



US 20250250331A1

(19) **United States**
(12) **Patent Application Publication** (10) **Pub. No.: US 2025/0250331 A1**
Gruber (43) **Pub. Date: Aug. 7, 2025**

(54) **ANTI-AGE ANTIBODIES FOR TREATING
NEURODEGENERATIVE DISORDERS**

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(21) Appl. No.: **18/611,415**

(22) Filed: **Mar. 20, 2024**

Related U.S. Application Data

(63) Continuation of application No. 16/092,743, filed on Oct. 10, 2018, now Pat. No. 11,958,900, filed as application No. PCT/US2017/027773 on Apr. 14, 2017.

(60) Provisional application No. 62/323,471, filed on Apr. 15, 2016.

Publication Classification

(51) **Int. Cl.**

C07K 16/24 (2006.01)

A61K 35/17 (2025.01)

A61K 38/00 (2006.01)

A61P 25/28 (2006.01)

C07K 16/44 (2006.01)

(52) **U.S. Cl.**

CPC **C07K 16/24** (2013.01); **A61K 35/17**

(2013.01); **A61P 25/28** (2018.01); **C07K 16/44**

(2013.01); **A61K 38/00** (2013.01); **C07K**

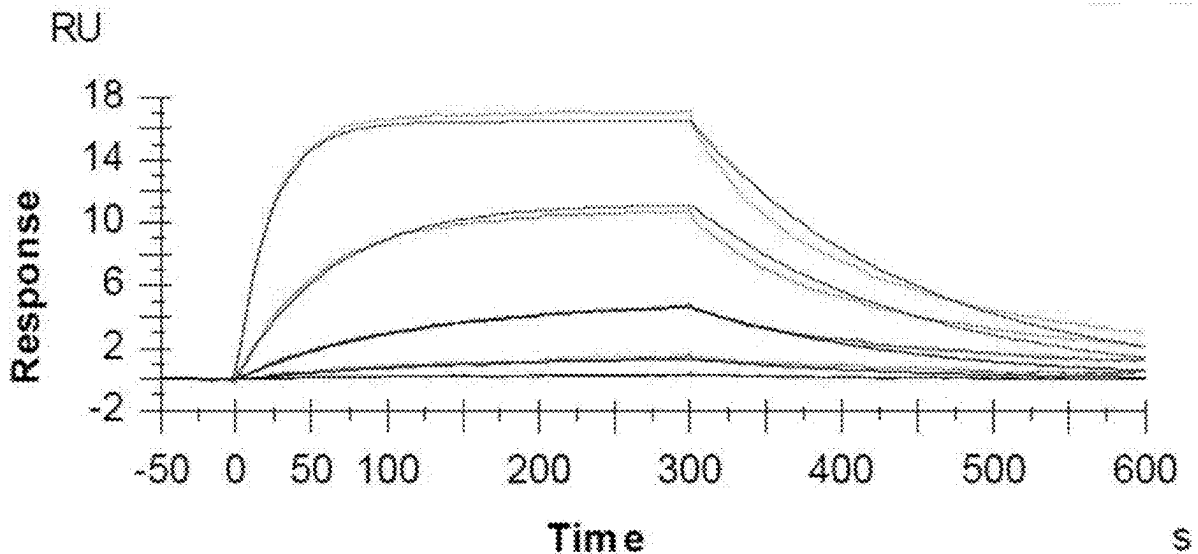
2317/24 (2013.01); **C07K 2317/92** (2013.01)

(57)

ABSTRACT

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

Specification includes a Sequence Listing.



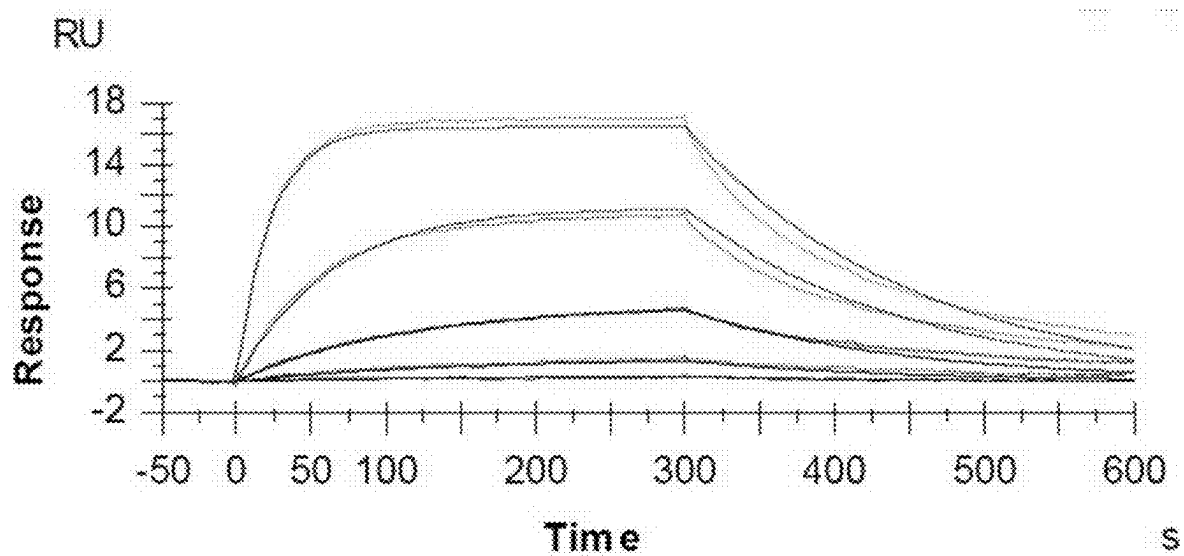


FIG. 1

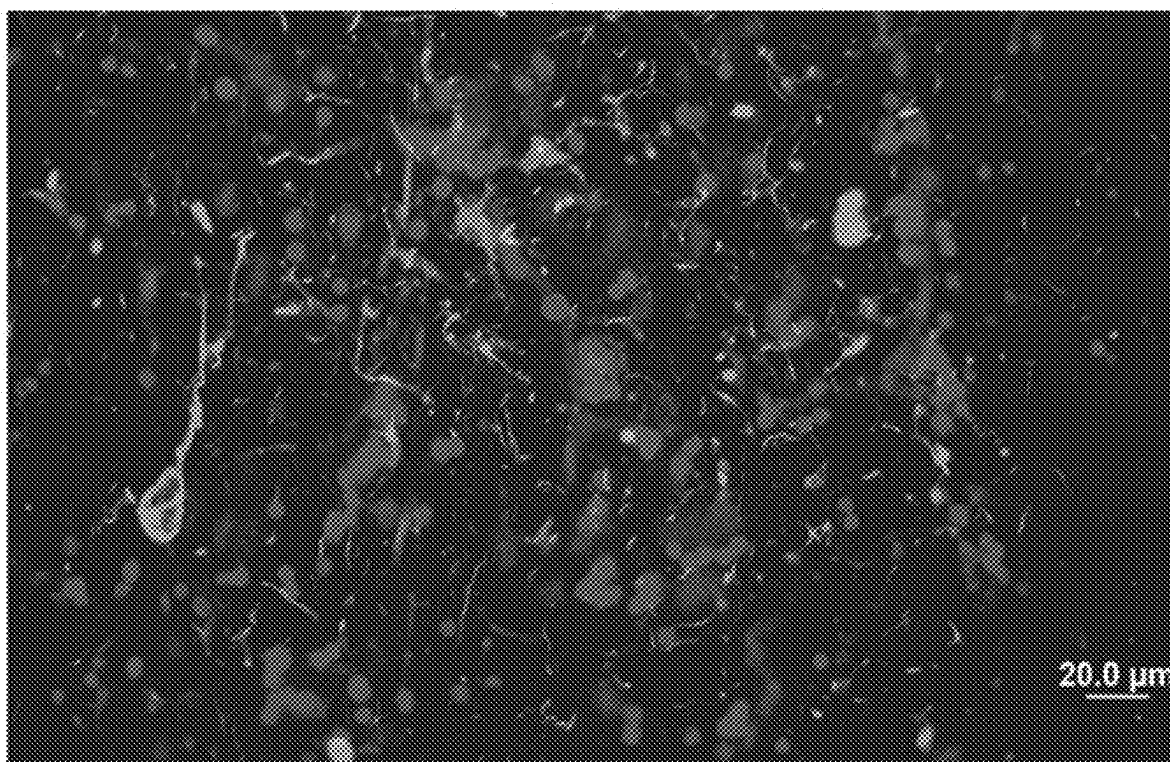


FIG. 2A

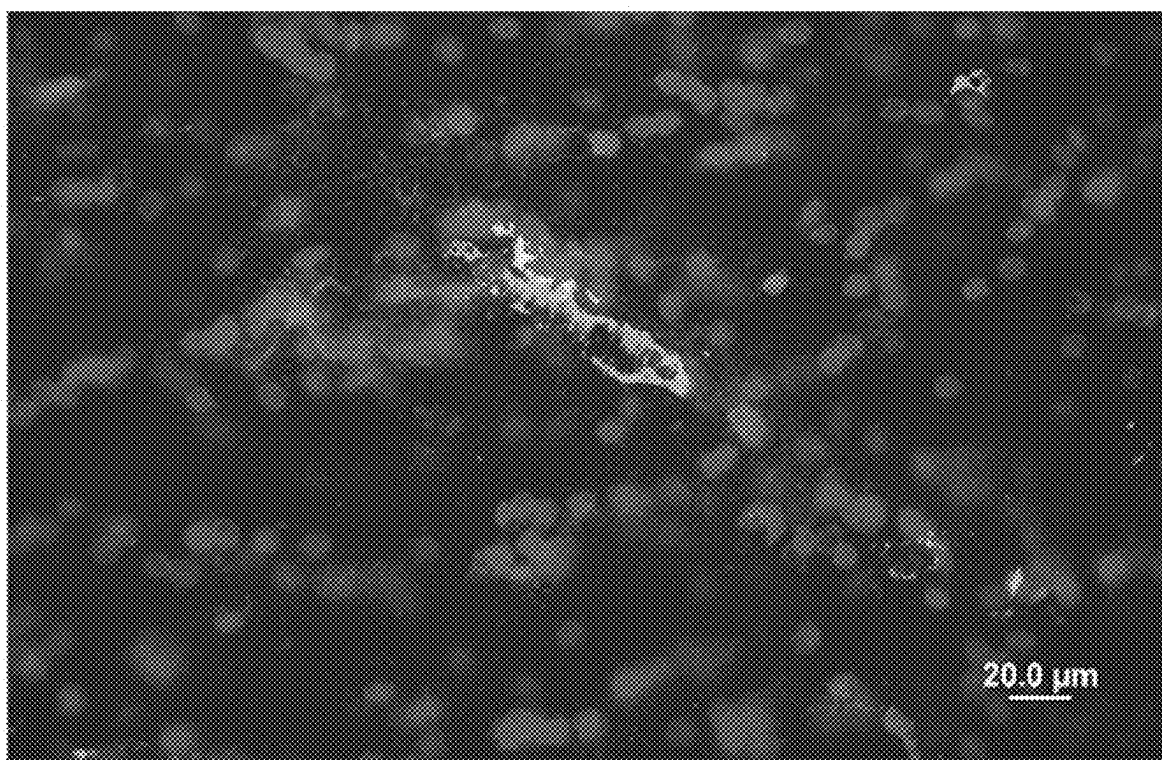


FIG. 2B



FIG. 2C

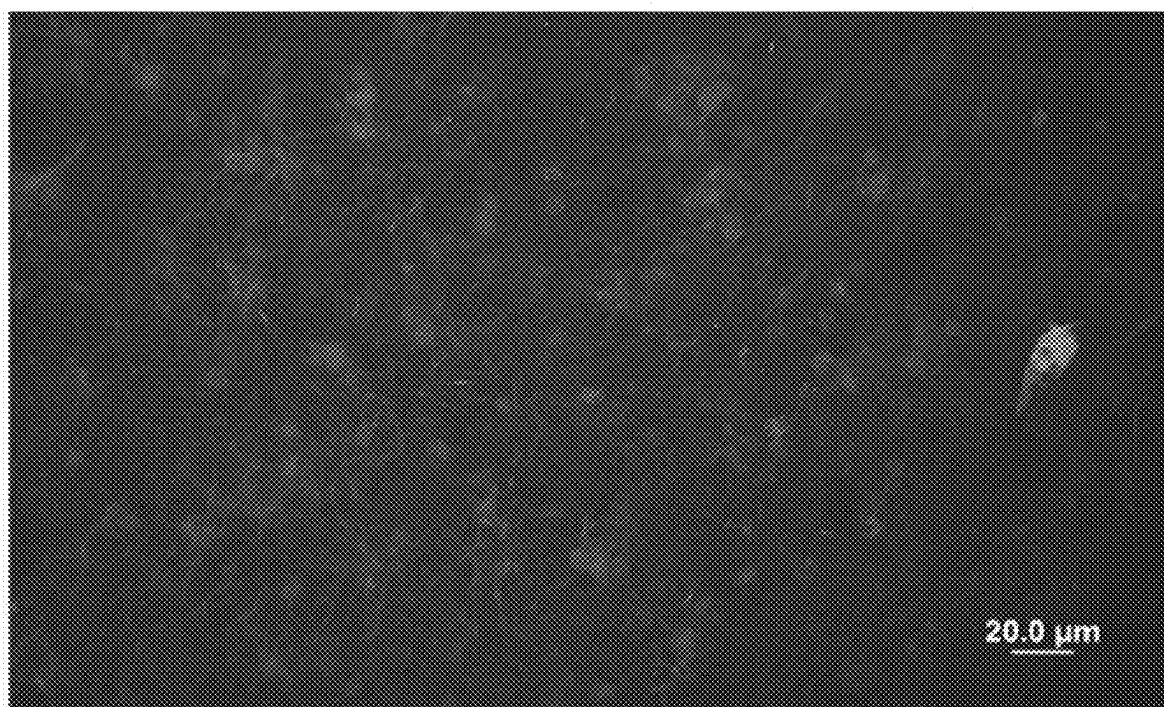


FIG. 2D

ANTI-AGE ANTIBODIES FOR TREATING NEURODEGENERATIVE DISORDERS

SEQUENCE LISTING INCORPORATION BY REFERENCE

[0001] A Sequence Listing XML file is submitted herewith. This file named “SIWO-011-CON-US_Sequence_Listing”, created on Apr. 24, 2025, having a file size of 65 KB is hereby incorporated by reference.

BACKGROUND

[0002] 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 J B, 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)).

[0003] 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.

[0004] 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. USA* 1, 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.

[0005] 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).

[0006] 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 (September 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 astrocytes 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 (Jun. 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 pro-inflammatory 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)).

[0007] 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.

[0008] 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).

[0009] 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, Ap 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)-posi-

tive 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)).

[0010] 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 Oct. 2009)). Spreading of these inflammation-inducing proteins may 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)).

[0011] 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

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

Definitions

[0018] 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 dis-

ease, 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.

[0019] 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. Pat. No. 5,702,704 to Bucala (“Bucala”) and U.S. Pat. No. 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.

[0020] “Neurodegenerative proteins” are proteins which accumulate in a patient having a neurodegenerative disorder 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.

[0021] “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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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

[0026] FIG. 1 is a graph of the response versus time in an antibody binding experiment.

[0027] FIG. 2A is a photograph of cells of an Alzheimer’s disease sample showing carboxymethyllysine stained gray and phosphorylated tau stained light gray.

[0028] FIG. 2B is a photograph of cells of an Alzheimer's disease sample showing carboxymethyllysine stained gray and amyloid precursor protein stained light gray.

[0029] FIG. 2C is a photograph of cells of a Parkinson's disease sample from the substantia nigra showing carboxymethyllysine stained gray and alpha synuclein stained light gray.

[0030] FIG. 2D is a photograph of cells of a Parkinson's disease sample from the ventral tegmental area showing carboxymethyllysine stained gray and alpha synuclein stained light gray.

DETAILED DESCRIPTION

[0031] 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.

[0032] 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.

[0033] 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 (November 2011).

[0034] 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.

[0035] 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).

[0036] 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. Pat. No. 5,702,704 (Bucala) and U.S. Pat. No. 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 as 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), equinized (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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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).

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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).

[0050] 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, HCAs, single-domain antibodies or sdAbs, and the variable domain of a camelid heavy chain antibody is known as the VH1. 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).

[0051] 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.

[0052] 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).

[0053] Additional DNA and protein sequences may be found in U.S. Provisional Patent Application No. 62/485,246, which is herein incorporated by reference.

[0054] 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.

[0055] 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.

[0056] 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).

[0057] 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.

[0058] Mixtures of antibodies that bind to more than one type AGE of AGE-modified proteins may also be used.

[0059] 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.

[0060] 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 known to pass through the blood-brain barrier. Antibody fragments may alternatively be produced recombinantly.

[0061] 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 hexaminase, 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 dicorynocolate, aluminum hydroxide (alum), heat shock proteins HSP 70 or HSP96, squalene emulsion containing monophosphoryl lipid A, α_2 -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.

[0062] 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.

[0063] 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.

[0064] 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 pharma-

ceutical 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 mannitol, 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.

[0065] 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 delivery 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.

[0066] 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.

[0067] 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.

[0068] 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 associa-

tion with the required pharmaceutical carrier. Preferably, the unit dosage form is in a sealed container and is sterile.

[0069] 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.

[0070] 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 NANTK-WEST®, engineered to bind directly to antibodies, or engineered to bind directly to an AGE antigen (such as carboxymethyllysine) (see www.nantkwest.com).

[0071] 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.

[0072] 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.

[0073] The one-letter amino acid sequence that corresponds to SEQ ID NO: 1 is shown below:

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      10      20      30      40
MNLILLITFV AAVAQVQLL QPGAELVKPG ASVKLACKAS

      50      60      70      80
GYLFTTYWMH WLKQRPQGL EWIGEISPTN GRAYYNARFK

      90     100     110     120
SEATLTVDKS SNTAYMQLSS LTSEASAVYY CARAYGNIEF

      130     140     150     160
AYWQGQTLVT VSVASTKGPS VFPLAPSSKS TSGGTAALGC

      170     180     190     200
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYLSLS

      210     220     230     240
VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH

      250     260     270     280
TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV

      290     300     310     320
DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS

      330     340     350     360
VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKQPR

      370     380     390     400
EPQVYTLPPS REEMTKNQVS LTCLVKGFPY SDIAVEWESN

      410     420     430     440
GQPENNYKTT PPVLDSGGSF FLYSKLTVDK SRWQQGNVFS

      450     460
CSVMHEALHN HYTKSLSLG PGK

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[0074] 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.

[0075] The one-letter amino acid sequence that corresponds to SEQ ID NO: 3 is shown below:

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      10      20      30      40
MNLILLITFV AAVADVMT QTPSLPVSL GDQASISCRS

      50      60      70      80
RQSLVNSNGN TPLQWYLQKP GQSPKLLIYK VSLRFSGVDP

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      90      100      110      120
RFSGSGSGTD FTLKISRVEA EDLGLYFCSQ STHVPPTFGG

      130      140      150      160
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY

      170      180      190      200
PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSLT

      210      220      230
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

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[0076] 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.

[0077] The DNA sequence that corresponds to SEQ ID NO: 12 is shown below:

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ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCTCTGAGCCT
GGCCTTCGAGCTGAGCTACGCCAGGTGCAGCTGCTGCAGCCAGGTGCCG
AGCTCGTGAACCTGGCGCCTCTGTGAAGCTGGCCTGCAAGGCTTCCGGC
TACCTGTTCAACCACTACTGGATGCACTGGCTGAAGCAGAGGCCAGGCCA
GGGCTGGAATGGATCGGCGAGATCTCCCCACCAACGGCAGAGCCTACT
ACAACGCCCGGTTCAAGTCCGAGGCCACCTGACCGTGACAAGTCTCTCC
AACACCGCCTACATGCAGCTGTCTCCCTGACCTCTGAGGCCTCCGCGCT
GTACTACTGCAGCAGAGCTTACGGCACTACGAGTTGCGCTACTGGGGCC
AGGGCACCCCTCGTGACAGTGTCTGTGGCTAAGACCACCCCTCCCTCCGTG
TACCCTCTGGCTCCTGGCTGTGGCGACACCACCGGATCCTCTGTGACCTT
GGGCTGCCTCGTGAAGGGCTACTTCCCTGAGTCCGTGACCGTGACCTGGA
ACTCCGGCTCCCTGTCTCTCCGTGCACACCTTTCAGCCCTGCTGCAG
TCCGGCCTGTACACCATGTCTCCAGCGTGACAGTGCCCTCTCCACCTG
GCCTTCCAGACCGTGACATGCTCTGTGGCCACCCCTGCCTCTTCCACCA
CCGTGGACAAGAAGCTGGAACCTCCGGCCCCATCTCCACCATCAACCTT
TGCCCTCCCTGCAAAGAATGCCACAAGTGCCCTGCCCCCAACCTGGAAGG
CGGCCCTTCCGTGTTTCATCTTCCACCCAACATCAAGGACGTGCTGATGA
TCTCCCTGACCCCCAAGTGACCTGCGTGGTGGTGAGCTGTCCGAGGAC
GACCTGACGTGCAGATCAGTTGGTTCTGTGAACAACGTGGAAGTGACAC
CGCCAGACCCAGACACACAGAGAGGACTACAACAGCACCATCAGAGTGG
TGTCTACCTTGCCCATCCAGCACCAGGACTGGATGTCCGGCAAAGAATTC
AAGTGCAAAGTGAACAACAAGGACCTGCCAGCCCATCGAGCGGACCAT
CTCCAAGATCAAGGGCTCGTGCGGGCTCCCCAGGTGTACATTCTGCCTC
CACCAGCCGAGCAGCTGTCCCGAAGGATGTGTCTCTGACATGTCTGGTC
GTGGGCTTCAACCCCGGCGACATCTCGTGAATGGACCTCCAACGCCCA

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CACCGAGGAAACTACAAGGACACCGCCCTGTGCTGGACTCCGACGGCT

CCTACTTCATCTACTCCAAGCTGAACATGAAGACCTCCAAGTGGGAAAAG

ACCGACTCCTTCTCTGCAACGTGCGGCACGAGGGCCTGAAGAACTACTA

CCTGAAGAAAACCATCTCCCGGTCCCCCGGCTAG

[0078] The DNA sequence that corresponds to SEQ ID NO: 13 is shown below:

ATGGACCCCAAGGCGACCTGAGCTGGAGAATCCTGCTGTTCTCTGAGCCT

GGCCTTCGAGCTGAGCTACGGCCAGGTGCAGCTGCTGCAGCCAGGTGCCG

AGCTCGTGAAACCTGGCGCCTCTGTGAAGCTGGCCTGCAAGGCTTCCGGC

TACCTGTTTACCACCTACTGGATGCACTGGCTGAAGCAGAGGCCAGGCCA

GGGCCTGGAATGGATCGGCGAGATCTCCCCACCAACGGCAGAGCCTACT

ACAACGCCCGTTCAAGTCCGAGGCCACCTGACCGTGGACAAGTCTCTC

AACACCGCCTACATGCAGCTGTCTCTCCCTGACCTCTGAGGCCTCCGCCGT

GTACTACTGCGCCAGAGCTTACGGCAACTACGAGTTCGCCTACTGGGGCC

AGGGCACCTCGTGACAGTGTCTGTGGCTAGCACCAAGGGCCCCAGCGTG

TTCCCTCTGGCCCCCAGCAGCAAGAGCACCGCGCGGAACGCCGCCCT

GGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTTGGA

ACAGCGCGCTCTGACCAGCGAGTGCACACCTTCCCTGCCGTGCTGCAG

AGCAGCGGCTGTACTCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAG

CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACA

CCAAGGTGACAGAAGGTGGAGCCTAAGAGCTGCGACAAGACCCACACC

TGCCCTCCTGCCCGCCCCGAGCTGTGGGCGGACCCAGCGTGTCTCT

GTTCCCTCCCAAGCCCAAGGACACCTGATGATCAGCCGACCCCCGAGG

TGACCTGCGTGGTGGTGGAGCTGAGCCACGAGGACCCGAGGTGAAGTTC

AACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCG

GGAGGAGCAGTACAACCTCACCTACCGCGTGGTGAAGCGTGTGACCGTGC

TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGAAGGTGAGCAAC

AAGGCCCTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCA

GCCCCGGGAGCCTCAGGTGTACACCTGCCCGCCAGCCGCGACGAGCTGA

CCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCC

GACATCGCGTGGAGTGGGAGAGCAACGCCAGCCTGAGAACAATAACAA

GACCACCCCTCCCGTGTGGACAGCGACGGCAGCTTCTCTGTACAGCA

AGCTGACCGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCACTGTC

AGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAG

CCTGAGCCCCGATAG

[0079] The DNA sequence that corresponds to SEQ ID NO: 14 is shown below:

ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGG

CTCCACCGGAGACGTCGTGATGACCCAGACCCCTCTGTCCCTGCCTGTGT

CTCTGGGCGACCCAGGCCCTCCATCTCCTGCCCGTCTAGACAGTCCCTCGTG

AACTCCAACGGCAACACCTTCTCAGTGGTATCTGCAGAAGCCCGGCCA

GTCCCCAAGCTGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGC

CCGACAGATTTTCCGGCTCTGGCTCTGGCACCAGCTTACCCCTGAAGATC

TCCCGGGTGAAGCCGAGGACCTGGGCTGTACTTCTGCAGCCAGTCCAC

CCACGTGCCCCCTACATTTGGCGGAGGCACCAAGCTGGAAATCAAACGGG

CAGATGCTGCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTTA

ACATCTGGAGGTGCCCTCAGTCGTGTGCTTCTTGAACAACCTTCTACCCCAA

AGACATCAATGTCAAGTGAAGATTGATGGCAGTGAACGACAAAATGGCG

TCCTGAACAGTTGGACTGATCAGGACAGCAAGACAGCACCTACAGCATG

AGCAGCACCTCAGCTTGACCAAGGACGAGTATGAACGACATAACAGCTA

TACCTGTGAGGCCACTCACAAGACATCAACTTACCCATTGTCAAGAGCT

TCAACAGGAATGAGTGTGA

[0080] The DNA sequence that corresponds to SEQ ID NO: 15 is shown below:

ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGG

CTCCACCGGAGACGTCGTGATGACCCAGACCCCTCTGTCCCTGCCTGTGT

CTCTGGGCGACCCAGGCCCTCCATCTCCTGCCCGTCTAGACAGTCCCTCGTG

AACTCCAACGGCAACACCTTCTCAGTGGTATCTGCAGAAGCCCGGCCA

GTCCCCAAGCTGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGC

CCGACAGATTTTCCGGCTCTGGCTCTGGCACCAGCTTACCCCTGAAGATC

TCCCGGGTGAAGCCGAGGACCTGGGCTGTACTTCTGCAGCCAGTCCAC

CCACGTGCCCCCTACATTTGGCGGAGGCACCAAGCTGGAAATCAAGCGGA

CCGTGGCGCCCCCAGCGTGTTCATCTTCCCTCCAGCGACGAGCAGCTG

AAGTCTGGCACCAGCGAGCGTGGTGTGCTGCTGAACAACCTTCTACCCCCG

CGAGGCCAAGGTGCAAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACA

GCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTG

AGCAGCACCTTGACCTGAGCAAGGCCGACTACGAGAAGCAAGGTGTA

CGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCT

TCAACCGGGGCGAGTGCTAA

[0081] The one-letter amino acid sequence that corre-

sponds to SEQ ID NO: 16 is shown below:

MDPKGSLSWRILLFLSLAFELSYGQVQLLPQGAELVKPGASVKLACKASG

YLFTTYWMHWLKRPGGLEWIGELISPTNGRAYYNARFKSEATLTVDKSS

NTAYMQLSLSTSEASAVYYCARAYGNVEFAYWGQGLTVTSVAKTTPPSV

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YPLAPGCGDTTGSSVTLGCLVKGYFPESVTVTNWNSGLSSSVHTFPALLQ
 SGLYTMSSSVTVPSSTWPSQTVTCSVAHPASSTTVDDKKLEPSGPISTINP
 CPPCKECHKCPAPNLEGGPSVFIFFPNIKDVLMLSTPKVTCVVVDVSED
 DPDVQISWVFNNEVHTAQQTQTHREDYNSTIRVVSTLPIQHGDWMSGKEF
 KCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLV
 VGFNPGDISVEWTSNGHTEENYKDTAPVLDSGSYFIYSKLNMKTSKWEK
 TDSFSCNVRHEGLKNYYLKKTISRSPG*

[0082] 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.
[0083] The one-letter amino acid sequence that corresponds to SEQ ID NO: 17 is shown below:

MDPKGSLSWRILLFLSLAFELSYGQVQLLQPGAELVKGASVKLACKASG
 YLFTTYWMHWLKQRPQGLEWIGEISPTNGRAYYNARFKSEATLTVDKSS
 NTAYMQLSSLTSEASAVVYCARAYGNIEFAYWGQGLTVTVSVASTKGPSV
 FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
 SSGLYSLSSVTVPSSSLGTYICNVNHNKPSNTKVDKKVEPKSCDKTHT
 CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKF
 NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
 KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
 DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
 CVMHEALHNHYTQKSLSLSPG*

[0084] The one-letter amino acid sequence that corresponds to SEQ ID NO: 18 is shown below:

METDTLLLWVLLLWVPGSTGDVMTQTPLSLPVSLGDQASISCRSRQSLV
 NSNGNTFLQWYLQKPGQSPKLLIYKVSIRFSGVPDRFSGSGGTDFTLKI
 SRVEAEDLGLYFCSSQSTHVPPTFGGGTKLEIKRADAAPTVISIFPPSSEQL
 TSGGASVVCFLNNFYPKDINVKKIDGSEKQNGVLNSWTDQDSKSTYSM
 SSTLTTLTKDEYERHNSYTCETHKTSTSPIVKSFNRNEC*

[0085] Positions 21-132 of the above amino acid sequence correspond to SEQ ID NO: 21.

[0086] The one-letter amino acid sequence that corresponds to SEQ ID NO: 19 is shown below:

METDTLLLWVLLLWVPGSTGDVMTQTPLSLPVSLGDQASISCRSRQSLV
 NSNGNTFLQWYLQKPGQSPKLLIYKVSIRFSGVPDRFSGSGGTDFTLKI
 SRVEAEDLGLYFCSSQSTHVPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQL

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KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYSL
 SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

[0087] The one-letter amino acid sequence that corresponds to SEQ ID NO: 22 is shown below:

10	20	30	40
ASTKGPSVFP	LAPCSRSTSE	STAALGCLVK	DYFPEFVTVS
50	60	70	80
WNSGALTSGV	HTFPAVLQSS	GLYSLSSVVT	VPSSNFGTQT
90	100	110	120
YTCNVDPKPS	NTKVDKTVR	KCCVECPPCP	APPVAGPSVF
130	140	150	160
LFPKPKDITL	MISRTPEVTC	VVVDVSHEDP	EVQFNWYVDG
170	180	190	200
VEVHNAKTKP	REEQFNSTFR	VVSVLTVVHQ	DWLNGKEYKC
210	220	230	240
KVSNKGLPAP	IEKTISKTKG	QPREPQVYTL	PPSREEMTKN
250	260	270	280
QVSLTCLVKG	FYPDSISVEW	ESNGQPPENNY	KTPPMLDSD
290	300	310	320
GSFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL
SLSPGK			

[0088] The one-letter amino acid sequence that corresponds to SEQ ID NO: 23 is SYTMGVVS.

[0089] The one-letter amino acid sequence that corresponds to SEQ ID NO: 24 is

TISSGGGSTYYPDSVKG.

[0090] The one-letter amino acid sequence that corresponds to SEQ ID NO: 25 is QGGWLPPFAX, where X may be any naturally occurring amino acid.

[0091] The one-letter amino acid sequence that corresponds to SEQ ID NO: 26 is

RASKSVSTSSRGYSYMH.

[0092] The one-letter amino acid sequence that corresponds to SEQ ID NO: 27 is LVSNLES.

[0093] The one-letter amino acid sequence that corresponds to SEQ ID NO: 28 is

QHIRELTRS.

[0094] The one-letter amino acid sequence that corresponds to SEQ ID NO: 29 is

MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVCKASG
 YLFTTYWMHWVRQAPQGLEWNGEISPTNGRAYYNQKFGQGRVTMTVDKST
 NTVYMELSSLRSEDAVYYCARAYGNIEFAYWGQGLTVTVSSASTKGPSVF
 PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

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SGLYSLSSWTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCP
PCPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQCSVMH
EALHNHYTQKSLSLSPG.

[0095] The DNA sequence that corresponds to SEQ ID NO: 30 is

ATGGACCCCAAGGCGAGCCTGAGCTGGAGAATCCTGCTGTTCTCTGAGCCT
GGCCTTCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCG
AAGTGAAGAAACCTGGCGCCTCCGTGAGGTGTCTTGCAAGGCTTCCGGCT
ACCTGTTTACCACCTACTGGATGCACTGGGTGCGACAGGCCCTGGACAG
GGCCTGGAATGGATGGGCGAGATCTCCCTACCAACGGCAGAGCCTACTA
CAACAGAAATTCAGGGCAGAGTGACCATGACCGTGGACAAGTCCACCAA
CACCGTGTACATGGAACGTCTCTCCCTGCGGAGCGAGACACCGCCGTGT
ACTACTGCGCTAGAGCCTACGGCAACTACGATTTCGCTACTGGGGCCAGG
GCACCTCTGTGACAGTGTCTCTGCTAGCACCAAGGGCCCCAGCGTGTTC
CCTCTGGCCCCCAGCAGCAAGAGCACACGCGCGGAACCGCCGCTGGG
CTGCCTGGGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTGGAACAG
CGGCGCTCTGACCAGCGGAGTGACACCTTCCCTGCGCTGTGTCAGAGCA
GCGGCTGTACTCCCTGAGCAGCGTGGTACCGTGCCAGCAGCAGCCTGG
GCACCCAGACCTACATCTGCAACGTGAACCAAGCCCTCCAACACCAAG
GTGGACAAGAAGGTGGAGCCTAAGAGCTGCGACAAGACCCACACCTGCC
TCCCTGCCCGCCCGAGCTGTGGGCGGACCCAGCGTGTCTCTGTTCCC
TCCCAAGCCCAAGGACACCTGATGATCAGCCGACCCCGAGGTGACCT
GCGTGGTGGTGGAGCTGAGCCACGAGGACCCCGAGGTGAGTTCAACTGGT
ACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGGGAGGAG
CAGTACAACCTCCACCTACCGCTGGTGAGCGTGTGACCGTGTGACCA
GGACTGGCTGAACGGCAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT
GCCCCGTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGG
AGCCTCAGGTGTACACCTGCCCCCAGCCGCGACGAGCTGACAAGAACC
AGGTGAGCCTGACCTGCGCTGGTGAAGGGCTTCTACCCCTCCGACATCGCC
GTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACCTACAAGACCAACCC
TCCCGTGTGGACAGCGACGAGCTTCTTCTGTACAGCAAGCTGACCGT
GGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTAGCTGCAGCGTGATGC
ACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCG
GATAGTAA.

[0096] The one-letter amino acid sequence that corresponds to SEQ ID NO: 31 is

MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVSKASG
YLFTTYWMHVVRQAPGGGLEWMGEISPTNGRAYYNAKFQGRVTMTVDKS
TNTAYMELSSLRSEDTAVYYCARAYGNYFAYWGQGLTVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHT
CPPCPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
VVYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQCS
VMHEALHNHYTQKSLSLSPG.

[0097] The DNA sequence that corresponds to SEQ ID NO: 32 is

ATGGACCCCAAGGCGAGCCTGAGCTGGAGAATCCTGCTGTTCTCTGAGCCT
GGCCTTCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCG
AAGTGAAGAAACCTGGCGCCTCCGTGAGGTGTCTTGCAAGGCTTCCGGCT
ACCTGTTTACCACCTACTGGATGCACTGGGTGCGACAGGCCCTGGACAG
GGCCTGGAATGGATGGGCGAGATCTCCCTACCAACGGCAGAGCCTACTA
CAACAAAATTCAGGGCAGAGTGACCATGACCGTGGACAAGTCCACCAA
CACCGCTTACATGGAACGTCTCTCCCTGCGGAGCGAGACACCGCCGTGT
ACTACTGCGCTAGAGCCTACGGCAACTACGATTTCGCTACTGGGGCCAGG
GCACCTCTGTGACAGTGTCTCTGCTAGCACCAAGGGCCCCAGCGTGTTC
CCTCTGGCCCCCAGCAGCAAGAGCACACGCGCGGAACCGCCGCTGGG
CTGCCTGGGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTGGAACAG
CGGCGCTCTGACCAGCGGAGTGACACCTTCCCTGCGCTGTGTCAGAGCA
GCGGCTGTACTCCCTGAGCAGCGTGGTACCGTGCCAGCAGCAGCCTGG
GCACCCAGACCTACATCTGCAACGTGAACCAAGCCCTCCAACACCAAG
GTGGACAAGAAGGTGGAGCCTAAGAGCTGCGACAAGACCCACACCTGCC
TCCCTGCCCGCCCGAGCTGTGGGCGGACCCAGCGTGTCTCTGTTCCC
TCCCAAGCCCAAGGACACCTGATGATCAGCCGACCCCGAGGTGACCT
GCGTGGTGGTGGAGCTGAGCCACGAGGACCCCGAGGTGAGTTCAACTGGT
ACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGGGAGGAG
CAGTACAACCTCCACCTACCGCTGGTGAGCGTGTGACCGTGTGACCA
GGACTGGCTGAACGGCAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT
GCCCCGTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGG
AGCCTCAGGTGTACACCTGCCCCCAGCCGCGACGAGCTGACAAGAACC
AGGTGAGCCTGACCTGCGCTGGTGAAGGGCTTCTACCCCTCCGACATCGCC
GTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACCTACAAGACCAACCC
TCCCGTGTGGACAGCGACGAGCTTCTTCTGTACAGCAAGCTGACCGT
GGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTAGCTGCAGCGTGATGC
ACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCG
GATAGTAA.

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ACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCG
GATAGTAA.

[0098] The one-letter amino acid sequence that corresponds to SEQ ID NO: 33 is

MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVCKASG
YLFTTYWMHVVRQAPGQGLEWMGEISPTNGRAYYNAKFQGRVTMTVDKS
INTAYMELSRLRSDTAVYYCARAYGNYPAYWGQGLTVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
VVYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLTCLVKGFYPSD
IAVEWESNQGPENNYKTTTPVLDSGSEFFLYSKLTVDKSRWQQGNVFCSS
VMHEALHNHYTQKSLSLSPG.

[0099] The DNA sequence that corresponds to SEQ ID NO: 34 is

ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCTTGAGCCT
GGCCTTCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCG
AAGTGAAGAACTGGCGCCTCCGTGAGGTGTCTTGCAAGGCTTCCGGCT
ACCTGTTCAACCACTACTGGATGCACTGGGTGCGACAGGCCCTGGACAG
GGCCTGGAATGGATGGGCGAGATCTCCCTACCAACGGCAGAGCCTACTA
CAACCAAAATTCCAGGGCAGAGTGACCATGACCGTGGACAAGTCCATCAA
CACCGCTTACATGGAAGTGTCCAGACTGCGGAGCGATGACACGCCGTGT
ACTACTGCCTAGAGCCTACGGCAACTACGATTGCGCTACTGGGCGCAGG
GCACCTCTGTGACAGTGTCTCTGCTAGCACCAAGGGCCCCAGCGTGTTC
CCTCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGAACGCCGCCCTGGG
CTGCCTGGGAAGGACTACTTCCCCGAGCCCCGTGACCGTGTCTTGAACAG
CGGCGCTCTGACCAGCGGAGTGACACACCTTCCCTGCCGTGTGCAGAGCA
GCGGCTGTACTCCCTGAGCAGCGTGGTACCGTGCCAGCAGCAGCCTGG
GCACCCAGACCTACATCTGCAACGTGAACCAAGCCCTCCAACACCAAG
GTGGACAAGAAGGTGGAGCCTAAGAGCTGCGACAAGACCCACACCTGCC
TCCCTGCCCGCCCCGAGCTGTGGGCGGACCCAGCGTGTCTCTGTTCC
TCCCAAGCCCAAGGACACCTGATGATCAGCCGACCCCGAGGTGACCT
GCGTGGTGGTGGACGTGAGCCACGAGGACCCCGAGGTGAGTTCAACTGGT
ACGTGGACGGCGTGGAGGTGCAACGCCAAGACCAAGCCTCGGAGGAG
CAGTACAACCTCCACCTACCGCGTGGTGAAGCTGTGACCGTGTGACCA
GGACTGGCTGAACGGCAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT
GCCCCCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGG

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AGCCTCAGGTGTACACCTGCCCCCAGCCGCGACGAGCTGACAAGAACC
AGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACATCGCC
GTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACACAGACCACCCC
TCCCGTGTGGACAGCGACGCGAGCTTCTTCTGTACAGCAAGCTGACCGT
GGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTTCTGCTGACGCGTGTGTC
ACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCG
GATAGTAA.

[0100] The one-letter amino acid sequence that corresponds to SEQ ID NO: 35 is

METDTLLLVLLLVPGSTGDVMTQSPVLSLPVTLGQPASISCRSSQSLV
NSNGNTFLQWYQRPQSPRLLIYKVSRLRFGVDPDRFSGSGSGTDFTLKI
SRVEAEDVGVVYCSQSTHVPTFGGGTVEIKRTVAAPSVFIFPPSDEQLK
SGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

[0101] The DNA sequence that corresponds to SEQ ID NO: 36 is

ATGGAGACCGACACCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGG
CTCCACCGGAGACGTCGTGATGACCCAGTCCCTCTGTCTCTGCTGTGA
CCCTGGGACAGCCTGCCTCCATCTCCTCAGATCTCCAGTCCCTCGTGA
ACTCCAACGGCAACACCTTCTGTCAGTGGTATCAGCAGCGGCTGGCCAG
AGCCCCAGACTGCTGATCTACAAGGTGTCCCTGCGGTTCTCCGGCGTGCC
CGACGATTTTCCGGCTCTGGCTCTGGCACCAGCTTACCCCTGAAGATCTC
CCGGTGGAGCCGAGGACGTGGGCGTGTAATACTGCTCCAGAGCACCC
ACGTGCCCCCTACATTTGGCGGAGGCACCAAGTGGAAATCAAGCGGACCG
TGGCGCCCCCAGCGTGTTCATCTTCCCTCCAGCAGCAGCAGCTGAAG
TCTGGCACCGCCAGCGTGGTGTGCTGTGAACAACCTTACCCCCGCGA
GGCCAAGGGCAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCA
GGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCA
GCACCTGACCTGAGCAAGGCCGACTACGAGAAGACAAGGTGTACGCCT
GCGAGGTGACCCACCAGGACTGTCTAGCCCCGTGACCAAGAGCTTCAAC
CGGGGCGAGTGCTAA.

[0102] The one-letter amino acid sequence that corresponds to SEQ ID NO: 37 is

METDTLLLVLLLVPGSTGDVMTQSPVLSLPVTLGQPASISCRSRQSLV
NSNGNTFLQWYQRPQSPRLLIYKVSRLRFGVDPDRFSGSGSGTDFTLKI
SRVEAEDVGVVYCSQSTHVPTFGGGTVEIKRTVAAPSVFIFPPSDEQLK

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SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLG
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

[0103] The DNA sequence that corresponds to SEO ID NO: 38 is

ATGGAGACCGACACCTGCTGCTCTGGGTGCTGCTCTGGGTGCCCCG
CTCCACCGGAGACGTCGTGATGACCCAGTCCCCCTGTCCCTGCCTGTGA
CCCTGGGACAGCCTGCCTCCATCTCCTCAGATCCAGGAGTCCCTCGTGA
ACTCCAACGGCAACACCTTCTGTCAGTGGTATCAGCAGCGGCTGGCCAG
AGCCCCAGACTGCTGATCTACAAGGTGTCCTGCGGTTCTCCGGCGTGCC
CGACGATTTTCCGGCTCTGGCTCTGGCACCAGTTCACCTGAAGATCTC
CCGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCTCCAGAGCACCC
ACGTGCCCCCTACATTTGGCGGAGGCACCAAGTGAAATCAAGCGGACCG
TGCCCGCCCCAGCGTGTTTCATCTTCCCTCCAGCAGCAGCAGCTGAAG
TCTGGCACCGCCAGCGTGGTGTGCTGTGAACAACCTTACCCCCGCGA
GGCCAAGGGCAGTGAAGGTGGACAACGCCCTGCAGAGCGCAACAGCCA
GGAGAGCGTGACCGAGCAGGACTCCAAGGACGACCTACAGCCTGAGCA
GCACCTGACCTGAGCAAGGCCGACTACGAGAAGACAAGGTGTACGCCT
GCGAGGTGACCCACCAGGACTGTCTAGCCCCGTGACCAAGAGCTTCAAC
CGGGGCGAGTGCTAA.

[0104] The one-letter amino acid sequence that corresponds to SEQ ID NO: 39 is

METDTLLLVVLLLVPGSTGDVMTQSPVLTGQPASISCRSSQSLV
NSNGNTFLQWYHQRPQPPRLLIYKVSIRFSGVDPDRFSGSGAGKDFTLKI
SRVEAEDVGVIYCSQSTHVPPTFGQGTLEIKRTVAAPSVFIFPPSDEQLK
SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLG
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

[0105] The DNA sequence that corresponds to SEQ ID NO: 40 is

ATGGAGACCGACACCTGCTGCTCTGGGTGCTGCTCTGGGTGCCCCG
CTCCACCGGAGACGTCGTGATGACCCAGTCCCCCTGTCCAGTCTGTGA
CCCTGGGACAGCCTGCCTCCATCTCCTCAGATCCCTCCAGTCCCTCGTGA
ACTCCAACGGCAACACCTTCTGTCAGTGGTATCACCAGCGGCTGGCCAG
CCTCCAGACTGCTGATCTACAAGGTGTCCTGCGGTTCTCCGGCGTGCC
CGACGATTTTCCGGCTCTGGCGCTGGCAAGGACTTCACCTGAAGATCTC
CCGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCTCCAGAGCACCC
ACGTGCCCCCTACATTTGGCCAGGGACCAACTGGAATCAAGCGGACCG
TGCCCGCCCCAGCGTGTTTCATCTTCCCTCCAGCAGCAGCAGCTGAAG

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TCTGGCACCGCCAGCGTGGTGTGCTGCTGTAACAACCTTACCCCCGCGA
GGCCAAGGGCAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCA
GGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCA
GCACCTGACCTGAGCAAGGCCGACTACGAGAAGACAAGGTGTACGCCT
GCGAGGTGACCCACCAGGACTGTCTAGCCCCGTGACCAAGAGCTTCAAC
CGGGGCGAGTGCTAA.

EXAMPLES

Example 1: Affinity and Kinetics of Test Antibody

[0106] The affinity and kinetics of a test antibody were analyzed using $N\alpha,N\alpha$ -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 immobilized with the test antibody (molecular weight of 150,000 Da). The running buffer was a HBS-EP buffer (10 mM HEPES, 150 mM NaCl, 3 mM EDTA and 0.05% P-20, pH of 7.4), at a temperature of 25° C. Software was BIACORE™ T200 evaluation software, version 2.0. A double reference (Fc2-1 and only buffer injection), was used in the analysis, and the data was fitted to a *Langmuir* 1:1 binding model.

TABLE 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

[0107] A graph of the response versus time is illustrated in FIG. 1. The following values were determined from the analysis: k_a (1/Ms)= 1.857×10^3 ; k_d (1/s)= 6.781×10^{-3} ; K_D (M)= 3.651×10^{-6} ; R_{max} (RU)=19.52; and $\chi^2=0.114$. Because the χ^2 value of the fitting is less than 10% of R_{max} , the fit is reliable.

Example 2: Construction and Production of Murine
Anti-AGE IgG2b Antibody and Chimeric
Anti-AGE IgG1 Antibody

[0108] 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.

[0109] 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.

[0110] 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:

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

[0111] CE-SDS analysis was performed (LabChip GXII, Perkin Elmer) and the electropherograms were plotted.

Example 3: Binding of Murine (Parental) and Chimeric Anti-AGE Antibodies

[0112] 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.

[0113] The antigens were diluted to 1 μg/mL in 1× 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 1×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 1×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 1×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 1×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.

[0114] 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.

[0115] Plate map of CML and CML-KLH ELISA:

Conc. (μg/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	Parental	Chimeric		R&D	Parental	Chimeric
	Positive	Anti-	Anti-		Positive	Anti-	Anti-
	Control	AGE	AGE		Control	AGE	AGE
	CML-KLH Coat				CML Coat		

[0116] 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.

Conc. (μg/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	Parental	Chimeric				
	Positive	Anti-	Anti-				
	Control	AGE	AGE				

[0117] The OD450 absorbance data was also plotted against antibody concentration.

[0118] The control and chimeric anti-AGE antibodies showed binding to both CML and CML-KLH. The murine (parental) anti-AGE antibody showed very weak to no binding to either CML or CML-KLH. Data from repeated ELISA confirms binding of the control and chimeric anti-AGE to CML. All buffer control showed negative signal.

Example 4: Humanized Antibodies

[0119] 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.

[0120] 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 (Jul. 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:

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

[0121] 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.

[0122] 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).

[0123] 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:

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

[0124] The binding of the humanized antibodies may be evaluated, for example, by dose-dependent binding ELISA or cell-based binding assay.

Example 5: Immunohistochemical Study

[0125] 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.)

[0126] FIG. 2A is a photograph of cells of the Alzheimer's disease sample showing carboxymethyllysine stained gray and phosphorylated tau stained light gray (CML (red) Phospho TAU (green) Hippocampus AD).

[0127] FIG. 2B is a photograph of cells of the Alzheimer's disease sample showing carboxymethyllysine stained gray and amyloid precursor protein stained light gray (CML (red) Amyloid Precursor Protein (green) Hippocampus AD).

[0128] FIG. 2C is a photograph of cells of the Parkinson's disease sample from the substantia nigra showing carboxymethyllysine stained gray and alpha synuclein stained light gray (CML (red) Alpha Synuclein (green) Substantia Nigra PD).

[0129] FIG. 2D is a photograph of cells of the Parkinson's disease sample from the ventral tegmental area showing carboxymethyllysine stained gray and alpha synuclein stained light gray (CML (red) Alpha Synuclein (green) Ventral Tegmental Area PD).

[0130] 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 progeni-

tors 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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SEQUENCE LISTING

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SGVHTFPAPVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH 240
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EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSGDSF 420
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TLRKSEPSTR HTQPETQKPR IPVDTPLKEC QSHTHPPSIY LLHPPLQGLW LKGEATFTCL 180
VVGDDLKDAH LSWELSESRN GMFVESGPLE KHTNGSQSRS SRLALPRSSW AMGTSVTCKL 240
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 SKTSPSVFPL SLCHQESEGY VVIGCLVQGF FPPEPVNVTV NAGKDSTSVK NFPPMKAATG 60
 SLYTMSSQLT LPAAQCPDDS SVKQCVQHAS SPSKAVSVPC KDNSHPCHPC PSCNEPRLSL 120
 QKPALEDLLL GSNASLTCTL SGLKDPKGAT FTWNPSKGKE PIQKNPERDS CGCYSVSSVL 180
 PGCADPNHNG DTFSCATHP ESKSPITVSI TKTTEHIPPO VHLLPPPSEE LALNELVTLT 240
 CLVRGFKPKD VLVRLWQGTQ ELPQEKYLTW EPLKEPDQTN MFAVTSMLRV TAEDWKQGEK 300
 FSCMVGHEAL PMSFTQKTID RLAGKPTHVN VSVV 334

SEQ ID NO: 8 moltype = AA length = 426
 FEATURE Location/Qualifiers
 source 1..426
 mol_type = protein
 note = Canis familiaris (subspecies)
 organism = Canis sp.

SEQUENCE: 8
 TSQDLSVFPL ASCCKDNIA TSVTLGCLVT GYLPMTSTVT WDTGSLNKNV TTFPTTFHET 60
 YGLHSIVSQV TASGKWAKQR FTCVVAHAES TAINKTFSAC ALNFIPPTVK LFHSSCNVPG 120
 DTHTTIQLLC LISGYVPGDM EVIWLVDGQK ATNIFPYTAP GTEGNTVST HSELNITQGE 180
 WVSQKTYTQC VTYQGFTEKD EARKCESDP RGVTSYLSPP SPLDLYVHKA PKITCLVVDL 240
 ATMEGMNLTW YRESKEPVNP GPLNKKDHPN GTITVTSTLP VNTNDWIEGE TYICRVTHPH 300
 LPKDIVRSIA KAPGKRAPPD VYLFLPPEEE QGTKDRVTLT CLIQNFPPAD ISVQWLRNDS 360
 PIQTDQYTTT GPHKVSRSR AFFIFSRLEV SRVDWEQKNK FTCQVVEAL SGSRLQKWV 420
 SKTPGK 426

SEQ ID NO: 9 moltype = AA length = 335
 FEATURE Location/Qualifiers
 source 1..335
 mol_type = protein
 organism = Felis catus

SEQUENCE: 9
 ASTTASSVFP LAPSCGTSG ATVALACLVL GYFPEPVTVS WNSGALTSGV HTFPSVLQAS 60
 GLYLSMMVT VPSSRWLSDT FTCNVAHRPS STKVDKTVPK TASTIESKTG EGPCKPVPEI 120
 PGAPSVFIFP PKPKDTLSIS RTEVTCLVV DLGPDSDNVQ ITWFDVNTM HTAKTRPRE 180
 QFNSTYRVVS VLPILHQDWL KGKEFKCKVN SKSLPSAMER TISKAKGQPH EPQVYVLPPT 240
 QEELSENKVS VTCLIKGFHP PDIAVEWEIT GQPEPENNYQ TTPPQLSDSG TYFLYSRLSV 300
 DRSHWQRGNT YTCVSHEAL HSHHTQKSLT QSPGK 335

SEQ ID NO: 10 moltype = AA length = 96
 FEATURE Location/Qualifiers
 source 1..96
 mol_type = protein
 organism = Camelus dromedarius

SEQUENCE: 10
 EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYDMSWVRQA PGREREGVAA INSGGGSTYY 60
 ADSVKGRFTI SQDNAKNITV LQMSLKPED TAMYCC 96

SEQ ID NO: 11 moltype = AA length = 96
 FEATURE Location/Qualifiers
 source 1..96
 mol_type = protein
 organism = Camelus dromedarius

SEQUENCE: 11
 EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYWYWVRQA PGKGLEWVST INSGGGSTYY 60
 ADSVKGRFTI SRDNAKNMLY LQMSLKPED TAMYCC 96

SEQ ID NO: 12 moltype = DNA length = 1434
 FEATURE Location/Qualifiers
 misc_feature 1..1434
 note = Murine anti-AGE IgG2b heavy chain
 source 1..1434
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 12
 atggacccca agggcagcct gagctggaga atcctgctgt tcctgagcct ggccttcgag 60
 ctgagctacg gccaggtgca gctgctgcag ccaggtgccg agctcgtgaa acctggcgcc 120
 tctgtgaagc tggcctgcaa ggcttccggc tacctgttca ccactactg gatgcactgg 180
 ctgaagcaga ggcaggcca gggcctggaa tggatcgccg agatctcccc caccacagcc 240
 agagcctact acaacgccc gttcaagtcc gagggcacc tgaccgtgga caagtccctcc 300
 aacaccgcct acatgcaget gtcctccctg acctctgagg cctccgcctg gtactactgc 360
 gccagagctt acggcaacta cgaggtcgcc tactggggcc agggcaccct cgtgacagt 420
 tctgtggcta agaccacccc tcctccgtg taccctctgg ctctggtgct tggcgacacc 480
 accggtacct ctgtgacct gggctgacct gtgaaggcct acctccctga gtcctgacc 540
 gtgacctgga actccgctc cctgtcctcc tccgtgcaca ccttccagc cctgctgcag 600
 tccggcctgt acaccatgtc ctccagcgtg acagtgcct cctccacctg gccttcccag 660
 accgtgacat gctctgtggc ccaccctgcc tcttccacca ccgtggacaa gaagctggaa 720
 ccctccggcc ccatctccac catcaaccct tgccctccct gcaaagaatg ccacaagtgc 780

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cctgccccca acctggaagg cggcccttcc gtgttcacat tcccacccaa catcaaggac 840
gtgctgatga tctcctgac ccccaaagtg acctgcgtgg tgggtggacgt gtccgaggac 900
gaccttgacg tgcagatcag ttggttcgtg aacaacgtgg aagtgcacac cggccagacc 960
cagacacaca gagaggacta caacagcacc atcagagtgg tgtctaccct gcccatccag 1020
caccaggact ggatgtccgg caaagaattc aagtgcacaa tgaacaacaa ggacctgccc 1080
agcccatcag agcggaccat ctccaagatc aagggcctcg tgcgggctcc ccagggtgac 1140
attctgcctc caccagccga gcagctgtcc cggaaggatg tgtctctgac atgtctggtc 1200
gtgggcttca acccggcgga catctccgtg gaatggacct ccaacggcca caccaggaa 1260
aactacaagg acacggcccc tgtgtcggac tccgacggct cctacttcat ctactccaag 1320
ctgaacatga agacctccaa gtgggaaaag accgactcct tctcctgcaa cgtgcggcac 1380
gagggcctga agaaactacta cctgaagaaa accatctccc ggtcccccg ctag 1434

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SEQ ID NO: 13      moltype = DNA length = 1416
FEATURE            Location/Qualifiers
misc_feature        1..1416
                    note = Chimeric anti-AGE human IgG1 antibody heavy chain
source              1..1416
                    mol_type = other DNA
                    organism = synthetic construct

```

```

SEQUENCE: 13
atggacccca agggcagcct gagctggaga atcctgctgt tccctgagcct ggccttcgag 60
ctgagctacg gccaggtgca gctgctgcag ccaggtgccg agctcgtgaa acctggcgcc 120
tctgtgaagc tggcctgcaa ggcttcggcg tacctgttca ccacctactg gatgcactgg 180
ctgaagcaga ggccaggcca gggcctggaa tggatcggcg agatctcccc caccacggcg 240
agagcctact acaacgcccg gttcaagtcc gaggccacc tgaccgtgga caagtctccc 300
aacaccgctc acatgcagct gtctcctcg acctctgagg cctccgctgt gtactactgc 360
gccagagctt acggcaacta cgagttcgcc tactggggcc agggcaccct cgtgacagtg 420
tctgtggcta gcaccaaggg cccacgcgtg tccctcttgg cccccagcag caagagcacc 480
agcggcgga aacggcgccc gggctgctgt gtgaaggact acttccccga gcccgtagcc 540
gtgtcctgga acagcggcgc tctgaccagc ggagtgcaca ccttccctgc cgtgctgcag 600
agcagcgccc tgtactcctc gagcagcgtg gtgaccgtgc ccagcagcag cctgggcacc 660
cagacctaca tctgcaacgt gaaccacaag cctcccaaca ccaaggtgga caagaagggtg 720
gagcctaaga gctgcgacaa gacccacacc tgcctccctc gcccgcgccc cgagctgctg 780
ggcggaccca cgtgttctct gttccctccc aagcccaagg acacctgat gatcagccgc 840
accccggagg tgcactcgct ggtggtggac gtgagccacg aggaccccga ggtgaagttc 900
aactggtagc tggacggcgt ggaggtgcac aacgccaaga ccaagcctcg ggaggagcag 960
tacaactcca cctaccgctt ggtgagcgtg ctgaccgtgc tgcaccagga ctggctgaac 1020
ggcaaggagt acaagtgcac ggtgagcaac aaggccctgc ccgctcccat cgagaagacc 1080
atcagcaagg ccaagggcca gccccgggag cctcagggtg acacctgcc cccacgcccg 1140
gacgagctga ccaagaacca ggtgagcctg acctgcttgg tgaagggtct ctaccctccc 1200
gacatcgccc tggagtggga gagcaacggc cagcctgaga acaactacaa gaccacccct 1260
cccgctgttg acagcgacgg cagcttcttc ctgtacagca agctgacctg ggacaagtcc 1320
cgggtggcag agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac 1380
tacaccaga agagcctgag cctgagcccc ggatag 1416

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SEQ ID NO: 14      moltype = DNA length = 720
FEATURE            Location/Qualifiers
misc_feature        1..720
                    note = Murine anti-AGE Kappa light chain
source              1..720
                    mol_type = other DNA
                    organism = synthetic construct

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SEQUENCE: 14
atggagaccg acaccctgct gctctgggtg ctgctgtctt gggtgcccgg ctccaccgga 60
gacgtcgtga tgaccagac cctctgtgcc ctgctgtgtt ctctggcgga ccaggcctcc 120
atctcctgcc ggtctagaca gtccctcgtg aactccaacg gcaacacctt cctgcagtgg 180
tatctgcaga agcccgccca gtcccccagg ctgctgatct acaaggtgtc cctgcgggtc 240
tccggcgtgc ccgacagatt ttccgctctt ggctctggca ccgacttcac cctgaagatc 300
tccccgggtg aagccgagga cctgggctct tacttctgca gccagtccac ccacgtgccc 360
cctacatttg gcggaggcac caagctggaa atcaaacggg cagatgctgc accaactgta 420
tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480
ttgaacaact tctaccccaa agacatcaat gtcaagtggg agattgatgg cagtgaacga 540
caaaatggcg tcttgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600
agcagcacc ctcagttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660
gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgttga 720

```

```

SEQ ID NO: 15      moltype = DNA length = 720
FEATURE            Location/Qualifiers
misc_feature        1..720
                    note = Chimeric anti-AGE human kappa light chain
source              1..720
                    mol_type = other DNA
                    organism = synthetic construct

```

```

SEQUENCE: 15
atggagaccg acaccctgct gctctgggtg ctgctgtctt gggtgcccgg ctccaccgga 60
gacgtcgtga tgaccagac cctctgtgcc ctgctgtgtt ctctggcgga ccaggcctcc 120

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atctcctgcc ggtctagaca gtccctcgtg aactccaacg gcaacacctt cctgcagtgg 180
tatctgcaga agcccgccga gtcccccagg ctgctgatct acaagggtgc cctgcgggtc 240
tccggcgtgc ccgacagatt ttccggctct ggctctggca ccgacttcac cctgaagatc 300
tcccgggtgg aagccgagga cctgggctct tacttctgca gccagtccac ccacgtgccc 360
cctacatttg gcggaggcac caagctggaa atcaagcgga ccgtggcgcg cccagcgctg 420
ttcatcttcc ctcccagcga cgagcagctg aagctctggca ccgccagcgt ggtgtgacct 480
ctgaacaact tctacccccg cgaggccaag gtgcagtggg aggtggacaa cgccctgcag 540
agcggcaaca gccaggagag cgtgaccgag caggactcca aggacagcac ctacagcctg 600
agcagcacco tgaccctgag caaggccgac tacgagaagc acaagggtga cgccctgcag 660
gtgacccacc agggactgtc tagccccgtg accaagagct tcaaccgggg cgagtgcata 720

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SEQ ID NO: 16      moltype = AA length = 477
FEATURE           Location/Qualifiers
REGION            1..477
                  note = Murine anti-AGE IgG2b heavy chain
source            1..477
                  mol_type = protein
                  organism = synthetic construct

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SEQUENCE: 16
MDPKGSLSWR ILLFLSLAFE LSYGQVQLLQ PGAEVLKPGA SVKLACKASG YLFTTYWMHW 60
LKQRPQGGLG WIGEISPTNG RAYYNARFKS EATLTVDKSS NTAYMQLSSL TSEASAVYYC 120
ARAYGNIEFA YWGQGLTLTV SVAKTTPPSV YPLAPGCGDT TGSSVTLGCL VKGYFPESVT 180
VTWNSGSLSS SVHTFPALLQ SGLYTMSSSV TVPSSWPSQ TVTCSVAHPA SSTTVDKKLE 240
PSGPISITNP CPPCKECHKC PPNLEGGPS VFIPFPNIK VLMISLTPKV TCVVVDVSED 300
DDPVQISWVF NNVEVHTAQ TTHREDYNST IRVVSTLPIQ HQDWMSGKEF KCKVNNKDL 360
SPIERTISKI KGLVRAPQVY ILPPPAEQLS RKDVSLTCLV VGFNPGDISV EWTNNGHTEE 420
NYKDTAPVLD SDGSYFIYSK LNMKTSKWEK TDSFSCNVRH EGLKNYYLKK TIIRSPG 477

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SEQ ID NO: 17      moltype = AA length = 471
FEATURE           Location/Qualifiers
REGION            1..471
                  note = Chimeric anti-AGE human IgG1 heavy chain
source            1..471
                  mol_type = protein
                  organism = synthetic construct

```

```

SEQUENCE: 17
MDPKGSLSWR ILLFLSLAFE LSYGQVQLLQ PGAEVLKPGA SVKLACKASG YLFTTYWMHW 60
LKQRPQGGLG WIGEISPTNG RAYYNARFKS EATLTVDKSS NTAYMQLSSL TSEASAVYYC 120
ARAYGNIEFA YWGQGLTLTV SVASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT 180
VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTPVSSSLGT QTYICNVNHK PSNTKVDKKV 240
EPKSCDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF 300
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEK 360
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCVLKGFYPS DIAVEWESNG QPENNYKTP 420
PVLDSGDSFF LYSLTLVDKS RWQQGNVFSC SVMHEALHMH YTKQSLSLSP G 471

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SEQ ID NO: 18      moltype = AA length = 239
FEATURE           Location/Qualifiers
REGION            1..239
                  note = Murine anti-AGE kappa light chain
source            1..239
                  mol_type = protein
                  organism = synthetic construct

```

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SEQUENCE: 18
METDTLLLWV LLLWVPGSTG DVVMTQTPLS LPVSLGDQAS ISCRSRQSLV NSNGNTFLQW 60
YLQKPGQSPK LLIIKVSRLR SGVPDRFSGS GSGTDFTLKI SRVEAEDLGL YFCSQSTHVP 120
PTFGGGTKLE IKRADAAPT VIFPPSDEQL TSGGASVVCV LNNFYPKDIN VKWKIDGSE 180
QNGVLNSWTD QDSKDYSTYS SSSLTLTKDE YERHNSYTCE ATHKTSTSPI VKSFNRNEC 239

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SEQ ID NO: 19      moltype = AA length = 239
FEATURE           Location/Qualifiers
REGION            1..239
                  note = Chimeric anti-AGE human kappa light chain
source            1..239
                  mol_type = protein
                  organism = synthetic construct

```

```

SEQUENCE: 19
METDTLLLWV LLLWVPGSTG DVVMTQTPLS LPVSLGDQAS ISCRSRQSLV NSNGNTFLQW 60
YLQKPGQSPK LLIIKVSRLR SGVPDRFSGS GSGTDFTLKI SRVEAEDLGL YFCSQSTHVP 120
PTFGGGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCV LNNFYPREAK VQWKVDNALQ 180
SGNSQESVTE QDSKDYSTYS SSSLTLTKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 239

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```

SEQ ID NO: 20      moltype = AA length = 118
FEATURE           Location/Qualifiers
REGION            1..118
                  note = Murine anti-AGE IgG2b heavy chain (variable region)
source            1..118

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mol_type = protein
organism = synthetic construct

SEQUENCE: 20
QVQLQPGAE LVKPGASVKL ACKASGYLFT TYWMHWLKQR PGQGLEWIGE ISPTNGRAYY 60
NARFKSEATL TVDKSSNTAY MQLSSLTSEA SAVYYCARAY GNYEFAYWGQ GTLVTVSV 118

SEQ ID NO: 21 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = Murine anti-AGE kappa light chain (variable region)
source 1..112
mol_type = protein
organism = synthetic construct

SEQUENCE: 21
DVVMTQTPLS LPVSLGDQAS ISCRSRQSLV NSNGNTFLQW YLQKPGQSPK LLIYKVSLRF 60
SGVPRDRFSGS GSGTDFTLKI SRVEAEDLGL YFCSQSTHVP PTFGGGTKLE IK 112

SEQ ID NO: 22 moltype = AA length = 326
FEATURE Location/Qualifiers
REGION 1..326
note = Human constant region
source 1..326
mol_type = protein
organism = synthetic construct

SEQUENCE: 22
ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTPPAVLQSS 60
GLYSLSSVVT VPSSNFGTQT YTCNVDPKPS NTKVDKTVR KCCVECPPCP APPVAGPSVF 120
LPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR 180
VVSVLTVVHQ DWLNGKEYKC KVSNGKGLPAP IEKTISKTKG QPREPQVYTL PPSREEMTKN 240
QVSLTCLVKG FYPDSISVEW ESNGQPENNY KTTTPMLDSD GSFFLYSKLT VDKSRWQQGN 300
VFSCSVMEHA LHNHYTQKSL SLSPGK 326

SEQ ID NO: 23 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
note = CDR1H (heavy chain)
source 1..7
mol_type = protein
organism = synthetic construct

SEQUENCE: 23
SYTMGV 7

SEQ ID NO: 24 moltype = AA length = 17
FEATURE Location/Qualifiers
REGION 1..17
note = CDR2H (heavy chain)
source 1..17
mol_type = protein
organism = synthetic construct

SEQUENCE: 24
TISSGGGSTY YPDSVKG 17

SEQ ID NO: 25 moltype = AA length = 10
FEATURE Location/Qualifiers
REGION 1..10
note = CDR3H (heavy chain)
VAR_SEQ 10
note = misc_feature - Xaa can be any naturally occurring amino acid
source 1..10
mol_type = protein
organism = synthetic construct

SEQUENCE: 25
QGGWLPPFAX 10

SEQ ID NO: 26 moltype = AA length = 17
FEATURE Location/Qualifiers
REGION 1..17
note = CDR1L (light chain)
source 1..17
mol_type = protein
organism = synthetic construct

SEQUENCE: 26
RASKSVSTSS RGYSYMH 17

SEQ ID NO: 27 moltype = AA length = 7

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FEATURE	Location/Qualifiers	
REGION	1..7	
	note = CDR2L (light chain)	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 27		
LVSNNLES		7
SEQ ID NO: 28	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
REGION	1..9	
	note = CDR3L (light chain)	
source	1..9	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 28		
QHIRELTRS		9
SEQ ID NO: 29	moltype = AA length = 468	
FEATURE	Location/Qualifiers	
REGION	1..468	
	note = Humanized heavy chain	
source	1..468	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 29		
MDPKGSLSWR ILLFLSLAFE	LSYGQVQLVQ SGAEVKKPGA SVKVSCKASG YLFTTYWMHW	60
VRQAPGQGLE WMGEISPTNG	RAYYNQKFQG RVTMTVDKST NTVYMELSSL RSEDYAVYYC	120
ARAYGNFYAY WQQGTLVTVS	SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYPPEPVTY	180
SWNSGALTSG VHTFPAVLQS	SGLYSLSSVV TVPSSSLGTQ TYICNVNHPK SNTKVDKKVE	240
PKSCDKHTHC PPCPELLGG	PSVFLPPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW	300
YVDGVEVHNA KTKPREEQYN	STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS	360
KAKGQPREPQ VYTLPPSRDE	LKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTTPVL	420
DSDSGSFFLYS KLTVDKSRWQ	QGNVFSCSVM HEALHNHYTQ KSLSLSPG	468
SEQ ID NO: 30	moltype = DNA length = 1408	
FEATURE	Location/Qualifiers	
misc_feature	1..1408	
	note = Humanized heavy chain	
source	1..1408	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 30		
atggacccca agggcagcct	gagctggaga atcctgctgt	60
ctgagctacg gccaggtgca	gctgggtgcag tctggcgccg	120
tccgtgaggt tccctgcaag	gcttccggct acctgttcac	180
tgcgacagcg cccctggacag	ggcctggaat ggatgggcga	240
gagcctacta caacagaaat	tccagggcag agtgaccatg	300
caccgtgtac atggaactgt	cctccctgcg gagcgaggac	360
tagagcctac ggcaactacg	attcgccctac tggggccagg	420
tctgctagca ccaaggggccc	cagcgtgttc cctctggccc	480
ggcggaacgg ccgcccctggg	ctgcctggga aggactactt	540
cctggaacag cggcgctctg	accagcggag tgcacacctt	600
gcggcctgta ctccctgagc	agcgtgggtga ccgtgccagc	660
ctacatctgc aacgtgaacc	acaagccctc caacaccaag	720
taagagctgc gacaagaccc	acacctgccc tccctgcccc	780
cccagcgtgt tccgtgtccc	tcccaagccc aaggacaccc	840
gaggtgacct gcgtgggtgt	ggacgtgagc caccgaggac	900
acgtggacgg cgtggagggtg	cacaacgcca agaccaagcc	960
ccacctaccg cgtgtgacgg	tgctgcacca ggactggctg	1020
gtacaagtgc aaggtgagca	acaaggccct gcccgtctcc	1080
ggccaaggcg cagccccggg	agcctcaggt gtacacctcg	1140
gacaagaacc aggtgagcct	gacctgctcg gtgaagggct	1200
gtggagtggg agagcaacgg	ccagcctgag aacaactaca	1260
gacagcgacg cagcttcttc	ctgtacagca agctgaccgt	1320
agggcaacgt gttcagctgc	agcgtgatgc acgaggccct	1380
agagcctgag cctgagcccc	gatagtaa	1408
SEQ ID NO: 31	moltype = AA length = 468	
FEATURE	Location/Qualifiers	
REGION	1..468	
	note = Humanized heavy chain	
source	1..468	
	mol_type = protein	
	organism = synthetic construct	

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SEQUENCE: 31

MDPKGSLSWR	ILLFLSLAFE	LSYGQVQLVQ	SGAEVKKPGA	SVKVSCKASG	YLFTTYWMHW	60
VRQAPGQGLE	WMGEISPTNG	RAYYNAKFQG	RVTMTVDKST	NTAYMELSSL	RSEDTAVYYC	120
ARAYGNYPAY	WGQGLTVTVS	SASTKGPSVF	PLAPSSKSTS	GGTAALGCLV	KDYFPEPVTV	180
SWNSGALTSG	VHTFPAVLQS	SGLYSLSSVV	TVPSSSLGTQ	TYICNVNHKP	SNTKVDKKVE	240
PKSCDKTHTC	PPCPPELLGG	PSVFLFPPKP	KDTLMISRTP	EVTCTVVVDVS	HEDPEVKFNW	300
YVDGVEVHNA	KTKPREEQYN	STYRVVSVLT	VLHQDWLNGK	EYCKKVSNKA	LPAPIEKTIS	360
KAKGQPREPQ	VYTLPPSRDE	LKNQVSLTCL	VKGFPSPDIA	VEWESNGQPE	NNYKTTTPVL	420
DSGGSFFLYS	KLTVDKSRWQ	QGNVFSQSV	HEALHNHYTQ	KSLSLSPG		468

SEQ ID NO: 32 moltype = DNA length = 1408
 FEATURE Location/Qualifiers
 misc_feature 1..1408
 note = Humanized heavy chain
 source 1..1408
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 32

atggacccca	agggcagcct	gagctggaga	atcctgctgt	tcctgagcct	ggccttcgag	60
ctgagctacg	gccaggtgca	gctgggtgag	tctggcgccg	aagtgaagaa	acctggcgcc	120
tcctgtaggt	gtcctgcaag	gcttcgggct	acctgttcac	cacctactgg	atgcaactgg	180
tgcgacaggc	ccctggacag	ggcctggaat	ggatggggca	gatctccctt	accaacggca	240
gagcctacta	caacccaaat	tccagggcag	agtgaccatg	accgtggaca	agtccaccaa	300
caccgcttac	atggaactgt	cctccctgag	gagcgaggac	accgcccgtg	actactgcgc	360
tagagcctac	ggcaactacg	attcgccctac	tggggccagg	gcaccctcgt	gacagtgtcc	420
tctgctagca	ccaagggccc	cagcgtgttc	cctctggccc	ccagcagcaa	gagcaccagc	480
ggcggaaccg	ccgcccctgg	ctgcctggga	aggactactt	ccccgagccc	gtgaccgtgt	540
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gcggcctgta	ctccctgagc	agcgtgggtg	ccgtgcccag	agcagcctgg	gcaccagagc	660
ctacatctgc	aacgtgaacc	acaagccctc	caacaccaag	gtggacaaga	aggtggagcc	720
taagagctgc	gacaagaccc	acacctgccc	tcctgtcccc	gccccgagct	gctggggcga	780
cccagcgtgt	tcctgttccc	tcccaagccc	aaggacaccc	tgatgatcag	ccgcaccccc	840
gaggtgacct	gcgtgggtgt	ggacgtgagc	cacgaggacc	ccgaggtgag	ttcaactggt	900
acgtggacgg	cgtggaggtg	cacaacgcca	agaccaagcc	tcgggaggag	cagtacaact	960
ccactacacg	gcgtggtagc	gtgctgaccc	tgctgcacca	ggactggctg	aacggcagga	1020
gtacaagtgc	aaggtgagca	acaagccctt	gcccgcctcc	atcgagaaga	ccatcagcaa	1080
ggccaaaggg	cagccccggg	agcctcaggt	gtacaccctg	ccccccagcc	gcgacgagct	1140
gacaagaacc	aggtgagcct	gacctgcctg	gtgaagggct	tctacccttc	cgacatgcgc	1200
gtggagtggt	agagcaacgg	ccagcctgag	aacaactaca	agaccacccc	tcccgtgctg	1260
gacagcgacg	cagctctctt	ctgtacagca	agctgaccgt	ggacaagtcc	cggtggcagc	1320
agggcaacgt	gttcagctgc	agcgtgatgc	acgaggccct	gcacaaccac	tacaccacga	1380
agagcctgag	cctgagcccc	gatagtaa				1408

SEQ ID NO: 33 moltype = AA length = 468
 FEATURE Location/Qualifiers
 REGION 1..468
 note = Humanized heavy chain
 source 1..468
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 33

MDPKGSLSWR	ILLFLSLAFE	LSYGQVQLVQ	SGAEVKKPGA	SVKVSCKASG	YLFTTYWMHW	60
VRQAPGQGLE	WMGEISPTNG	RAYYNAKFQG	RVTMTVDKSI	NTAYMELSSL	RSDDTAVYYC	120
ARAYGNYPAY	WGQGLTVTVS	SASTKGPSVF	PLAPSSKSTS	GGTAALGCLV	KDYFPEPVTV	180
SWNSGALTSG	VHTFPAVLQS	SGLYSLSSVV	TVPSSSLGTQ	TYICNVNHKP	SNTKVDKKVE	240
PKSCDKTHTC	PPCPPELLGG	PSVFLFPPKP	KDTLMISRTP	EVTCTVVVDVS	HEDPEVKFNW	300
YVDGVEVHNA	KTKPREEQYN	STYRVVSVLT	VLHQDWLNGK	EYCKKVSNKA	LPAPIEKTIS	360
KAKGQPREPQ	VYTLPPSRDE	LKNQVSLTCL	VKGFPSPDIA	VEWESNGQPE	NNYKTTTPVL	420
DSGGSFFLYS	KLTVDKSRWQ	QGNVFSQSV	HEALHNHYTQ	KSLSLSPG		468

SEQ ID NO: 34 moltype = DNA length = 1408
 FEATURE Location/Qualifiers
 misc_feature 1..1408
 note = Humanized heavy chain
 source 1..1408
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 34

atggacccca	agggcagcct	gagctggaga	atcctgctgt	tcctgagcct	ggccttcgag	60
ctgagctacg	gccaggtgca	gctgggtgag	tctggcgccg	aagtgaagaa	acctggcgcc	120
tcctgtaggt	gtcctgcaag	gcttcgggct	acctgttcac	cacctactgg	atgcaactgg	180
tgcgacaggc	ccctggacag	ggcctggaat	ggatggggca	gatctccctt	accaacggca	240
gagcctacta	caacccaaat	tccagggcag	agtgaccatg	accgtggaca	agtccaccaa	300
caccgcttac	atggaactgt	ccagactgag	gagcgatgac	accgcccgtg	actactgcgc	360
tagagcctac	ggcaactacg	attcgccctac	tggggccagg	gcaccctcgt	gacagtgtcc	420
tctgctagca	ccaagggccc	cagcgtgttc	cctctggccc	ccagcagcaa	gagcaccagc	480

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ggcggaaccg cgcgcctggg ctgcctggga aggactactt ccccgagccc gtgaccgtgt 540
cctggaacag cggcgctctg accagcggag tgcacacctt ccttgccgtg ctgcagagca 600
gcggcctgta ctcctcgagc agcgtgggtga ccggtgccagc agcagcctgg gcaccagac 660
ctacatctgc aacgtgaacc acaagccctc caacaccaag gtggacaaga aggtggagcc 720
taagagctgc gacaagaccc acacctgccc tccttgcccc gcccgagct gctgggcgga 780
cccagcgtgt tcctgttccc tcccaagccc aaggacaccc tgatgatcag ccgcaccccc 840
gaggtgacct gcgtgggtgt ggacgtgagc cagcaggacc ccgaggtgag ttcaactggt 900
acgtggacgg cgtggaggtg cacaacgcca agaccaagcc tcgggaggag cagtacaact 960
ccacctaccg cgtggtgagc gtgctgaccg tgctgcacca ggactggctg aacggcagga 1020
gtacaagtgc aaggtgagca acaagccctt gcccgctccc atcgagaaga ccatcagcaa 1080
ggccaagggc cagccccggg agcctcaggt gtacaccttg ccccccagcc gcgacgagct 1140
gacaagaacc aggtgagcct gacctgcctg gtgaagggct tctaccttc cgacatcgcc 1200
gtggagtggg agagcaacgg cagcctgag aacaactaca agaccacccc tcccgctgtg 1260
gacagcgacg cagcttcttc ctgtacagca agctgaccgt ggacaagtcc cgtgtggcagc 1320
agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac tacaccagaa 1380
agagcctgag cctgagcccc gatagtaa 1408

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SEQ ID NO: 35      moltype = AA length = 238
FEATURE           Location/Qualifiers
REGION            1..238
                  note = Humanized light chain
source            1..238
                  mol_type = protein
                  organism = synthetic construct

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SEQUENCE: 35
METDTLLLVV LLLWVPGSTG DVVMTQSPLS LPVTLGQPAS ISCRSSQSLV NSNGNTFLOW 60
YQORPGQSPR LLIYKVSRLR SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHVP 120
PTFGGGTVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFPYPREAKV QWKVDNALQS 180
GNSQESVTEQ DSKDSTYSLT STLTLKADY EKHKVYACEV THQGLSSPVT KSFNRGEC 238

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SEQ ID NO: 36      moltype = DNA length = 715
FEATURE           Location/Qualifiers
misc_feature       1..715
                  note = Humanized light chain
source            1..715
                  mol_type = other DNA
                  organism = synthetic construct

```

```

SEQUENCE: 36
atggagaccg acaccctgct gctctgggtg ctgctgctct gggtgcccgg ctccaccgga 60
gacgtcgtga tgaccagtc cctctgtgct ctgctgtgta ccctgggaca gctgctctcc 120
atctcctcag atctctccag tcctctgtga actccaacgg caacaccttc ctgcagtggt 180
atcagcagcg gcctggccag agccccagac tgctgatcta caaggtgtcc ctgcggttct 240
ccggcgtgcc cgacgatttt ccggctctgg ctctggcacc gacttcaccc tgaagatctc 300
ccgggtggaa gccgaggacg tgggctgtga ctactgctcc cagagcaccc acgtgcccc 360
tacatttggc ggaggcacca agtggaaatc aagcggaccg tggccgcccc cagcgtgttc 420
atcttccctc ccagcgacga gcaagctgaag tctggcaccg ccagcgtggt gtgctgctg 480
aacaacttct acccccgcga ggccaagggc agtggaaagg ggacaacgcc ctgcagagcg 540
gcaacagcca ggagagcgtg accgagcagg actccaagga cagcacctac agcctgagca 600
gcaccctgac cctgagcaag ccgagctacg agaagacaag gtgtacgctt gcgaggtgac 660
ccaccagggg ctgtctagcc ccgtgaccaa gagcttcaac cggggcgagt gctaa 715

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SEQ ID NO: 37      moltype = AA length = 238
FEATURE           Location/Qualifiers
REGION            1..238
                  note = Humanized light chain
source            1..238
                  mol_type = protein
                  organism = synthetic construct

```

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SEQUENCE: 37
METDTLLLVV LLLWVPGSTG DVVMTQSPLS LPVTLGQPAS ISCRSRQSLV NSNGNTFLQW 60
YQORPGQSPR LLIYKVSRLR SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHVP 120
PTFGGGTVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFPYPREAKV QWKVDNALQS 180
GNSQESVTEQ DSKDSTYSLT STLTLKADY EKHKVYACEV THQGLSSPVT KSFNRGEC 238

```

```

SEQ ID NO: 38      moltype = DNA length = 715
FEATURE           Location/Qualifiers
misc_feature       1..715
                  note = Humanized light chain
source            1..715
                  mol_type = other DNA
                  organism = synthetic construct

```

```

SEQUENCE: 38
atggagaccg acaccctgct gctctgggtg ctgctgctct gggtgcccgg ctccaccgga 60
gacgtcgtga tgaccagtc cctctgtgct ctgctgtgta ccctgggaca gctgctctcc 120
atctcctcag atccagcgag tcctctgtga actccaacgg caacaccttc ctgcagtggt 180
atcagcagcg gcctggccag agccccagac tgctgatcta caaggtgtcc ctgcggttct 240

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ccggcgtgcc cgaacgatttt ccggetcttg ctctggcacc gacttcaccc tgaagatctc 300
ccgggtggaa gccgaggacg tgggcgtgta ctactgctcc cagagcaccc acgtgcccc 360
tacatttgcc ggaggcacca agtggaaatc aagcggaccg tggccgcccc cagcgtgttc 420
atcttccttc ccagcgacga gcagctgaag tctggcaccg ccagcgtggt gtgcctgctg 480
aacaacttct acccccgca ggccaagggc agtggaaagt ggacaacgcc ctgcagagcg 540
gcaacagcca ggagagcgtg accgagcagg actccaagga cagcacctac agcctgagca 600
gcaccctgac cctgagcaag gccgactacg agaagacaag gtgtacgctc gcgaggtgac 660
ccaccaggga ctgtctagcc ccgtgaccaa gagcttcaac cggggcgagt gctaa 715

```

```

SEQ ID NO: 39      moltype = AA length = 238
FEATURE           Location/Qualifiers
REGION            1..238
                  note = Humanized light chain
source            1..238
                  mol_type = protein
                  organism = synthetic construct

```

```

SEQUENCE: 39
METDTLLLWV LLLWVPSTG DVVMTQSPLS SPVTLGQPAS ISCRSSQSLV NSNGNTFLQW 60
YHQRPGQPPR LLIYKVLRF SGVPDRFSGS GAGKDFTLKI SRVEAEDVGV YYCSQSTHVP 120
PTFGQGTLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFPYPREAKV QWKVDNALQS 180
GNSQESVTEQ DSKDSTYSLs STLTLKADY EKHKVYACEV THQGLSSPVT KSFNRGEC 238

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```

SEQ ID NO: 40      moltype = DNA length = 715
FEATURE           Location/Qualifiers
misc_feature       1..715
                  note = Humanized light chain
source            1..715
                  mol_type = other DNA
                  organism = synthetic construct

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SEQUENCE: 40
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atcaccagcg gctctggccag cctccagac tgctgatcta caagtggtcc ctgcggttct 240
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ccgggtggaa gccgaggacg tgggcgtgta ctactgctcc cagagcaccc acgtgcccc 360
tacatttgcc cagggcacca actggaaatc aagcggaccg tggccgcccc cagcgtgttc 420
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gcaacagcca ggagagcgtg accgagcagg actccaagga cagcacctac agcctgagca 600
gcaccctgac cctgagcaag gccgactacg agaagacaag gtgtacgctc gcgaggtgac 660
ccaccaggga ctgtctagcc ccgtgaccaa gagcttcaac cggggcgagt gctaa 715

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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, senescent myoblasts and/or senescent myosatellite cells, comprising administering to a subject a composition comprising an AGE antibody.

3. (canceled)

4. The method of claim 1, further comprising:

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. The method of claim 1, wherein the AGE antibody binds to and kills or induces 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 claim 1, wherein the composition further comprises a pharmaceutically acceptable carrier.

8. The method of claim 1, wherein the subject is selected from the group consisting of humans, mice, rats, goats, sheep, cows, horses, dogs and cats.

9. (canceled)

10. The method of claim 1, 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 of claim 1, wherein the AGE antibody binds an AGE antigen comprising 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 of claim 1, wherein the AGE antibody binds a carboxymethyllysine-modified protein.

13-20. (canceled)

21. The method of claim 1, wherein the composition further comprises:

(i) a pharmaceutically acceptable carrier,

(ii) serum, and

(iii) natural killer cells.

22. The method of claim 1, wherein the subject has a neurodegenerative disorder selected from the group consisting of AD, PD, Lewy body dementia, MS, prion diseases and ALS.

23. (canceled)

24. The method of claim 1, wherein the administering comprises administering the composition to the central nervous system of the subject.

25. (canceled)

26. The method of claim 1, wherein the subject has ALS or MD and the administering comprises administering the composition to muscles of the subject.

27-30. (canceled)

31. The composition of claim 6, wherein the composition comprises the serum and the immune system cells.

32-34. (canceled)

35. The method of claim 1, wherein the AGE antibody is a single domain antibody conjugated to an agent that causes the destruction of cells.

36. The method of claim 1, wherein the neurodegenerative disorder comprises Alzheimer's disease or Parkinson's disease.

37. The method of claim 5, wherein the neurodegenerative disorder comprises Alzheimer's disease or Parkinson's disease.

38. The method of claim 2, wherein the AGE antibody binds a carboxymethyllysine-modified protein.

39. The composition of claim 6, wherein the AGE antibody binds a carboxymethyllysine-modified protein.

* * * * *