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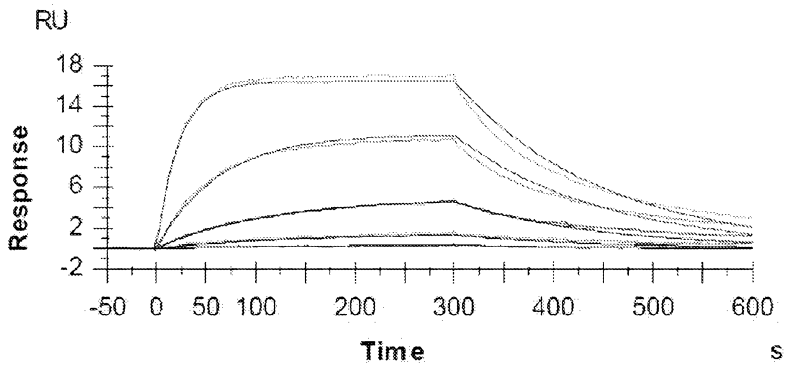

FIG. 1

(57) Abstract: A method of treating a neurodegenerative disorder or MD comprises administering to a subject a composition comprising an AGE antibody.

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ANTI-AGE ANTIBODIES FOR TREATING NEURODEGENERATIVE DISORDERS

BACKGROUND

[01] Advanced glycation end-products (AGEs; also referred to AGE-modified proteins, or glycation end-products) arise from a non-enzymatic reaction of sugars with protein side-chains in aging cells (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)).

[02] Senescent cells are cells that are partially-functional or non-functional and are in a state of irreversible proliferative arrest. Senescence is a distinct state of a cell, and is associated with biomarkers, such as activation of the biomarker $p16^{Ink4a}$, and expression of β-galactosidase. Senescent cells are also 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.

[03] AGE-modified proteins are also a marker of senescent cells. This association between glycation end-products 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 and lack of function.

[04] A recent study has identified a causal link between cellular senescence and age-related disorders, such as sarcopenia. A research team at the Mayo Clinic in Rochester, Minnesota, demonstrated that effects of aging in mice could be delayed by eliminating senescent cells in their fat and muscle tissues without overt side effects (Baker, D. J. *et al.*, "Clearance of $p16^{Ink4a}$-positive senescent cells delays ageing-associated disorders", *Nature*, Vol. 479, pp. 232-236, (2011)). Elimination of senescent cells in transgenic mice was shown to substantially delay the onset of sarcopenia and cataracts, and to reduce senescence indicators in skeletal muscle and the eye. The study established that life-long and late-life treatment of transgenic mice for removal of senescent cells has no negative side effects and selectively delays age-related phenotypes that depend on cells (*Id.*, page 234, col. 2, line 16 through page 235, col. 1, line 2). The authors theorized that removal of senescent cells may represent an avenue for treating or delaying age-related diseases in humans and improving healthy human lifespan (*Id.*, page 235, col. 2, lines 38-51).

[05] Neurodegenerative disorders are associated with abnormal cellular senescence in the central nervous system. Abnormal accumulation of senescent astrocytes has been associated with Alzheimer's disease (AD) (Bhat, R. *et al.*, "Astrocyte Senescence as a Component of Alzheimer's Disease", *PLOS ONE*, Vol. 7(9), e45069, pp. 1-10 (Sept. 2012)). Microglial cell senescence associated with normal aging is exacerbated by the presence of the amyloid plaques indicative of AD (Flanary, B. E. *et al.*, "Evidence That Aging And Amyloid Promote Microglial Cell Senescence", *Rejuvenation Research*, Vol. 10(1), pp. 61-74 (March 2007)). The presence of AGEs with astrocytes and microglial cells in AD is further evidence of the presence of senescent cells (Takeda, A., *et al.* "Advanced glycation end products co-localize with astrocyes and microglial cells in Alzheimer's disease brain", *Acta Neuropathologica*, Vol. 95, pp. 555-558 (1998)). On the basis of recently reported findings, Chinta *et al.* proposed that environmental stressors associated with Parkinson's disease (PD) may act in part by eliciting senescence within non-neuronal glial cells, contributing to the characteristic decline in neuronal integrity that occurs in this disorder (Chinta, S. J. *et al.* "Environmental stress, ageing and glial cell senescence: a novel mechanistic link to Parkinson's disease?", *J Intern Med*, Vol. 273, pp. 429-436 (2013)). Astrocyte senescence is also associated with PD (M. Mori, "The Parkinsonian Brain: Cellular Senescence and Neurodegeneration, *SAGE* (June 30, 2015) (sage.buckinstitute.org/the-parkinsonian-brain-cellular-senescence-and-neurodegeneration/). In a rodent model of familial amyotrophic lateral sclerosis (ALS) overexpressing mutant superoxide dismutase-1 (m-SOD1), the rate of astrocytes acquiring a senescent phenotype is accelerated (Das, M. M. and Svendsen, C. N., "Astrocytes show reduced support of motor neurons with aging that is accelerated in a rodent model of ALS", *Neurobiology of Aging*, Vol. 36, pp. 1130-1139 (2015)). Even in multiple sclerosis (MS), microglia and macrophages are shifted toward a strongly proinflammatory phenotype, reminiscent of SASP, and may potentiate neuronal damage by releasing proinflammatory cytokines and molecules (Luessi, F., *et al.* "Neurodegeneration in multiple sclerosis: novel treatment strategies" *Expert Rev. Neurother.*, Vol 9, pp.1061-1077 (2012)).

[06] Glial cells, such as astrocytes and microglial cells, provide support for normal brain functions. Astrocytes, also known collectively as astroglia, are star-shaped glial cells found in the brain and spinal cord. Astrocytes perform many functions, such as providing nutrients to nervous tissue, maintaining ion balance in extracellular fluids, and biochemical support of the cells that form the blood-brain barrier. Microglial cells act as macrophages in the brain and spinal cord. Microglial cells scavenge plaques, damaged neurons and infectious agents from the brain and spinal cord.

[07] Some neurodegenerative disorders are also associated with abnormal cellular senescence outside the central nervous system. Most satellite cells, also known as myosatellite cells, present in the muscle tissue of ALS patients exhibit an abnormal senescent-like morphology, although they may be capable of proliferating *in vitro* (Pradat, P.-F. *et al.*, "Abnormalities of satellite cells function in amyotrophic lateral sclerosis" *Amyotrophic Lateral Sclerosis*, Vol. 12, pp. 264-271 (2011)). Satellite cells are small multipotent cells found in mature muscle, which are able to give rise to additional satellite cells, or differentiate into myoblasts as well as provide additional myonuclei. In an animal model of Duchenne muscular dystrophy (MD), reduced proliferative capacity and premature senescence of myoblasts was observed (Wright, W. E., "Myoblast Senescence in Muscular Dystrophy" *Exp Cell Res*, Vol. 157, pp. 343-354 (1985)). Myoblasts are precursor cells which differentiate into myocytes (also referred to as muscle cells).

[08] Neurodegenerative disorders are also associated with abnormal protein accumulations (King, O.D., *et al.*, "The tip of the iceberg: RNA-binding proteins with prion-like domains in neurodegenerative disease" *Brain Res.* Vol.1462, pp. 61–80 (2012)). A characteristic of PD and Lewy body dementia is the formation of Lewy bodies that form inside nerve cells. The primary structural component of the Lewy bodies is alpha-synuclein protein, in the form of fibrils. The presence of tangles and plaques are a characteristic of AD, the presence of which is used to definitively diagnose the condition. Plaques, composed of beta-amyloid protein (also referred to as amyloid beta, Aβ or Abeta), accumulate between nerve cells. Tangles, composed of tau protein, form twisted fibers within cells. Prion diseases (also known as

transmissible spongiform encephalopathies (TSEs)), include a variety of human and animal disorder such as Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, bovine spongiform encephalopathy ("mad cow" disease), scrapie (in sheep and goats), chronic wasting disease (in deer and elk), kuru and fatal familial insomnia. Prion protein is a misfolded protein molecule which may propagate by transmitting a misfolded protein state, resulting in the accumulation of the misfolded protein and causing tissue damage and cell death (Dobson, D.M., "The structural basis of protein folding and its links with human disease" *Phil. Trans. R. Soc. Lond.* B, Vol. 356, pp. 133-145 (2001)). In these diseases, it is believed the protein is a normal protein which misfolds or forms an abnormal aggregate. In the case of some patients with familial ALS, a mutated superoxide dismutase-1 (SOD1) forms inclusions and accumulates (Kato, S., *et al.* "Advanced glycation endproduct-modified superoxide dismutase-1 (SOD1)-positive inclusions are common to familial amyotrophic lateral sclerosis patients with SOD1 gene mutations and transgenic mice expressing human SOD1 with a G85R mutation" *Acta Neuropathol*, Vol. 100, pp. 490-505 (2000)).

[09] In some cases, the proteins are believed to directly cause the death of cells, while in others the protein is believed to cause inflammation indirectly causing death of cells. The inflammation is also believed to induce senescence in cells, which in turn further exacerbates inflammation due to the SASP, leading to a positive feedback advancing neurodegeneration (Golde, T.E., *et al.* "Proteinopathy-induced neuronal senescence: a hypothesis for brain failure in Alzheimer's and other neurodegenerative diseases" *Alzheimer's Research & Therapy*, Vol. 1, No. 5 (13 October 2009)). Spreading of these inflammation-inducing proteins may also be exacerbated by senescent cells, through intercellular protein transfer (Biran, A., *et al.* "Senescent cells communicate via intercellular protein transfer" *Genes & Development*, Vol. 29, pp. 791-802 (2015)).

[10] Immunotherapy for neurodegenerative disorders, using antibodies to neurodegenerative proteins associated with the neurodegenerative disorders, is showing some promise. Even when the antibodies are administered peripherally (that is, not into the CNS), positive effects have been observed.

SUMMARY

[11] In a first aspect, the present invention is a method of treating a neurodegenerative disorder or MD comprising administering to a subject a composition comprising an AGE antibody.

[12] In a second aspect, the present invention is a method of killing senescent glial cells comprising administering to a subject a composition comprising an AGE antibody.

[13] In a third aspect, the present invention is a method of killing senescent myoblasts and/or senescent myosatellite cells comprising administering to a subject a composition comprising an AGE antibody.

[14] In a fourth aspect, the present invention is a method of treating a subject with a neurodegenerative disorder or MD comprising a first administering of an AGE antibody; followed by testing the subject for effectiveness of the first administration at treating the neurodegenerative disorder or MD; followed by a second administering of the AGE antibody.

[15] In a fifth aspect, the present invention is a method of treating a neurodegenerative disorder or MD comprising killing or inducing apoptosis in senescent glial cells, senescent myoblasts and/or senescent myosatellite cells.

[16] In a sixth aspect, the present invention is a composition for treating a neurodegenerative disorder comprising (i) an AGE antibody and (ii) serum, immune system cells, or both.

[17] **DEFINITIONS**

[18] The term "neurodegenerative disorder" means disorders which result in neurons losing function and/or dying, in the central nervous system including the brain. Such disorders included central nervous system neurodegenerative disorders such as AD, PD, Lewy body dementia, MS, prion diseases (also known as transmissible spongiform encephalopathies (TSEs), including Creutzfeldt-Jakob

disease, variant Creutzfeldt-Jakob disease, bovine spongiform encephalopathy ("mad cow" disease), scrapie (in sheep and goats), chronic wasting disease (in deer and elk), kuru and fatal familial insomnia), and ALS.

[19] 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.

[20] "Neurodegenerative proteins" are proteins which accumulate in a patient having a neurodegenerative disorders and which are associated with the neurodegenerative disorder. Examples include, beta-amyloid protein plaques (associated with AD), tau protein tangles (associated with AD), mutated superoxide dismutase-1 (associated with ALS), prion protein aggregates (associated with TSEs) and alpha-synuclein protein fibrils (associated with PD and Lewy Body dementia). A "neurodegenerative protein" is the form of the protein which accumulates during the neurodegenerative disorder, typically a mutant or mis-folded form.

[21] "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 possible.

[22] The term "senescent cell" means a cell which is in a state of irreversible proliferative arrest and expresses one or more biomarkers of senescence, such as activation of $p16^{Ink4a}$ or expression of β-galactosidase. Also included are cells which express one or more biomarkers of senescence, do not proliferate *in vivo*, but may proliferate *in vitro* under certain conditions, such as some satellite cells found in the muscles of ALS patients.

[23] 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.

[24] 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.

[25] 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.

BRIEF DESCRIPTION OF THE DRAWING

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

[27] FIG. 2A is a photograph of cells of an Alzheimer's disease sample showing carboxymethyllysine stained red and phosphorylated tau stained green.

[28] FIG. 2B is a photograph of cells of an Alzheimer's disease sample showing carboxymethyllysine stained red and amyloid precursor protein stained green.

[29] FIG. 2C is a photograph of cells of a Parkinson's disease sample from the substantia nigra showing carboxymethyllysine stained red and alpha synuclein stained green.

[30] FIG. 2D is a photograph of cells of a Parkinson's disease sample from the ventral tegmental area showing carboxymethyllysine stained red and alpha synuclein stained green.

DETAILED DESCRIPTION

[31] The present invention makes use of antibodies that bind to an AGE-modified protein on a cell, to remove or kill senescent glial cells, such as senescent astrocytes, and senescent microglial cells, to treat neurodegenerative disorders such as AD, PD, Lewy body dementia, MS, prion diseases (also known as transmissible spongiform encephalopathies (TSEs), including Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, bovine spongiform encephalopathy ("mad cow" disease), scrapie (in sheep and goats), chronic wasting disease (in deer and elk), kuru and fatal familial insomnia), and ALS. Preferably, the antibodies are administered into the central nervous system to most efficiently remove these senescent cells; however, peripheral administration (that is, not into the central nervous system but into the peripheral circulatory system) is also effective, since the astrocytes help form the blood-brain barrier. Stem cell present in the patient's central nervous system will then grow and expand to replace cells which were removed. Alternatively, autologous transplantation of the patient's own stem cells, or transplantation of donor stem cells (which may be expanded *ex vivo*) may also be used to replace cells which were removed.

[32] The present invention also makes use of antibodies that bind to an AGE-modified protein on a cell, to remove or kill senescent glial cells and/or senescent myosatellite cells, to treat ALS. Preferably, the antibodies are administered into the peripheral circulation (such as traditional intravenous administration) to most efficiently remove these senescent cells. The antibodies may also be administered intramuscularly, where the senescent myosatellite cells are found. Stem cell present in the patient's muscles will then grow and expand to replace cells which were removed. Alternatively, autologous transplantation of the patient's own stem cells, or transplantation of donor stem cells (which may be expanded *ex vivo*) may also be used to replace cells which were removed.

[33] The present invention also makes use of antibodies that bind to an AGE-modified protein on a cell, to remove or kill senescent myoblasts and/or senescent myosatellite cells, to treat MD and ALS. Preferably, the antibodies are administered into the peripheral circulation (such as traditional intravenous administration) to most efficiently remove these senescent cells. The antibodies may also be administered intramuscularly, where the senescent myoblasts and myosatellite cells are found. Stem cell present in the patient's muscles will then grow and expand to replace cells which were removed. Alternatively, autologous transplantation of the patient's own stem cells, or transplantation of donor stem cells (which may be expanded *ex vivo*) may also be used to replace cells which were removed. See, for example, Rouger *et al.* "Systemic Delivery of Allogenic Muscle Stem Cells Induces Long-Term Muscle Repair and Clinical Efficacy in Duchenne Muscular Dystrophy Dogs" *The American Journal of Pathology*, Vol. 179, No. 5, 2501-2518 (Nov. 2011).

[34] 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, glyoxal reacts to form carboxymethyllysine, which is an AGE. AGEs also form from non-enzymatic reaction of sugars in the blood with external cell proteins.

[35] 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 (1) mTOR production, which in turn activates protein synthesis and inactivates protein breakdown, and (2) an SASP (senescence associated secretory phenotype) wherein growth stimulatory and inhibitory factors are secreted to cause senescence in other cells (the senescent cell bystander effect). Further stimulation of the cells leads to programmed cell death (apoptosis).

[36] 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. Preferably, the antibody binds 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.

[37] A particularly preferred AGE antibody is an antibody which binds to a protein or peptide that exhibits a carboxymethyllysine modification. Carboxymethyllysine (also known as CML, N(epsilon)-(carboxymethyl)lysine, N(6)-carboxymethyllysine, or

2-Amino-6-(carboxymethylamino)hexanoic acid) is found on proteins or peptides and lipids as a result of oxidative stress and chemical glycation, and has been correlated with aging. CML-modified proteins or peptides are recognized by the receptor RAGE which is expressed on a variety of cells. CML has been well-studied and CML-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). 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.

[38] The 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 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 AGE antibody is greater than, similar to, or the same as, the carboxymethyl lysine MAb (Clone 318003) available from R&D Systems, Inc. (Minneapolis, MN; catalog no. MAB3247), illustrated in FIG. 1.

[39] 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.

[40] The 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.

[41] 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 AGE antibody may be injected into a patient to selectively target and remove AGE-modified cells. The 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.

[42] Magnetic nanoparticles conjugated to the 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.

[43] 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 AGE antibodies specifically target AGE-modified cell types, without removing other cells.

[44] 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 each antigen; these are referred to as bi-specific antibodies.

[45] A humanized anti-AGE antibody 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).

[46] 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 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. 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.

[47] 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.

[48] A humanized anti-AGE antibody 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.

[49] 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).

[50] 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).

[51] 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.

[52] 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).

[53] Additional DNA and protein sequences may be found in U.S. Provisional Patent Application No. 62/485,246, which is herein incorporated by reference.

[54] 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.

[55] 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.

[56] 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).

[57] The antibody may have or may include constant regions which permit destruction of targeted cells by a subject's immune system. Particularly preferred is a monoclonal antibody specific for carboxymethyllysine which is the AGE most commonly found in humans. Preferably, such an antibody includes a complement binding portion (Fc) which stimulates an increase in system natural killer (NK) cell Fc receptors (1) causing the NK cells to bind to the antibody, which in turn, has bound to senescent cells, and (2) initiate a lytic reaction. This causes the senescent cells to undergo apoptosis and be broken up into fragments which are taken up by macrophages, broken down and cleared from the body.

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

[59] Bi-specific antibodies, which are 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 AGE antibody, and a variable region (or complementary determining region) from a different antibody.

[60] 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'. Single domain antibodies, which include a heavy chain CDR and are conjugated to a toxin or other moiety for causing cell death or destruction, may also be used, and are know to pass through the blood-brain barrier. Antibody fragments may alternatively be produced recombinantly.

[61] 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, 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, α2-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. Alternatively, pAbs may be made in chickens, producing IgY molecules.

[62] 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.

[63] 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.

[64] 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 administration by injection, 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.

[65] For administration by inhalation, the antibodies are 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 AGE antibodies which are chicken antibodies (IgY) may be non-immunogenic in a variety of animals, including humans, when administered by inhalation.

[66] 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.

[67] A subject that receives administration of an AGE antibody may be tested to determine if it has been effective to treat the neurodegenerative disorder, by measuring changes in neurological function or cognitive function, or by the increase or decrease in the presence of a neurodegenerative protein associated with the neurodegenerative disorder. In the case of most neurodegenerative disorders, tests to measure the presence, severity and/or progression of the neurodegenerative disorder are well known. Administration of antibody and subsequent testing may be repeated until the desired therapeutic result is achieved, for example by evaluating the patient for the neurodegenerative disorder or evaluating the patient if the senescent cells have been killed.

[68] 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.

[69] Any mammal that could develop neurodegenerative disorders 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 neurodegenerative disorder.

[70] In the case of central nervous system neurodegenerative disorders, it may be preferably to administer the composition containing the AGE antibody directly into the central nervous system. Examples of such administration include intrathecal administration; administration into the ventricular system of the brain (intraventricular administration), for example, through a catheter or a permanent shunt, or other administration device which may be placed during a ventriculostomy (see, for example, Takami, A. *et al.* "Treatment of primary central nervous system lymphoma with induction of complement-dependent cytotoxicity by intraventricular administration of autologous-serum-supplemented rituximab", *Cancer Sci.* Vol. 97, pp. 80-83 (January 2006)); and administered by convection enhanced delivery (CED) (see, for example, Chen, K.S., *et al.* "MONOCLONAL ANTIBODY THERAPY FOR MALIGNANT GLIOMA" chapter 10 of *Glioma: Immunotherapeutic Approaches*, pp. 132-141 (ed. R. Yamanaka; Landes Bioscience and Springer Science+Business Media, 2012)). All such central nervous system administration may optionally also include administration of a serum supplement (such as autologous serum), to enhance the cell killing properties of the AGE antibody; administration of serum supplement may be prior to, simultaneous with, or subsequent to, the administration of the AGE antibody. Optionally, any of the composition containing AGE antibodies described herein may further contain a serum supplement (such as an autologous serum supplement). In place of a serum supplement, or in addition to a serum supplement, purified immune system cells may also be used, either autologous immune system cells, or immune system cells from a donor; examples of such cells include natural killer cells. In addition to, or instead of, the patient's or a donor's natural killer cells, artificial natural killer cells such as those of NANTKWEST®, engineered to bind directly to antibodies, or engineered to bind directly to an AGE antigen (such as carboxymethyllysine) (see www.nantkwest.com).

[71] The anti-AGE antibodies may be used in cell separation processes, such as magnetic cell separation. In magnetic cell separation, the anti-AGE antibodies are attached to magnetic beads through a process called coating. The coated magnetic beads may then specifically bind to AGE-modified cells. The AGE-modified cells that have bound to anti-AGE antibodies coated on magnetic beads will then respond to

an applied magnetic field, allowing the AGE-modified cells to be separated from non-AGE-modified cells. Magnetic cell separation may be used to isolate AGE-modified cells from tissue samples and fluid samples. The magnetic beads may be microbeads (0.5 – 500 μm) or nanoparticles (5 – 500 nm). Anti-AGE antibodies coated on magnetic beads may also be used in isolation processes such as immunoassays and immunoprecipitation. Similarly, anti-AGE antibodies coated on magnetic beads may be used to specifically target and separate AGE-modified proteins or peptides from tissue samples and fluid samples. The anti-AGE antibodies may be used in other cell separation processes such as flow cytometry and cell sorting.

[72] 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 AGE-modified cells from a tissue culture, cell culture or blood sample.

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

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          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
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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

[74] 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.

[75] 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

[76] 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.

[77] 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

[78] 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
CCAGCGTGTTCCTGTTCCCTCCCAAGCCCAAGGACACCCTGATGATCAGCCGC
ACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCCGAGG
TGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAG
CCTCGGGAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCG
TGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAA
CAAGGCCCTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAG
CCCCGGGAGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCTGACCA
AGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACATC
GCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCC

CTCCCGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
GACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACG
AGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCCGGATA
G

[79] The DNA sequence that corresponds to SEQ ID NO: 14 is shown below:

ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCT
CCACCGGAGACGTCGTGATGACCCAGACCCCTCTGTCCCTGCCTGTGTCTCTG
GGCGACCAGGCCTCCATCTCCTGCCGGTCTAGACAGTCCCTCGTGAACTCCAA
CGGCAACACCTTCCTGCAGTGGTATCTGCAGAAGCCCGGCCAGTCCCCCAAGC
TGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACAGATTTTCC
GGCTCTGGCTCTGGCACCGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGA
GGACCTGGGCCTGTACTTCTGCAGCCAGTCCACCCACGTGCCCCCTACATTTG
GCGGAGGCACCAAGCTGGAAATCAAACGGGCAGATGCTGCACCAACTGTATCC
ATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGC
TTCTTGAACAACTTCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGGC
AGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGATCAGGACAGCAAAGA
CAGCACCTACAGCATGAGCAGCACCCTCACGTTGACCAAGGACGAGTATGAAC
GACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCACCCATTG
TCAAGAGCTTCAACAGGAATGAGTGTTGA

[80] 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

[81] 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*

[82] 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.

[83] 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*

[84] The one-letter amino acid sequence that corresponds to SEQ ID NO: 18 is shown below:

METDTLLLWVLLLWVPGSTGDVVMTQTPLSLPVSLGDQASISCRSRQSLVNSNGN
TFLQWYLQKPGQSPKLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGLYF
CSQSTHVPPTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDI
NVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHK
TSTSPIVKSFNRNEC*

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

[86] The one-letter amino acid sequence that corresponds to SEQ ID NO: 19 is shown below:

METDTLLLWVLLLWVPGSTGDVVMTQTPLSLPVSLGDQASISCRSRQSLVNSNGN
TFLQWYLQKPGQSPKLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGLYF
CSQSTHVPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC*

[87] 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

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

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

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

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

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

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

[94] The one-letter amino acid sequence that corresponds to SEQ ID NO: 29 is MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVSCKASGYLFTTY WMHWVRQAPGQGLEWMGEISPTNGRAYYNQKFQGRVTMTVDKSTNTVYMELSS LRSEDTAVYYCARAYGNYFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ

TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPG.

[95] 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.

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

[97] 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.

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

[99] 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
GACCCACACCTGCCCTCCCTGCCCCGCCCCGAGCTGCTGGGCGGACCCAGCG
TGTTCCTGTTCCCTCCCAAGCCCAAGGACACCCTGATGATCAGCCGCACCCCC
GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCCGAGGTGAGTT
CAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGG
GAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCGTGCTGC
ACCAGGACTGGCTGAACGGCAGGAGTACAAGTGCAAGGTGAGCAACAAGGCC
CTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGG
AGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCTGACAAGAACCAG
GTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACATCGCCGTGGA
GTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCCGTG
CTGGACAGCGACGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCC
CGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGC
ACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCGGATAGTAA.

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

[101] 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.

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

[103] 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.

[104] The one-letter amino acid sequence that corresponds to SEQ ID NO: 39 is
METDTLLLWVLLLWVPGSTGDVVMTQSPLSSPVTLGQPASISCRSSQSLVNSNGN
TFLQWYHQRPGQPPRLLIYKVSLRFSGVPDRFSGSGAGKDFTLKISRVEAEDVGVY

YCSQSTHVPPTFGQGTLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC.

[105] 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.

[106] **EXAMPLES**

[107] Example 1: Affinity and kinetics of test antibody

[108] The affinity and kinetics of a test antibody were analyzed using Nα,Nα-bis(carboxymethyl)-L-lysine trifluoroacetate salt (Sigma-Aldrich, St. Louis, MO) as a model substrate for an AGE-modified protein. 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.

[109] Table 1: 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

[110] 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.

[111] Example 2: Construction and production of murine anti-AGE IgG2b antibody and chimeric anti-AGE IgG1 antibody

[112] 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.

[113] 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.

[114] 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 2:

[115] Table 2: 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

[116] CE-SDS analysis was performed (LabChip GXII, Perkin Elmer) and the electropherograms were plotted.

[117] Example 3: Binding of murine (parental) and chimeric anti-AGE antibodies

[118] The binding of the murine (parental) and chimeric anti-AGE antibodies described in Example 2 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.

[119] 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 µg/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.

[120] 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.

[121] 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
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		

[122] 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.

[123] 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				

[124] The OD450 absorbance data was also plotted against antibody concentration.

[125] 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.

[126] Example 4: Humanized antibodies

[127] 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.

[128] 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 3:

[129] Table 3: 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

[130] 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.

[131] 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).

[132] 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 4:

[133] Table 4: The antibodies and their respective 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

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

[135] Example 5: Immunohistochemical study

[136] Tissue samples were obtained from patients with Alzheimer's disease and Parkinson's disease. Two Alzheimer's disease samples were taken from the hippocampus. One Parkinson's disease sample was taken from the substantia nigra, and a second Parkinson's disease sample was taken from the ventral tegmental area. All cells were stained for carboxymethyllysine (CML) using anti-AGE antibodies as described above. The Alzheimer's disease cells were stained for phosphorylated tau (phospho tau) or separately amyloid precursor protein. The Parkinson's disease cells were stained for alpha synuclein. Nuclear staining of the cells was identified using DAPI counter stain. (Experiments were carried out and images were prepared by Dr. Diego Mastroeni of Arizona State University.)

[137] FIG. 2A is a photograph of cells of the Alzheimer's disease sample showing carboxymethyllysine stained red and phosphorylated tau stained green.

[138] FIG. 2B is a photograph of cells of the Alzheimer's disease sample showing carboxymethyllysine stained red and amyloid precursor protein stained green.

[139] FIG. 2C is a photograph of cells of the Parkinson's disease sample from the substantia nigra showing carboxymethyllysine stained red and alpha synuclein stained green.

[140] FIG. 2D is a photograph of cells of the Parkinson's disease sample from the ventral tegmental area showing carboxymethyllysine stained red and alpha synuclein stained green.

[141] CML, a well-known AGE, did not co-localize with established pathologies in Alzheimer's disease and Parkinson's disease. Instead, the CML presented on glial cells. It was suspected that the CML immunoreactivity in the Alzheimer's disease samples was with microglia, and the CML immunoreactivity in the Parkinson's disease samples was with astrocytes. The results demonstrate the presence of senescent glial cells in Alzheimer's disease and Parkinson's disease. Removal of senescent glial cells using an anti-AGE antibody would be expected to result in regeneration of the glial cells by neural stem/progenitor cells. (See, for example, Leonard, B.W. *et al.*, "Subventricular zone neural progenitors from rapid brain

autopsies of elderly subjects with and without neurodegenerative disease", The Journal of Comparative Neurology, Vol. 515, pp. 269-294 (2009)).

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WHAT IS CLAIMED IS:

1. A method of treating a neurodegenerative disorder or MD, comprising administering to a subject a composition comprising an AGE antibody.

2. A method of killing senescent glial cells, comprising administering to a subject a composition comprising an AGE antibody.

3. A method of killing senescent myoblasts and/or senescent myosatellite cells, comprising administering to a subject a composition comprising an AGE antibody.

4. A method of treating a subject with a neurodegenerative disorder or MD, comprising:

a first administering of an AGE antibody; followed by

testing the subject for effectiveness of the first administration at treating the neurodegenerative disorder or MD; followed by

a second administering of the AGE antibody.

5. A method of treating a neurodegenerative disorder or MD, comprising killing or inducing apoptosis in senescent glial cells, senescent myoblasts and/or senescent myosatellite cells.

6. A composition for treating a neurodegenerative disorder, comprising:

(i) an AGE antibody,

(ii) serum, immune system cells, or both.

7. The method of any of the preceding claims, wherein the composition further comprises a pharmaceutically acceptable carrier.

8. The method of any of the preceding claims, wherein the subject is selected from the group consisting of humans, mice, rats, goats, sheep, cows, horses, dogs and cats.

9. The method of any of the preceding claims, wherein the subject is a human.

10. The method or composition of any of the preceding claims, wherein the AGE antibody is non-immunogenic to a species selected from the group consisting of humans, cats, dogs, horses, camels, alpaca, cattle, sheep, and goats

11. The method or composition of any of the preceding claims, wherein the AGE antibody binds an AGE antigen comprises at least one protein or peptide that exhibits AGE modifications selected from the group consisting of FFI, pyrraline, AFGP, ALI, carboxymethyllysine, carboxyethyllysine and pentosidine.

12. The method or composition of any of the preceding claims, wherein the AGE antibody binds a carboxymethyllysine-modified protein.

13. The method or composition of any of the preceding claims, wherein
the composition is sterile, and
the composition is in unit dosage form.

14. The method of any of the preceding claims, wherein the composition further comprises serum.

15. The method of any of the preceding claims, wherein the serum is autologous serum.

16. The method of any of the preceding claims, wherein the composition further comprises immune system cells.

17. The method of any of the preceding claims, wherein the immune system cells are from the subject.

18. The method of any of the preceding claims, wherein the immune system cells comprise natural killer cells.

19. The method of any of the preceding claims, wherein the natural killer cells are from the subject.

20. The method of any of the preceding claims, wherein the natural killer cells comprise artificial natural killer cells.

21. The method of any of the preceding claims, wherein the composition further comprises:

(i) a pharmaceutically acceptable carrier,

(ii) serum, and

(iii) natural killer cells.

22. The method of any of the preceding claims, wherein the subject has a neurodegenerative disorder selected from the group consisting of AD, PD, Lewy body dementia, MS, prion diseases and ALS.

23. The method of any of the preceding claims, wherein the subject has a neurodegenerative disorder selected from the group consisting of AD, PD and ALS.

24. The method of any of the preceding claims, wherein the administering comprises administering to the central nervous system of the subject.

25. The method of any of the preceding claims, wherein administering to the central nervous system comprises intrathecal administration, intraventricular administration and administered by convection enhanced delivery.

26. The method of any of the preceding claims, wherein the subject has ALS or MD and the administering comprising administering to muscles of the subject.

27. The method of any of the preceding claims, wherein the administering kills senescent glial cells in the subject.

28. The method of any of the preceding claims, wherein the senescent glial cells are senescent astrocytes and/or senescent microglial cells.

29. The method of any of the preceding claims, wherein the administering kills senescent myoblasts and/or senescent myosatellite cells in the subject.

30. The method of any of the preceding claims, wherein the subject has MD or ALS.

31. The composition of any of the preceding claims, wherein the composition comprises the serum.

32. The composition of any of the preceding claims, wherein the composition comprises the immune system cells.

33. The composition of any of the preceding claims, wherein the immune system cells are natural killer cells.

34. The composition of any of the preceding claims, wherein the natural killer cells are artificial natural killer cells.

35. The method or composition of any of the preceding claims, wherein the AGE antibody is a single domain antibody conjugated to an agent that causes the destruction of cells.

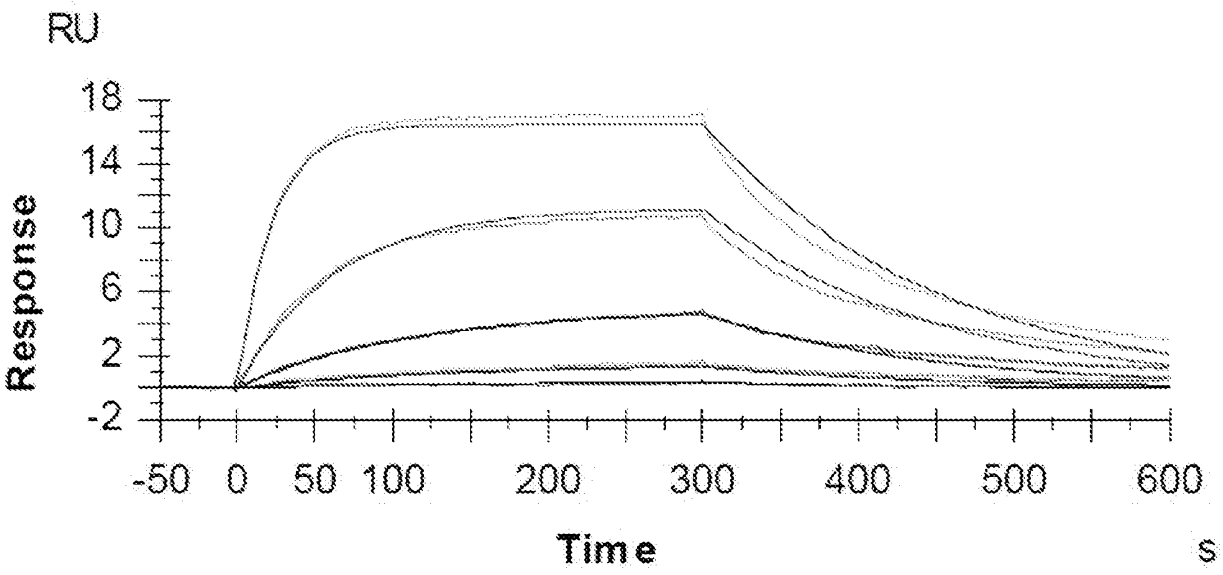

FIG. 1

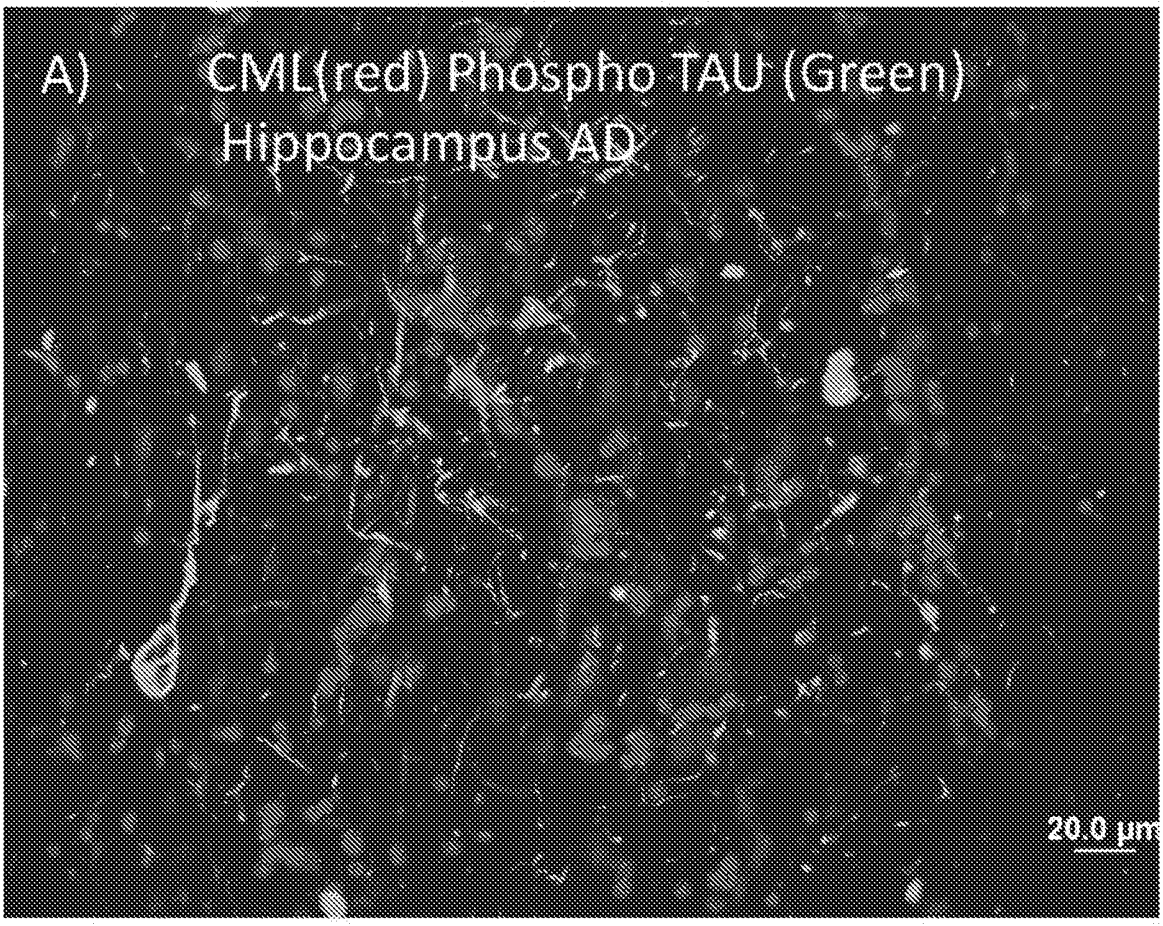

FIG. 2A

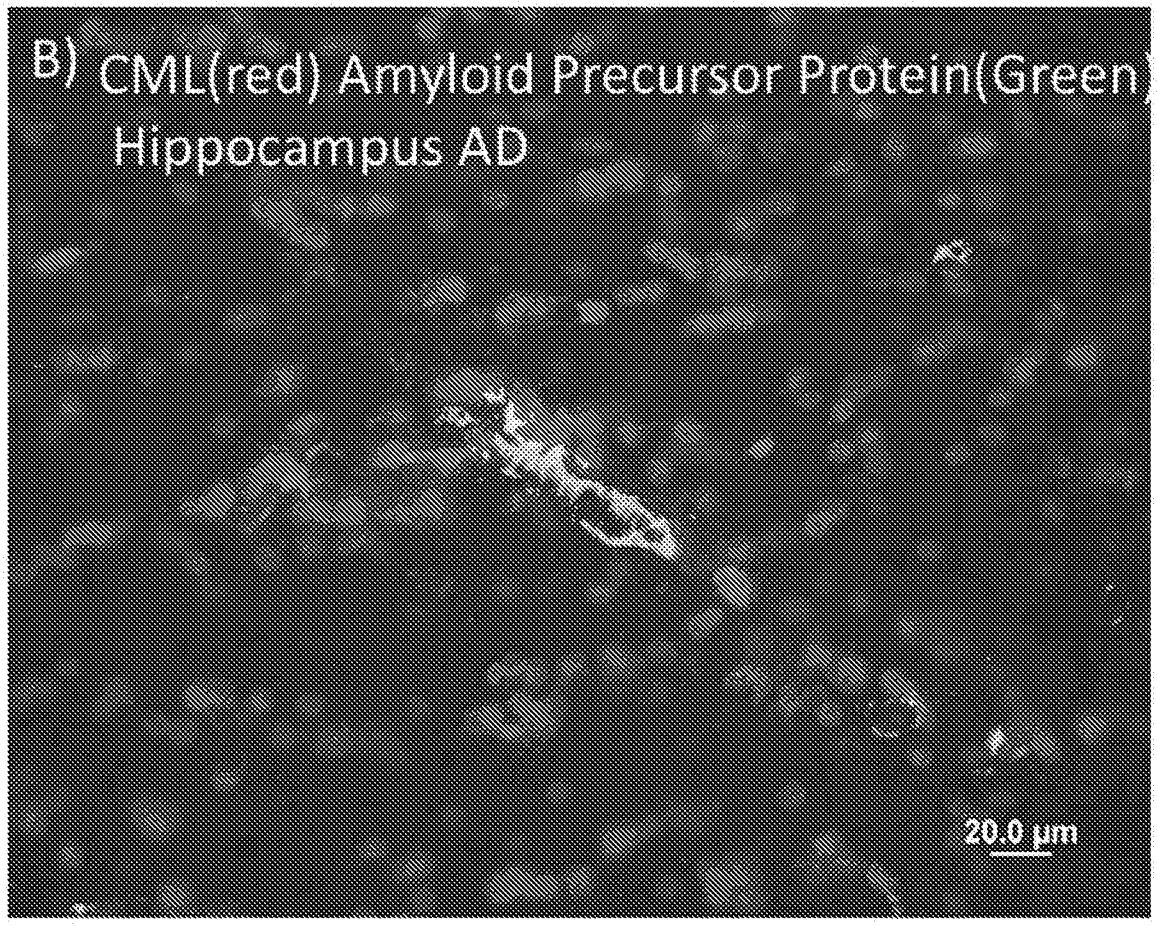
B) CML(red) Amyloid Precursor Protein(Green)
Hippocampus AD
20.0 µm

FIG. 2B

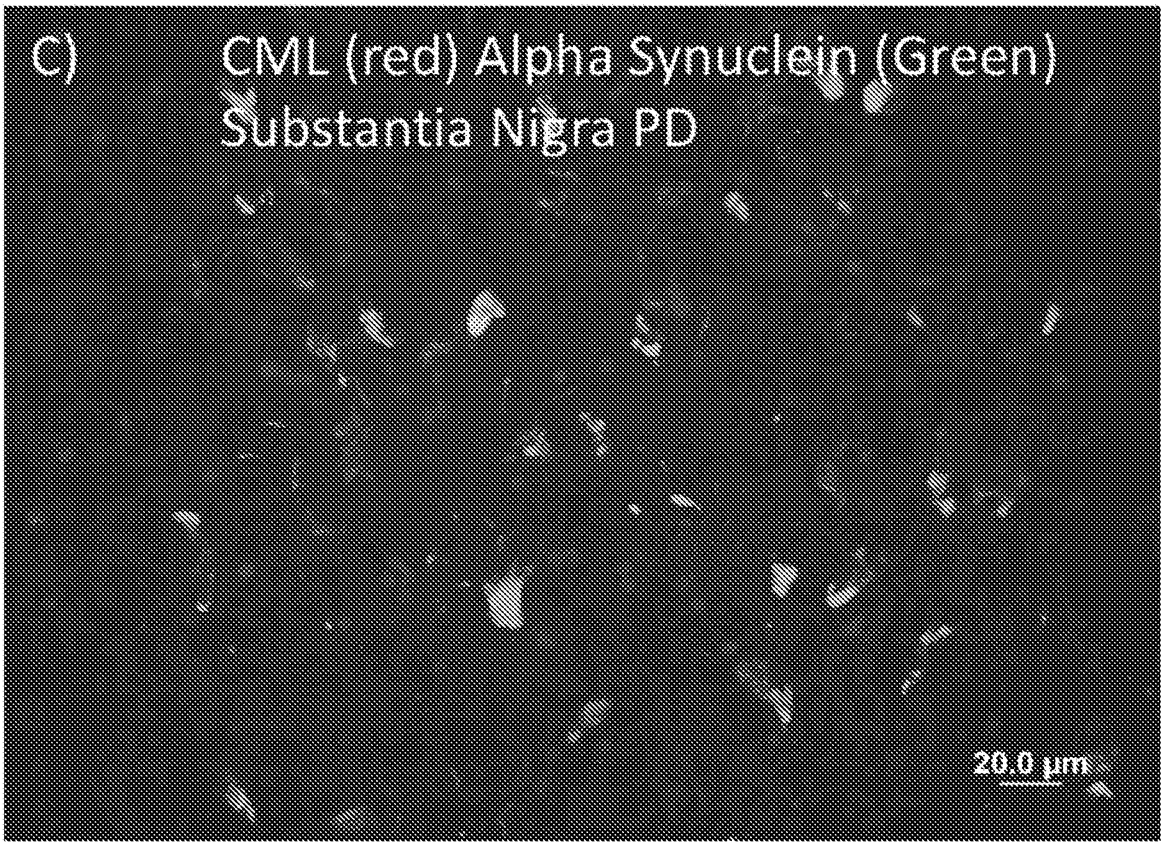

FIG. 2C

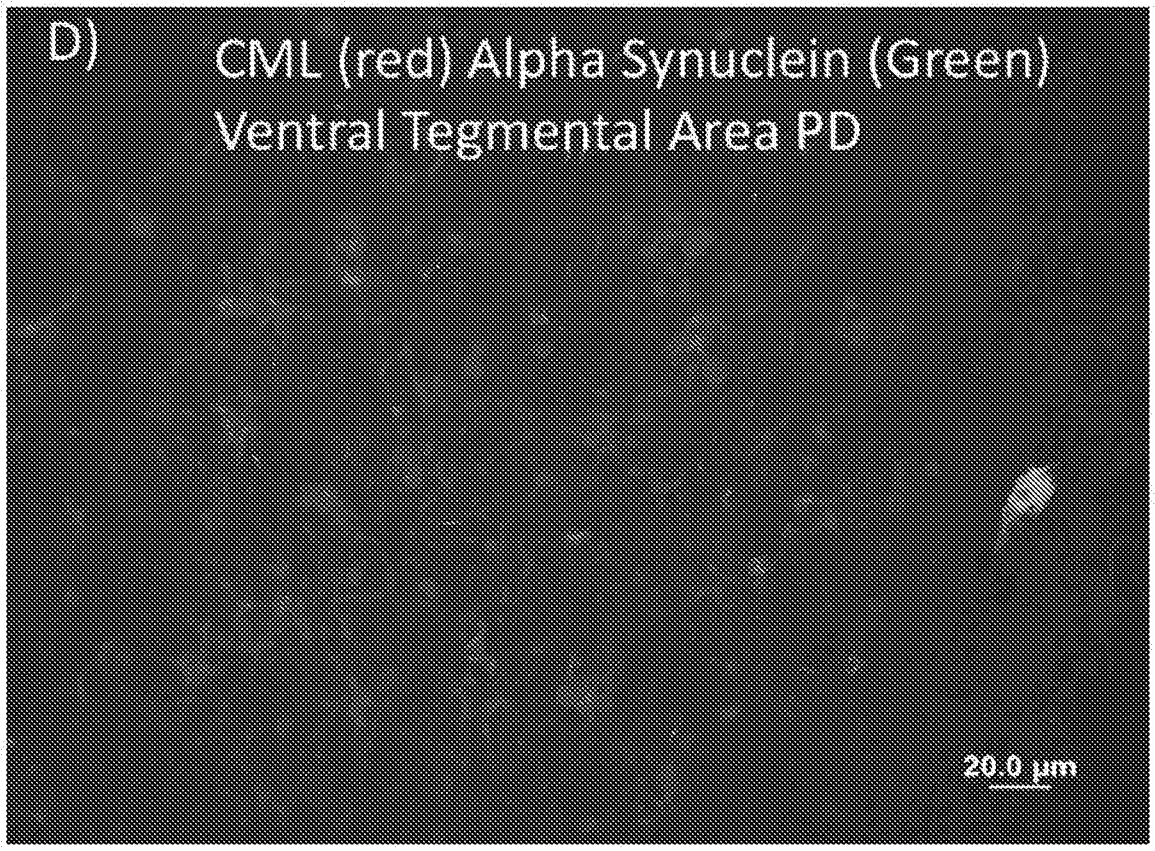
D)
CML (red) Alpha Synuclein (Green)
Ventral Tegmental Area PD
20.0 µm

FIG. 2D

Sequence Listing

<110> Lewis S. Gruber

<120> ANTI-AGE ANTIBODIES FOR TREATING NEURODEGENERATIVE DISORDERS

<130> SIW01-011-WO

<160> 40

<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

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
```

```
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
        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 cccccagcag 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 tctacccccg 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 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

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
        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
    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 gatctcccct 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

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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 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> 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 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>  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