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 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    210                 215                 220

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

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln 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> 48

<211> 467

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized heavy chain

<400> 48

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

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

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

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

Glu Trp Met Gly Glu Ile Ser Pro Thr Asn Gly Arg Ala Tyr Tyr Asn
65 70 75 80

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

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

Tyr Tyr Cys Ala Arg Ser Phe Gly Asn Tyr Glu Phe 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 Ser Ser Lys Ser Thr Ser Gly Gly 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 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

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

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln 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> 49

<211> 467

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized heavy chain

<400> 49

```
Met Gly Trp Thr Leu Val Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
```

```
1               5                  10                  15

Val 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 Leu Phe
        35                  40                  45

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

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

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

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

Tyr Tyr Cys Ala Arg Ser Phe Gly Asn Tyr Glu Phe 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 Ser Ser Lys Ser Thr Ser Gly Gly 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 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    210                 215                 220

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

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His
        275                 280                 285

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

    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln 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> 50

<211> 467

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized heavy chain

<400> 50

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

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

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

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

Glu Trp Met Gly Glu Ile Ser Pro Thr Asn Gly Arg Ala Tyr Tyr Asn
65                  70                  75                  80

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

```
                85                  90                  95

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

Tyr Tyr Cys Ala Arg Ser Phe Gly Asn Tyr Glu Phe 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 Ser Ser Lys Ser Thr Ser Gly Gly 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 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    210                 215                 220

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

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His

        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln 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> 51

<211> 467

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized heavy chain

<400> 51

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

Val 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 Glu Ala Ser Gly Tyr Leu Phe
        35                  40                  45

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

Glu Trp Met Gly Glu Ile Ser Pro Thr Asn Gly Arg Ala Tyr Tyr Asn
65                  70                  75                  80

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

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

Tyr Tyr Cys Ala Arg Ser Phe Gly Asn Tyr Glu Phe 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 Ser Ser Lys Ser Thr Ser Gly Gly 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 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    210                 215                 220

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

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln 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> 52

<211> 118

<212> PRT

<213> Mus musculus

<400> 52

```
Gln Val Gln Leu Leu Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala

1               5                   10                  15

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

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

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

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

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

Ala Arg Ser Phe Gly Asn Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Val
        115
```

<210> 53

<211> 118

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized heavy chain variable region

<400> 53

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

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

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

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

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

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

Ala Arg Ser Phe Gly Asn Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115
```

<210> 54

<211> 118

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized heavy chain variable region

<400> 54

```
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 Leu Phe Thr Thr Tyr
            20                  25                  30

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

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

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

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

Ala Arg Ser Phe Gly Asn Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115
```

<210> 55

<211> 118

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized heavy chain variable region

<400> 55

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1               5                   10                  15
```

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

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

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

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

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

Ala Arg Ser Phe Gly Asn Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115
```

<210> 56

<211> 118

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized heavy chain variable region

<400> 56

```
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 Glu Ala Ser Gly Tyr Leu Phe Thr Thr Tyr
            20                  25                  30

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

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

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

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

Ala Arg Ser Phe Gly Asn Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115
```

<210> 57

<211> 239

<212> PRT

<213> Mus musculus

<400> 57

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

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

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

Leu Val Asn Ser Asn Gly Asn Thr Phe Leu Gln Trp Tyr Leu Gln Lys
    50                  55                  60

Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

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

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

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

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

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

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

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

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

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

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

<210> 58

<211> 239

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized light chain

<400> 58

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

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

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

Leu Val Asn Ser Asn Gly Asn Thr Phe Leu Gln Trp Leu Gln Gln Arg
    50                  55                  60

Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

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

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

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

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

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

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

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

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

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

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

<210> 59

<211> 239

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized light chain

<400> 59

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

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

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

Leu Val Asn Ser Asn Gly Asn Thr Phe Leu Gln Trp Tyr Leu Gln Lys
    50                  55                  60

Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

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

Thr Leu Lys Ile Ser Arg Val Glu Pro Glu Asp Val Gly Val Tyr Tyr
            100                 105                 110

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

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

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

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

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

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

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

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

<210> 60

<211> 239

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized light chain

<400> 60

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

Gly Thr Arg Cys Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro
            20                  25                  30
```

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

Leu Val Asn Ser Asn Gly Asn Thr Phe Leu Gln Trp Phe Gln Gln Arg
    50                  55                  60

Pro Gly Gln Ser Pro Arg Arg Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

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

Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Leu Tyr Tyr

            100                 105                 110

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

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

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

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

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

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

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

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

<210> 61

<211> 239

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized light chain

<400> 61

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

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

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

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

Pro Gly Gln Pro Pro Gln Leu Leu Ile Tyr Lys Val Ser Leu Arg Phe
65                  70                  75                  80

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

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

Cys Ser Gln Ser Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

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

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

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

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

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

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

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

<210> 62

<211> 112

<212> PRT

<213> Mus musculus

<400> 62

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

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

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

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

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
```

```
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Leu Tyr Phe Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 63

<211> 112

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized light chain variable region

<400> 63

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

Gln Pro Ala Ser Ile Ser Cys Arg Ser Arg Gln Ser Leu Val Asn Ser
            20                  25                  30

Asn Gly Asn Thr Phe Leu Gln Trp Leu Gln Gln Arg Pro Gly Gln Pro
        35                  40                  45

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

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

Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Phe Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 64

<211> 112

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized light chain variable region

<400> 64

```
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly

1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Arg Gln Ser Leu Val Asn Ser
            20                  25                  30

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

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

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

Ser Arg Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Val Lys
            100                 105                 110
```

<210> 65

<211> 112

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized light chain variable region

<400> 65

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

Gln Pro Ala Ser Ile Ser Cys Arg Ser Arg Gln Ser Leu Val Asn Ser
            20                  25                  30

Asn Gly Asn Thr Phe Leu Gln Trp Phe Gln Gln Arg Pro Gly Gln Ser
        35                  40                  45

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

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

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

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 66

<211> 112

<212> PRT

<213> Artificial sequence

<220>

<223> Humanized light chain variable region

<400> 66

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

Gln Pro Ala Ser Ile Ser Cys Arg Ser Arg Gln Ser Leu Val Asn Ser
```

```
            20                  25                  30

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

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

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

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

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO2009143411A [0007] [0179]
- US5702704A [0031] [0042] [0179]
- US6380165B [0031] [0042] [0179]
- US7541150B [0178]
- US6387373B [0179]
- US4217344A [0179]
- US4917951A [0179]
- US4911928A [0179]
- US2010226932A [0179]

Non-patent literature cited in the description

- **ROMAGOSA, C. et al.**p16Ink4a overexpression in cancer: a tumor suppressor gene associated with senescence and high-grade tumorsOncogene, 2011, vol. 30, 2087-

2097 [0003]

- **DI, G-H. et al.**IL-6 Secreted from Senescent Mesenchymal Stem Cells Promotes Proliferation and migration of Breast Cancer CellsPLOS One, 2014, vol. 9, 11e113572- [0004]
- **LIU, D. et al.**Senescent Human Fibroblasts Increase the Early Growth of Xenograft Tumors via Matrix Metalloproteinase SecretionCancer Res, 2007, vol. 67, 3117-3126 [0004]
- **NELSON, G.**A senescent cell bystander effect: senescence-induced senescenceging Cell, 2012, vol. 11, 345-349 [0005]
- **RAYESS, H. et al.**Cellular senescence and tumor suppressor gene p16Int J Cancer, 2012, vol. 130, 1715-1725 [0005]
- **ANDO, K. et al.**Membrane Proteins of Human Erythrocytes Are Modified by Advanced Glycation End Products during Aging in the CirculationBiochem Biophys Res Commun., 1999, vol. 258, 123125- [0006] [0007]
- **LINDSEY JB et al.**Receptor For Advanced Glycation End-Products (RAGE) and soluble RAGE (sRAGE): Cardiovascular ImplicationsDiabetes Vascular Disease Research, 2009, vol. 6, 17-14 [0006] [0179]
- **BIERHAUS A**AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE conceptCardiovasc Res, 1998, vol. 37, 3586-600 [0006] [0179]
- **AHMED, E.K. et al.**Protein Modification and Replicative Senescence of WI-38 Human Embryonic FibroblastsAging Cells, 2010, vol. 9, 252260- [0007]
- **VLASSARA, H. et al.**Advanced Glycosylation Endproducts on Erythrocyte Cell Surface Induce Receptor-Mediated Phagocytosis by MacrophagesJ. Exp. Med., 1987, vol. 166, 539545- [0007] [0179]
- **VLASSARA et al.**High-affinity-receptor-mediated Uptake and Degradation of Glucose-modified Proteins: A Potential Mechanism for the Removal of Senescent MacromoleculesProc. Natl. Acad. Sci. USAI, 1985, vol. 82, 55885591- [0007]
- **FU, M.-X. et al.**The Advanced Glycation End Product, NE-(Carboxymethyl)lysine, Is a Product of both Lipid Peroxidation and Glycoxidation ReactionsJ. Biol. Chem, 1996, vol. 271, 9982-9986 [0007]
- **VAN HEIJST J. W. J. et al.**Advanced glycation end products in human cancer tissues: detection of NE-(carboxymethyl)lysine and argpyrimidineAnn. N. Y. Acad. Sci., 2005, vol. 1043, 725-733 [0008]
- **MATUS et al.**Invasive Cell Fate Requires G1 Cell-Cycle arrest and Histone Deacetylase-Mediated Changes in Gene ExpressionDevelopmental Cell, 2015, vol. 35, 162-174 [0039]
- **PORPORATO, P. E. et al.**A Mitochondrial Switch Promotes Tumor MetastasisCell Reports, 2014, vol. 8, 754-766 [0039]
- **AROIAN R. et al.**Pore-Forming Toxins and Cellular Non-Immune Defenses (CNIDs)Current Opinion in Microbiology, 2007, vol. 10, 57-61 [0047]
- **GAO, S. H. et al.**Monoclonal antibody humanness score and its applicationsBMC Biotechnology, 2013, vol. 13, 55- [0158]
- **ANDO K et al.**Membrane Proteins of Human Erythrocytes Are Modified by Advanced Glycation End Products During Aging in the CirculationBiochemical and Biophysical Research Communications, 1999, vol. 258, 123-27 [0179]
- **MEUTER A. et al.**Markers of cellular senescence are elevated in murine blastocysts cultured in vitro: molecular consequences of culture in atmospheric oxygenJ Assist Reprod

Genet., 2014, [0179]

- **BAKER, D.J. et al.**Clearance of p16Ink4a-positive senescent cells delays ageing-associated disordersNature, 2011, vol. 479, 232-236 [0179]
- **JANA HADRABOVÁ et al.**Chicken immunoglobulins for prophylaxis: Effect of inhaled antibodies on inflammatory parameters in rat airwaysJournal of Applied Biomedicine, 2014, [0179]
- **VLASSARA, H. et al.**High-affinity-receptor-mediated Uptake and Degradation of Glucose-modified Proteins: A Potential Mechanism for the Removal of Senescent MacromoleculesProc. Natl. Acad. Sci. USA, 1985, vol. 82, 55885591- [0179]
- **ROLL, P. et al.**Anti-CD20 Therapy in Patients with Rheumatoid ArthritisArthritis & Rheumatism, 2008, vol. 58, 61566-1575 [0179]
- **KAJSTURA, J. et al.**Myocite Turnover in the Aging Human HeartCirc. Res., 2010, vol. 107, 111374-86 [0179]
- **DE GROOT, K. et al.**Vascular Endothelial Damage and Repair in Antineutrophil Cytoplasmic Antibody-Associated VasculitisArthritis and Rheumatism, 2007, vol. 56, 113847-3847- [0179]
- **MANESSO, E. et al.**Dynamics of β-Cell Turnover: Evidence for β-Cell Turnover and Regeneration from Sources of β-Cells other than β-cell Replication in the HIP RatAm. J. Physiol. Endocrinol. Metab., 2009, vol. 297, E323-E324- [0179]
- **KIRSTEIN, M. et al.**Receptor-specific Induction of Insulin-like Growth Factor I in Human Monocytes by Advanced Glycosylation End Product-modified ProteinsJ. Clin. Invest., 1992, vol. 90, 439439-440 [0179]
- **MURPHY, J. F.**Trends in cancer immunotherapyClinical Medical Insights: Oncology, 2010, vol. 14, 467-80 [0179]
- **VIRELLA, G. et al.**Autoimmune Response to Advanced Glycosylation End-Products of Human LDLJournal of Lipid Research, 2003, vol. 44, 487-493 [0179]
- **AMELI, S. et al.**Effect of Immunization With Homologous LDL and Oxidized LDL on Early Atherosclerosis in Hypercholesterolemic RabbitsArteriosclerosis, Thrombosis, and Vascular Biology, 1996, vol. 16, 1074 [0179]
- Sarcopenia, 2014, [0179]
- What is sarcopenia?, 2014, [0179]
- **BLAHD, W.**Sarcopenia with aging, 2014, [0179]
- Keyhole limpet hemocyanin, 2014, [0179]
- CML-BSA Product Data Sheet, 2010, [0179]
- CML (N-epsilon-(Carboxymethyl)Lysine) Assays and Reagents, 2014, [0179]
- **CRUZ-JENTOFT, A. J. et al.**Sarcopenia: European consensus on definition and diagnosisAge and Ageing, 2010, vol. 39, 412-423 [0179]
- **ROLLAND, Y. et al.**Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectivesJ. Nutr. Health Aging, 2008, vol. 12, 7433-450 [0179]
- **MERA, K. et al.**An autoantibody against Nε-(carboxyethyl)lysine (CEL): Possible involvement in the removal of CEL-modified proteins by macrophagesBiochemical and Biophysical Research Communications, 2011, vol. 407, 420-425 [0179]
- **REDDY, S. et al.**Nε-(carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteinsBiochemistry, 1995, vol. 34, 10872-10878 [0179]
- **NAYLOR, R. M. et al.**Senescent cells: a novel therapeutic target for aging and age-related diseasesClinical Pharmacology & Therapeutics, 2012, vol. 93, 1105-116 [0179]
- **KATCHER, H. L.**Studies that shed new light on agingBiochemistry (Moscow), 2013, vol. 78,

91061-1070 [0179]

- **AHMED, E. K. et al.**Protein Modification and Replicative Senescence of WI-38 Human Embryonic FibroblastsAging Cells, 2010, vol. 9, 252260- [0179]
- **FIELDING, R. A. et al.**Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequencesJournal of the American Medical Directors Association, 2011, vol. 12, 4249-256 [0179]
- **MAASS, D. R. et al.**Alpaca (Lama pacos) as a convenient source of recombinant camelid heavy chain antibodies (VHHs)Journal of Immunological Methods, 2007, vol. 324, 1-213-25 [0179]
- **STRIETZEL, C.J. et al.**In vitro functional characterization of feline IgGsVeterinary Immunology and Immunopathology, 2014, vol. 158, 214-223 [0179]
- **PATEL, M. et al.**Sequence of the dog immunoglobulin alpha and epsilon constant region genesImmunogenetics, 1995, vol. 41, 282-286 [0179]
- **WAGNER, B. et al.**The complete map of the Ig heavy chain constant gene region reveals evidence for seven IgG isotypes and for IgD in the horseThe Journal of Immunology, 2004, vol. 173, 3230-3242 [0179]
- **HAMERS-CASTERMAN, C. et al.**Naturally occurring antibodies devoid of light chainsNature, 1993, vol. 363, 446-448 [0179]
- **DE GENST, E. et al.**Antibody repertoire development in camelidsDevelopmental & Comparative Immunology, 2005, vol. 30, 187-198 [0179]
- **GRIFFIN, L.M. et al.**Analysis of heavy and light chain sequences of conventional camelid antibodies from Camelus dromedarius and Camelus bactrianus speciesJournal of Immunological Methods, 2014, vol. 405, 35-46 [0179]
- **NGUYEN, V.K. et al.**Camel heavy-chain antibodies: diverse germline VHH and specific mechanisms enlarge the antigen-binding repertoireThe European Molecular Biology Organization, 2000, vol. 19, 5921-930 [0179]
- **MUYLDERMANS, S. et al.**Sequence and structure of VH domain from naturally occurring camel heavy chain immunoglobulins lacking light chainsProtein Engineering, 1994, vol. 7, 91129-1135 [0179]

Patentkrav

1. Sammensætning omfattende et anti-AGE-antistof til brug til behandling af metastatisk cancer og/eller forebyggelse af cancermetastase hos et individ, hvori anti-AGE-antistoffet binder et carboxymethyllysinmodificeret protein.

2. Sammensætningen til brug ifølge krav 1, hvori sammensætningen yderligere omfatter en farmaceutisk acceptabel.

3. Sammensætningen ifølge krav 1 eller krav 2, hvori individet er valgt fra gruppen bestående af mennesker, mus, rotter, geder, får, køer, heste, hunde og katte.

4. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori individet er et menneske.

5. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori anti-AGE-antistoffet er non-immunogent hos en art valgt fra gruppen bestående af mennesker, katte, hunde, heste, kameler, alpaca, kvæg, får og geder.

6. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori individet har metastatisk cancer.

7. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori individet ikke har metastatisk cancer.

8. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori sammensætningen er i en enhedsdosisform.

9. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori:
(a) individet er et menneske;
(b) anti-AGE-antistoffet er non-immunogent hos en art valgt fra gruppen bestående af mennesker, katte, hunde, heste, kameler, alpaca, kvæg, får og geder;
(c) individet har metastatisk cancer; og
(d) sammensætningen er i enhedsdosisform.

10. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori sammensætningen er i multidosisform.

11. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori sammensætningen er steril.

12. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori anti-AGE-antistoffet binder en metastatisk cancercelle, der udtrykker en AGE-modifikation.

13. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori anti-AGE-antistoffet binder en cirkulerende celle, der udtrykker en AGE-modifikation.

14. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori individet er gravidt/drægtigt.

15. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori individet tidligere er blevet diagnosticeret med cancer-kakeksi.

16. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori individet har et kompromitteret immunsystem.

17. Sammensætningen til brug ifølge et hvilket som helst af de foregående krav, hvori den metastatiske cancer er metastatisk brystcancer.

DRAWINGS

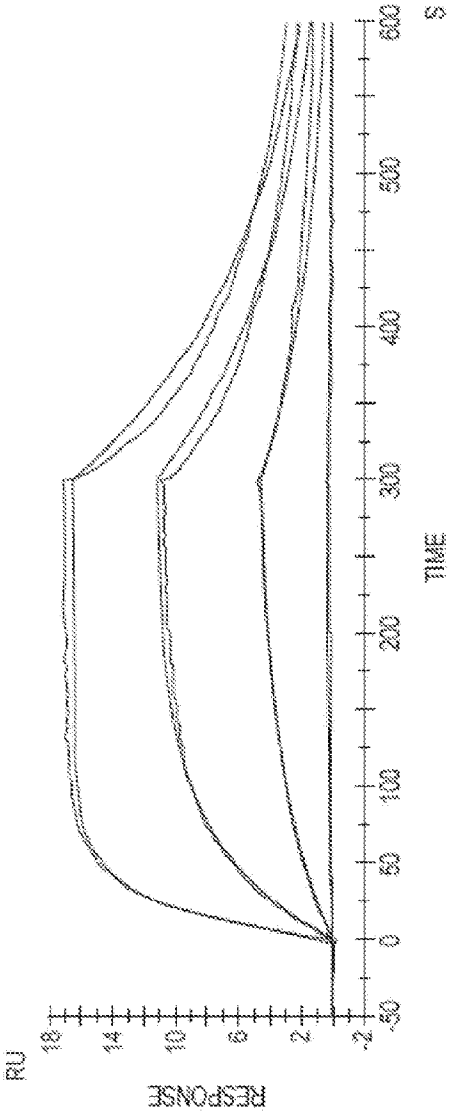

FIG. 1

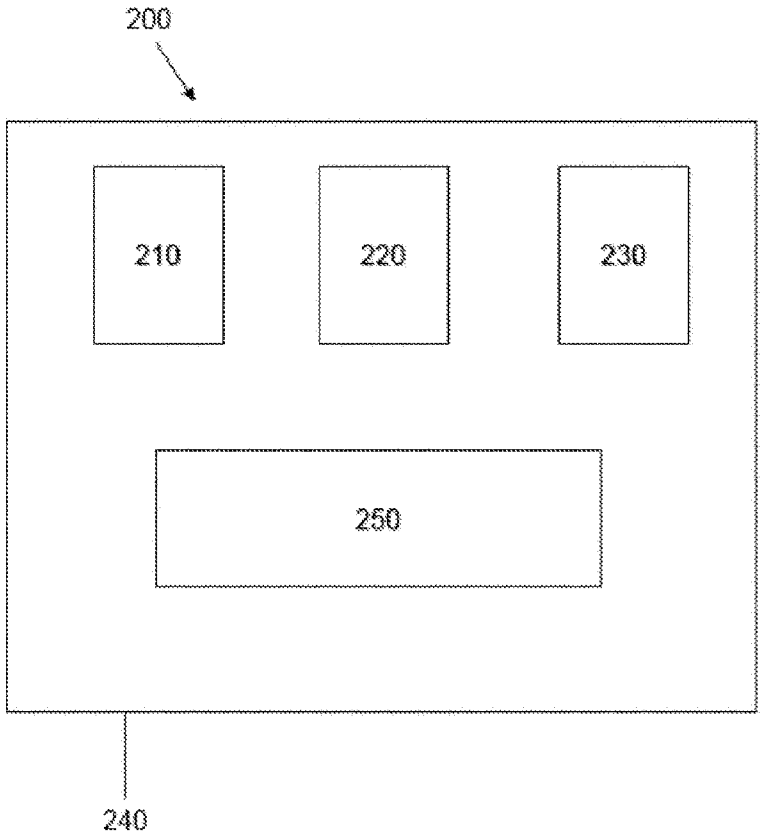

FIG. 2

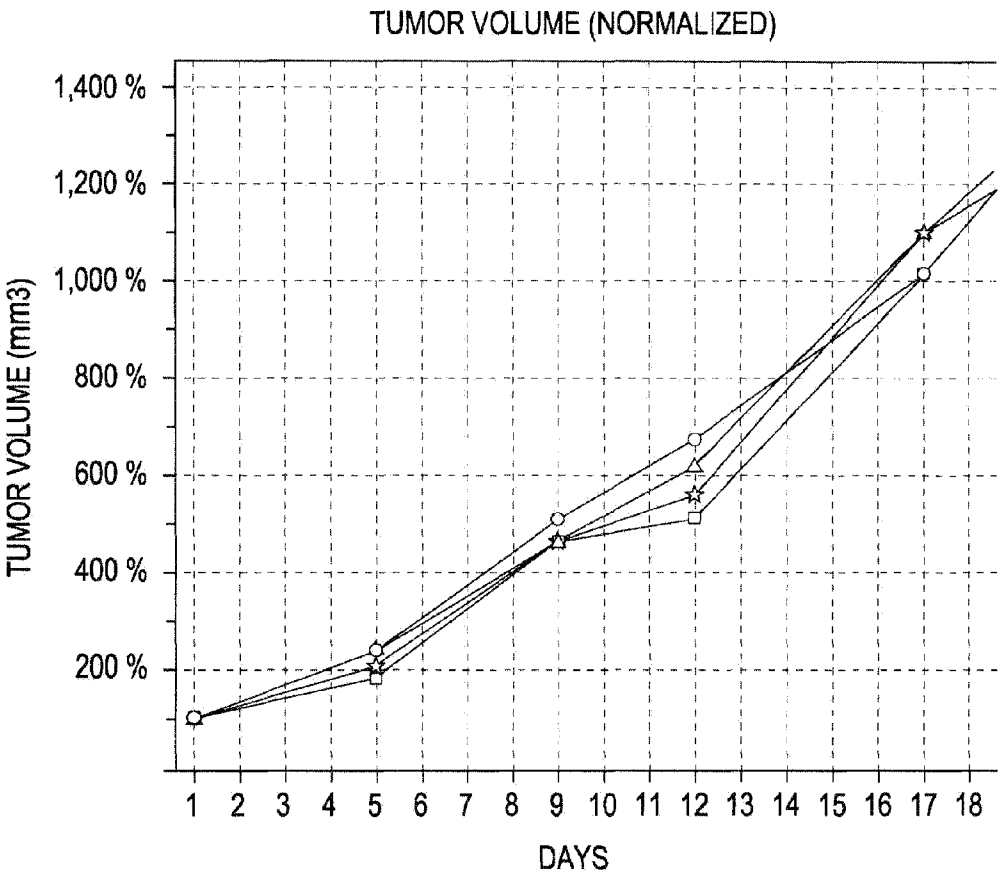
TUMOR VOLUME (NORMALIZED)
TUMOR VOLUME (mm3)
1,400 %
1,200 %
1,000 %
800 %
600 %
400 %
200 %
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
DAYS

FIG. 3

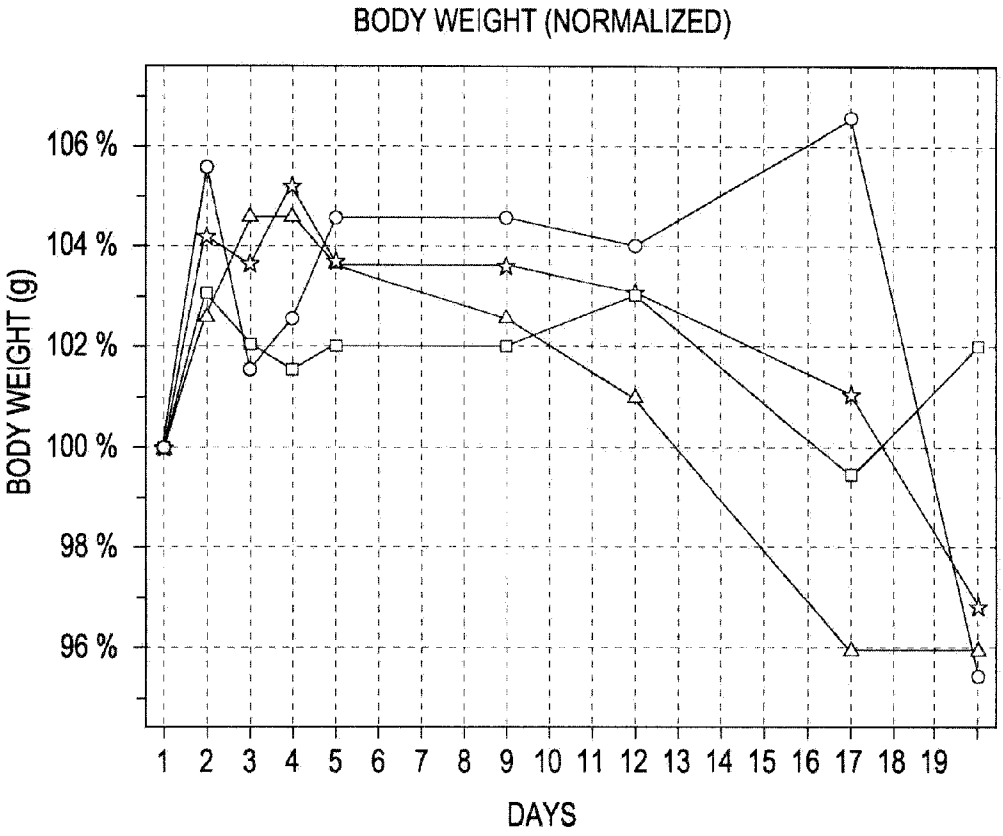
BODY WEIGHT (NORMALIZED)
BODY WEIGHT (g)
106 %
104 %
102 %
100 %
98 %
96 %
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
DAYS

FIG. 4