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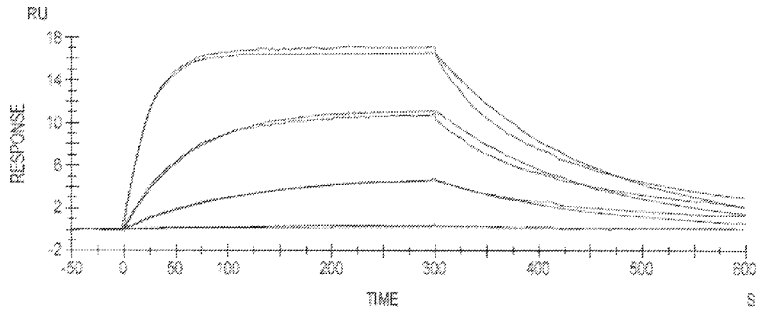

FIG. 1

(57) Abstract: An anti-AGE antibody comprises a protein or peptide that comprises at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with specific amino acid sequences. The anti-AGE antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification. The anti-AGE antibody may be used for killing senescent cells, killing partially-functional or non-functional cells, treating sarcopenia, promoting tissue or organ regeneration, promoting regenerative processes or overcoming aging effects, treating atherosclerosis, preventing or delaying the onset of cataracts, preventing or delaying the onset of loss of adipose tissue, increasing health span, preventing or delaying the onset of lordokyphosis, treating inflammation or autoimmune disorders, treating neurodegenerative disorders or treating cancer.

ANTI-AGE ANTIBODIES AND METHODS OF USE THEREOF

BACKGROUND

[01] Sarcopenia is the loss of muscle mass, quality and strength associated with aging. Humans begin to lose muscle mass and function at some point in the third decade of life. This loss of muscle mass typically accelerates around age 75. Sarcopenia develops in both physically active and physically inactive people. As the average human lifespan continues to increase, sarcopenia is becoming a significant health concern. The loss of muscle mass from sarcopenia may lead to poor balance, reduced gait speed and frailty. Individuals suffering from sarcopenia are more susceptible to injury and disability, and may be unable to live independently as a result. The spread of sarcopenia will likely result in increases in health care and assisted living expenses.

[02] Sarcopenia has been considered to be an inevitable result of aging and the natural deterioration of the body over time. The primary treatment for sarcopenia is exercise. Physical exercise, particularly resistance training or strength training, can reduce the impact of sarcopenia. Testosterone, anabolic steroids, ghrelin, vitamin D, angiotensin converting enzyme inhibitors (ACE inhibitors), eicosapentaenoic acid (EPA), myostatin, selective androgen receptor modulators (SARMs), urocortin II (Ucn2) and hormone replacement therapy have been investigated or are being studied as potential treatments for sarcopenia. Despite this research, there are currently no U.S. Food and Drug Administration (FDA)-approved agents for treating sarcopenia.

[03] 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).

[04] 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.

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

their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept," Cardiovasc Res, Vol. 37(3), 586-600 (1998)).

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

[07] Cellular senescence and the accumulation of AGEs have been implicated in a number of diseases and disorders in addition to sarcopenia and age-related disorders. Senescence of cells in the central nervous system such as glial cells, astrocytes and microglial cells has been associated with neurodegenerative disorders. Abnormal accumulation of senescent astrocytes has been associated with Alzheimer's disease (AD) (Bhat, R. *et al.*, "Astrocyte Senescence as a Component of Alzheimer's Disease", *PLOS ONE*, Vol. 7(9), e45069, pp. 1-10 (Sept. 2012)). Microglial cell senescence associated with normal aging is exacerbated by the presence of the amyloid plaques indicative of AD (Flanary, B. E. *et al.*, "Evidence That Aging And Amyloid Promote Microglial Cell Senescence", *Rejuvenation Research*, Vol. 10(1), pp. 61-74 (March

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

[08] Some neurodegenerative disorders are 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).

[09] Neurodegenerative disorders are also associated with abnormal protein accumulations (King, O.D., *et al.*, "The tip of the iceberg: RNA-binding proteins with prion-like domains in neurodegenerative disease" *Brain Res.* Vol.1462, pp. 61–80 (2012)). A characteristic of PD and Lewy body dementia is the formation of Lewy bodies that form inside nerve cells. The primary structural component of the Lewy bodies is alpha-synuclein protein, in the form of fibrils. The presence of tangles and plaques are a characteristic of AD, the presence of which is used to definitively diagnose the condition. Plaques, composed of beta-amyloid protein (also referred to as amyloid beta, Aβ or Abeta), accumulate between nerve cells. Tangles, composed of tau protein, form twisted fibers within cells. Prion diseases (also known as transmissible spongiform encephalopathies (TSEs)), include a variety of human and animal disorder such as Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, bovine spongiform encephalopathy ("mad cow" disease), scrapie (in sheep and goats), chronic wasting disease (in deer and elk), kuru and fatal familial insomnia. Prion protein is a misfolded protein molecule which may propagate by transmitting a misfolded protein state, resulting in the accumulation of the misfolded protein and causing tissue damage and cell death (Dobson, D.M., "The structural basis of protein folding and its links with human disease" *Phil. Trans. R. Soc. Lond.* B, Vol. 356, pp. 133-145 (2001)). In these diseases, it is believed the protein is a normal protein which misfolds or forms an abnormal aggregate. In the case of some patients with familial ALS, a mutated superoxide dismutase-1 (SOD1) forms inclusions and accumulates (Kato, S., *et al.* "Advanced glycation endproduct-modified superoxide dismutase-1 (SOD1)-positive inclusions are common to familial amyotrophic lateral sclerosis patients with SOD1 gene

mutations and transgenic mice expressing human SOD1 with a G85R mutation" *Acta Neuropathol*, Vol. 100, pp. 490-505 (2000)).

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

SUMMARY

[11] In a first aspect, the present invention is an anti-AGE antibody, comprising a protein or peptide comprising at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, and SEQ ID NO: 39. The antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

[12] In a second aspect, the present invention is an anti-AGE antibody, comprising a protein or peptide comprising at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID

NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28. The antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

[13] In a third aspect, the present invention is an anti-AGE antibody comprising a heavy chain and a light chain. The heavy chain comprises an amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 17, SEQ ID NO: 29, SEQ ID NO: 31, and SEQ ID NO: 33, or the light chain comprises an amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 19, SEQ ID NO: 35, SEQ ID NO: 37, and SEQ ID NO: 39. The antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

[14] In a fourth aspect, the present invention is an anti-AGE antibody comprising a heavy chain and a light chain. The heavy chain comprises an amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 17, SEQ ID NO: 29, SEQ ID NO: 31, and SEQ ID NO: 33, and the light chain comprises an amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 19, SEQ ID NO: 35, SEQ ID NO: 37, and SEQ ID NO: 39. The antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

[15] In a fifth aspect, the present invention is an anti-AGE antibody, comprising complementary determining region comprising at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from

the group consisting of SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28. The antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification. The antibody is substantially non-immunogenic to a species selected from the group consisting of mice, rats, goats, sheep, cows, horses, dogs and cats.

[16] In a sixth aspect, the present invention is an antibody conjugate, comprising an anti-AGE antibody fragment comprising a protein or peptide comprising at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, and SEQ ID NO: 39, and an agent that causes the destruction of AGE-modified cells. The agent that causes the destruction of AGE-modified cells is conjugated to the anti-AGE antibody fragment. The antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

[17] **DEFINITIONS**

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

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

[20] The term "sarcopenia" means the syndrome characterized by the presence of (1) low muscle mass and (2) low muscle function (low muscle strength or reduced physical performance). Muscle mass may be measured by body imaging techniques, such as computed tomography scanning (CT scan), magnetic resonance imaging (MRI) or dual energy X-ray absorptiometry (DXA or DEXA); bioimpedance analysis (BIA); body potassium measurement, such as total body potassium (TBK) or partial body potassium (PBK); or anthropometric measurements, such as mid-upper arm circumference, skin fold thickness or calf circumference. Preferably, muscle mass is measured by CT scan,

MRI or DXA. Muscle strength may be measured by handgrip strength, knee flexion/extension or peak expiratory flow. Preferably, muscle strength is measured by handgrip strength. Physical performance may be measured by the Short Physical Performance Battery, gait speed measurement, timed get-up-and-go (TGUG) or the stair climb power test. Preferably, physical performance is measured by gait speed measurement. A subject may be identified as having sarcopenia or in need of treatment if (1) the subject is at least 25 years old and (2) his or her measured muscle mass and measured muscle function are two standard deviations or more below the mean value for healthy 25 year olds of the same gender and no alternative pathology has been identified to account for the reduced muscle mass and reduced muscle function. Preferably, a subject being treated for sarcopenia is at least 40 years old. More preferably, a subject being treated for sarcopenia is at least 50 years old. Most preferably, a subject being treated for sarcopenia is at least 60 years old. Alternatively, a subject may be identified as having sarcopenia or in need of treatment if (1) his or her gait speed is less than 1.0 m/s across a 4 m course and (2) he or she has an objectively measured low muscle mass, such as, for example, an appendicular mass relative to the square of height less than or equal to 7.23 kg/m^2 for male subjects or less than or equal to 5.67 kg/m^2 for female subjects (Fielding, R. A., *et al.*, "Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences", *Journal of the American Medical Directors Association*, Vol. 12(4), pp. 249-256 (May 2011).

[21] The term "neurodegenerative disorder" means disorders which result in neurons loosing function and/or dying, in the central nervous system including the brain. Such disorders included central nervous system neurodegenerative disorders such as AD, PD, Lewy body dementia, MS, prion diseases (also known as transmissible spongiform encephalopathies (TSEs), including Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, bovine spongiform encephalopathy ("mad cow" disease), scrapie (in sheep and goats), chronic wasting disease (in deer and elk), kuru and fatal familial insomnia), and ALS.

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

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

[24] "An antibody that binds to an AGE-modified protein on a cell", "anti-AGE antibody" or "AGE antibody" means an antibody, antibody fragment or other protein or peptide that binds to an AGE-modified protein or peptide which preferably 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.

[25] 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 senescence-associated 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.

[26] The term "increasing health span" means reducing age-related phenotypes. Age-related phenotypes include, for example, sarcopenia, cataracts, loss of adipose tissue and lordokyphosis.

[27] 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.

[28] 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.

[29] 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

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

DETAILED DESCRIPTION

[31] The identification of a link between cellular senescence and sarcopenia allows for new treatment possibilities. For example, if anti-AGE antibodies are administered to a subject, the antibodies will specifically and selectively target senescent cells, and kill or induce apoptosis in such cells expressing an AGE-modified protein or peptide.

[32] The present invention makes use of the discovery that enhanced clearance of cells expressing AGE-modified proteins or peptides (AGE-modified cells) is beneficial in treating or ameliorating sarcopenia. This may be accomplished by administering anti-AGE antibodies to a subject.

[33] Administering anti-AGE antibodies to a subject may also be used for increasing health span. Health span may be increased by reducing age-related phenotypes. Administering anti-AGE antibodies may be used, for example, to prevent or delay the onset of cataracts, lordokyphosis or loss of adipose tissue.

[34] Other diseases or disorders that are associated with cellular senescence may also be treated or ameliorated with anti-AGE antibodies. For example, anti-AGE antibodies may be used therapeutically to treat neurodegenerative disorders or cancer.

[35] An antibody that binds to an AGE-modified protein on a cell ("anti-AGE antibody" or "AGE antibody") is known in the art. Examples include those described in U.S. 5,702,704 (Bucala) and U.S. 6,380,165 (Al-Abed *et al.*). Examples include an antibody that binds to one or more AGE-modified proteins having an AGE modification such as

FFI, pyrraline, AFGP, ALI, carboxymethyllysine, carboxyethyllysine and pentosidine, and mixtures of such antibodies. Preferably, the antibody binds carboxymethyllysine-modified proteins. Preferably, the antibody is non-immunogenic to the animal in which it will be used, such as non-immunogenic to humans; companion animals including cats, dogs and horses; and commercially important animals, such camels (or alpaca), cattle (bovine), sheep, and goats. More preferably, the antibody has the same species constant region as antibodies of the animal to reduce the immune response against the antibody, such as being humanized (for humans), felinized (for cats), caninized (for dogs), equuinized (for horses), camelized (for camels or alpaca), bovinized (for cattle), ovinized (for sheep), or caperized (for goats). Most preferably, the antibody is identical to that of the animal in which it will be used (except for the variable region), such as a human antibody, a cat antibody, a dog antibody, a horse antibody, a camel antibody, a bovine antibody, a sheep antibody or a goat antibody. Details of the constant regions and other parts of antibodies for these animals are described below. Preferably, the antibody is a monoclonal antibody.

[36] A particularly preferred anti-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.

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

[38] 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.

[39] The anti-AGE antibody may be conjugated to an agent that causes the destruction of AGE-modified cells. Such agents may be a toxin, a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

[40] A toxin, such as pore-forming toxins (PFT) (Aroian R. *et al.*, "Pore-Forming Toxins and Cellular Non-Immune Defenses (CNIDs)," *Current Opinion in Microbiology*, 10:57-61 (2007)), conjugated to an anti-AGE antibody may be injected into a patient to selectively target and remove AGE-modified cells. The anti-AGE antibody recognizes

and binds to AGE-modified cells. Then, the toxin causes pore formation at the cell surface and subsequent cell removal through osmotic lysis.

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

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

[43] 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.

[44] 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).

[45] The heavy chain of human (*Homo sapiens*) antibody immunoglobulin G1 may have or may include the protein sequence of SEQ ID NO: 1. The variable domain of the heavy chain may have or may include the protein sequence of SEQ ID NO: 2. The complementarity determining regions of the variable domain of the heavy chain (SEQ ID NO: 2) are shown in SEQ ID NO: 41, SEQ ID NO: 42 and SEQ ID NO: 43. The kappa light chain of human (*Homo sapiens*) antibody immunoglobulin G1 may have or may include the protein sequence of SEQ ID NO: 3. The variable domain of the kappa light chain may have or may include the protein sequence of SEQ ID NO: 4. Optionally, the arginine (Arg or R) residue at position 128 of SEQ ID NO: 4 may be omitted. The complementarity determining regions of the variable domain of the light chain (SEQ ID NO: 4) are shown in SEQ ID NO: 44, SEQ ID NO: 45 and SEQ ID NO: 46. The variable regions may be codon-optimized, synthesized and cloned into expression vectors containing human immunoglobulin G1 constant regions. In addition, the variable regions may be used in the humanization of non-human antibodies.

[46] 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.

[47] 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.

[48] 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).

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

[50] 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.

[51] 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).

[52] 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.

[53] 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.

[54] 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).

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

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

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

[58] Antibody fragments may be used in place of whole antibodies. For example, immunoglobulin G may be broken down into smaller fragments by digestion with enzymes. Papain digestion cleaves the N-terminal side of inter-heavy chain disulfide bridges to produce Fab fragments. Fab fragments include the light chain and one of the two N-terminal domains of the heavy chain (also known as the Fd fragment). Pepsin digestion cleaves the C-terminal side of the inter-heavy chain disulfide bridges to produce $F(ab')_2$ fragments. $F(ab')_2$ fragments include both light chains and the two N-terminal domains linked by disulfide bridges. Pepsin digestion may also form the Fv (fragment variable) and Fc (fragment crystallizable) fragments. The Fv fragment contains the two N-terminal variable domains. The Fc fragment contains the domains which interact with immunoglobulin receptors on cells and with the initial elements of the complement cascade. Pepsin may also cleave immunoglobulin G before the third constant domain of the heavy chain (C_H3) to produce a large fragment F(abc) and a small fragment pFc'. Antibody fragments may alternatively be produced recombinantly.

[59] If additional antibodies are desired, they can be produced using well-known methods. For example, polyclonal antibodies (pAbs) can be raised in a mammalian host by one or more injections of an immunogen, and if desired, an adjuvant. Typically, the immunogen (and adjuvant) is injected in a mammal by a subcutaneous or intraperitoneal injection. The immunogen may be an AGE-modified protein of a cell, such as AGE-antithrombin III, AGE-calmodulin, AGE-insulin, AGE-ceruloplasmin, AGE-collagen, AGE-cathepsin B, AGE-albumin, AGE-crystallin, AGE-plasminogen activator, AGE-endothelial plasma membrane protein, AGE-aldehyde reductase, AGE-transferrin, AGE-fibrin, AGE-copper/zinc SOD, AGE-apo B, AGE-fibronectin, AGE-pancreatic ribose, AGE-apo A-I and II, AGE-hemoglobin, AGE-Na^+/K^+-ATPase, AGE-plasminogen, AGE-myelin, AGE-lysozyme, AGE-immunoglobulin, AGE-red cell Glu transport protein, AGE-β-N-acetyl hexominase, AGE-apo E, AGE-red cell membrane protein, AGE-aldose reductase, AGE-ferritin, AGE-red cell spectrin, AGE-alcohol dehydrogenase, AGE-haptoglobin, AGE-tubulin, AGE-thyroid hormone, AGE-fibrinogen, AGE-β_2-microglobulin, AGE-sorbitol dehydrogenase, AGE-α_1-antitrypsin, AGE-carbonate dehydratase, AGE-RNAse, AGE-low density lipoprotein, AGE-hexokinase, AGE-apo C-I, AGE-RNAse, AGE-hemoglobin such as AGE-human hemoglobin, AGE-albumin such as AGE-bovine serum albumin (AGE-BSA) and AGE-human serum albumin, AGE-low density lipoprotein (AGE-LDL) and AGE-collagen IV. AGE-modified cells, such as AGE-modified erythrocytes, whole, lysed, or partially digested, may also be used as AGE antigens. Examples of adjuvants include Freund's complete, monophosphoryl Lipid A synthetic-trehalose dicorynomycolate, aluminum hydroxide (alum), heat shock proteins HSP 70 or HSP96, squalene emulsion containing monophosphoryl lipid A, α2-macroglobulin and surface active substances, including oil emulsions, pleuronic polyols, polyanions and dinitrophenol. To improve the immune response, an immunogen may be conjugated to a polypeptide that is immunogenic in the host, such as keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, cholera toxin, labile enterotoxin, silica particles or soybean trypsin inhibitor. Alternatively, pAbs may be made in chickens, producing IgY molecules.

[60] 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.

[61] 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.

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

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

[64] 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.

[65] A subject that receives administration of an anti-AGE antibody may be tested to determine if it has been effective to treat the sarcopenia, by measuring changes in muscle mass over time. For example, a baseline muscle mass in a subject may be measured followed by administration of the anti-AGE antibody. The effectiveness of the treatment may be determined by periodically measuring muscle mass in the subject and comparing the subsequent measurements to the baseline measurement. A subject may be considered to have effective treatment of sarcopenia if he or she does not demonstrate loss of muscle mass between subsequent measurements or over time. Alternatively, the concentration and/or number of senescent cells in fat or muscle tissue may also be monitored. Administration of antibody and subsequent testing may be repeated until the desired therapeutic result is achieved.

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

[67] Any mammal that could develop sarcopenia or other diseases or disorders associated with cellular senescence 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 disease or disorder that is known to cause elevated levels of AGEs such as, for example, diabetes (both Type 1 and Type 2), or the presence of a pathological condition associated with AGEs such as, for example, atherosclerosis, inflammation, retinopathy, nephropathy, stroke, endothelial cell dysfunction, neurodegenerative disorders or cancer. In addition, subjects may be identified for treatment based on their age. For example, a human over 75 years of age may be treated for sarcopenia, while a human under 30 years of age might not be identified as in need of treatment for sarcopenia. Alternatively, any of the mammals or subjects identified above may be excluded from the patient population in need of treatment for sarcopenia.

[68] A subject may be identified as having sarcopenia or in need of treatment if (1) the subject is at least 25 years old and (2) his or her measured muscle mass and measured muscle function are two standard deviations or more below the mean value for healthy 25 year olds of the same gender and no alternative pathology has been identified to account for the reduced muscle mass and reduced muscle function. Preferably, a subject being treated for sarcopenia is at least 40 years old. More preferably, a subject being treated for sarcopenia is at least 50 years old. Most preferably, a subject being treated for sarcopenia is at least 60 years old. Alternatively, a subject may be identified as having sarcopenia or in need of treatment if (1) his or her gait speed is less than 1.0 m/s across a 4 m course and (2) he or she has an objectively measured low muscle mass, such as, for example, an appendicular mass relative to the square of height less than or equal to 7.23 kg/m^2 for male subjects or less than or equal to 5.67 kg/m^2 for female subjects.

[69] In the case of central nervous system neurodegenerative disorders, it may be preferable to administer a composition containing the anti-AGE antibody directly into the central nervous system. Examples of such administration include intrathecal administration; administration into the ventricular system of the brain (intraventricular

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

[70] In the case of cancer, a mammal that could develop metastatic cancer may be treated by the methods herein described. Humans are a preferred mammal for treatment. Other mammals that may be treated include mice, rats, goats, sheep, cows, horses and companion animals, such as dogs or cats. A subject in need of treatment may be identified by the diagnosis of a cancer. Cancers which are particularly subject to metastasis include lung cancer, melanoma, colon cancer, renal cell carcinoma, prostate cancer, cancer of the cervix, bladder cancer, rectal cancer, esophageal cancer, liver cancer, mouth and throat cancer, multiple myeloma, ovarian cancer, and stomach

cancer. Treatment may be of patients experiencing metastatic cancer. Treatment may also be administered to patients who have cancer, but prior to any identified metastasis, in order to prevent metastasis. A subject that receives administration of an anti-AGE antibody may be tested to determine if it has been effective to treat the cancer by examining the patient for the spread of the cancer to different parts of the body, particularly in lymph nodes. Administration of antibody and subsequent testing may be repeated until the desired therapeutic result is achieved.

[71] 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 malignant cells and concentrate beneficial stem cells, such as hematopoietic cells expressing the CD34 protein ($CD34^+$ cells). Immunopanning or immunoadsorption using an anti-AGE antibody may isolate partially-functional or non-functional cells, such as senescent cells, from a tissue culture, cell culture or blood sample. For example, an immunopanning process may involve immobilizing the anti-AGE antibody on a surface, such as a cell culture plate. A tissue culture or cell culture may then be applied to the surface. Any senescent cells present in the tissue culture or cell culture will bind to the anti-AGE antibody, leaving a purified tissue culture or cell culture that is free from senescent cells. Similarly, an immunoadsorption process may involve binding the anti-AGE antibody to senescent cells in a cell culture. The cells may then be passed through a column packed with beads that are coated with a protein that binds to the anti-AGE labeled senescent cells. The cells which pass through the column without binding will be cells that do not express AGE, such as fully-functional cells. An immunoadsorption process may be carried out with a CEPRATE SC Stem Cell Concentration System (CellPro, Inc., Bothell, WA) or similar apparatus.

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

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          10         20         30         40         50
MNLLLILTFV AAAVAQVQLL QPGAELVKPG ASVKLACKAS GYLFTTYWMH
          60         70         80         90
WLKQRPGQGL EWIGEISPTN GRAYYNARFK SEATLTVDKS
         100        110        120        130
SNTAYMQLSS LTSEASAVYY CARAYGNYEF AYWGQGTLVT
         140        150        160        170
VSVASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV
         180        190        200        210        220
TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH
         230        240        250        260
KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP
         270        280        290        300
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV
         310        320        330        340
HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
         350        360        370        380        390
NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
         400        410        420        430
SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK
          440        450        460
SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK
```

[73] 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.

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

10 20 30 40 50
MNLLLILTFV AAAVADVVMT QTPLSLPVSL GDQASISCRS RQSLVNSNGN
60 70 80 90 100
TFLQWYLQKP GQSPKLLIYK VSLRFSGVPD RFSGSGSGTD FTLKISRVEA
110 120 130 140 150
EDLGLYFCSQ STHVPPTFGG GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA
160 170 180 190
SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD
200 210 220 230
STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

[75] 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.

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

ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGC
CTGGCCTTCGAGCTGAGCTACGGCCAGGTGCAGCTGCTGCAGCCAGGT
GCCGAGCTCGTGAAACCTGGCGCCTCTGTGAAGCTGGCCTGCAAGGCT
TCCGGCTACCTGTTCACCACCTACTGGATGCACTGGCTGAAGCAGAGGC
CAGGCCAGGGCCTGGAATGGATCGGCGAGATCTCCCCCACCAACGGCA
GAGCCTACTACAACGCCCGGTTCAAGTCCGAGGCCACCCTGACCGTGG
ACAAGTCCTCCAACACCGCCTACATGCAGCTGTCCTCCCTGACCTCTGA
GGCCTCCGCCGTGTACTACTGCGCCAGAGCTTACGGCAACTACGAGTTC
GCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTCTGTGGCTAAGACC
ACCCCTCCCTCCGTGTACCCTCTGGCTCCTGGCTGTGGCGACACCACCG
GATCCTCTGTGACCCTGGGCTGCCTCGTGAAGGGCTACTTCCCTGAGTC
CGTGACCGTGACCTGGAACTCCGGCTCCCTGTCCTCCTCCGTGCACACC

TTTCCAGCCCTGCTGCAGTCCGGCCTGTACACCATGTCCTCCAGCGTGA
CAGTGCCCTCCTCCACCTGGCCTTCCCAGACCGTGACATGCTCTGTGGC
CCACCCTGCCTCTTCCACCACCGTGGACAAGAAGCTGGAACCCTCCGGC
CCCATCTCCACCATCAACCCTTGCCCTCCCTGCAAAGAATGCCACAAGT
GCCCTGCCCCCAACCTGGAAGGCGGCCCTTCCGTGTTCATCTTCCCACC
CAACATCAAGGACGTGCTGATGATCTCCCTGACCCCCAAAGTGACCTGC
GTGGTGGTGGACGTGTCCGAGGACGACCCTGACGTGCAGATCAGTTGG
TTCGTGAACAACGTGGAAGTGCACACCGCCCAGACCCAGACACACAGAG
AGGACTACAACAGCACCATCAGAGTGGTGTCTACCCTGCCCATCCAGCA
CCAGGACTGGATGTCCGGCAAAGAATTCAAGTGCAAAGTGAACAACAAG
GACCTGCCCAGCCCCATCGAGCGGACCATCTCCAAGATCAAGGGCCTC
GTGCGGGCTCCCCAGGTGTACATTCTGCCTCCACCAGCCGAGCAGCTG
TCCCGGAAGGATGTGTCTCTGACATGTCTGGTCGTGGGCTTCAACCCCG
GCGACATCTCCGTGGAATGGACCTCCAACGGCCACACCGAGGAAAACTA
CAAGGACACCGCCCCTGTGCTGGACTCCGACGGCTCCTACTTCATCTAC
TCCAAGCTGAACATGAAGACCTCCAAGTGGGAAAAGACCGACTCCTTCT
CCTGCAACGTGCGGCACGAGGGCCTGAAGAACTACTACCTGAAGAAAAC
CATCTCCCGGTCCCCCGGCTAG

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

ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGC
CTGGCCTTCGAGCTGAGCTACGGCCAGGTGCAGCTGCTGCAGCCAGGT
GCCGAGCTCGTGAAACCTGGCGCCTCTGTGAAGCTGGCCTGCAAGGCT
TCCGGCTACCTGTTCACCACCTACTGGATGCACTGGCTGAAGCAGAGGC
CAGGCCAGGGCCTGGAATGGATCGGCGAGATCTCCCCCACCAACGGCA
GAGCCTACTACAACGCCCGGTTCAAGTCCGAGGCCACCCTGACCGTGG
ACAAGTCCTCCAACACCGCCTACATGCAGCTGTCCTCCCTGACCTCTGA
GGCCTCCGCCGTGTACTACTGCGCCAGAGCTTACGGCAACTACGAGTTC
GCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTCTGTGGCTAGCACC
AAGGGCCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAGAGCACCAGC
GGCGGAACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG
CCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGAGTGCAC

ACCTTCCCTGCCGTGCTGCAGAGCAGCGGCCTGTACTCCCTGAGCAGC
GTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGC
AACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAG
CCTAAGAGCTGCGACAAGACCCACACCTGCCCTCCCTGCCCCGCCCCC
GAGCTGCTGGGCGGACCCAGCGTGTTCCTGTTCCCTCCCAAGCCCAAG
GACACCCTGATGATCAGCCGCACCCCCGAGGTGACCTGCGTGGTGGTG
GACGTGAGCCACGAGGACCCCGAGGTGAAGTTCAACTGGTACGTGGAC
GGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGGGAGGAGCAGTAC
AACTCCACCTACCGCGTGGTGAGCGTGCTGACCGTGCTGCACCAGGAC
TGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCTG
CCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGG
GAGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCTGACCAAG
AACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACA
TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGA
CCACCCCTCCCGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA
GCTGACCGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCAGCTG
CAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCT
GAGCCTGAGCCCCGGATAG

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

ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCC
GGCTCCACCGGAGACGTCGTGATGACCCAGACCCCTCTGTCCCTGCCT
GTGTCTCTGGGCGACCAGGCCTCCATCTCCTGCCGGTCTAGACAGTCCC
TCGTGAACTCCAACGGCAACACCTTCCTGCAGTGGTATCTGCAGAAGCC
CGGCCAGTCCCCCAAGCTGCTGATCTACAAGGTGTCCCTGCGGTTCTCC
GGCGTGCCCGACAGATTTTCCGGCTCTGGCTCTGGCACCGACTTCACCC
TGAAGATCTCCCGGGTGGAAGCCGAGGACCTGGGCCTGTACTTCTGCA
GCCAGTCCACCCACGTGCCCCCTACATTTGGCGGAGGCACCAAGCTGG
AAATCAAACGGGCAGATGCTGCACCAACTGTATCCATCTTCCCACCATCC
AGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACA
ACTTCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGGCAGTGAA
CGACAAAATGGCGTCCTGAACAGTTGGACTGATCAGGACAGCAAAGACA

GCACCTACAGCATGAGCAGCACCCTCACGTTGACCAAGGACGAGTATGA
ACGACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCAC
CCATTGTCAAGAGCTTCAACAGGAATGAGTGTTGA

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

ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCC
GGCTCCACCGGAGACGTCGTGATGACCCAGACCCCTCTGTCCCTGCCT
GTGTCTCTGGGCGACCAGGCCTCCATCTCCTGCCGGTCTAGACAGTCCC
TCGTGAACTCCAACGGCAACACCTTCCTGCAGTGGTATCTGCAGAAGCC
CGGCCAGTCCCCCAAGCTGCTGATCTACAAGGTGTCCCTGCGGTTCTCC
GGCGTGCCCGACAGATTTTCCGGCTCTGGCTCTGGCACCGACTTCACCC
TGAAGATCTCCCGGGTGGAAGCCGAGGACCTGGGCCTGTACTTCTGCA
GCCAGTCCACCCACGTGCCCCCTACATTTGGCGGAGGCACCAAGCTGG
AAATCAAGCGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAG
CGACGAGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAA
CAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGC
CCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAA
GGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGA
CTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACT
GTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA

[80] The one-letter amino acid sequence that corresponds to SEQ ID NO: 16 is shown below:

MDPKGSLSWRILLFLSLAFELSYGQVQLLQPGAELVKPGASVKLACKASGYL
FTTYWMHWLKQRPGQGLEWIGEISPTNGRAYYNARFKSEATLTVDKSSNTA
YMQLSSLTSEASAVYYCARAYGNYEFAYWGQGTLVTVSVAKTTPPSVYPLA
PGCGDTTGSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYT
MSSSVTVPSSTWPSQTVTCSVAHPASSTTVDKKLEPSGPISTINPCPPCKEC
HKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQISWFV
NNVEVHTAQTQTHREDYNSTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPS
PIERTISKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSN

GHTEENYKDTAPVLDSDGSYFIYSKLNMKTSKWEKTDSFSCNVRHEGLKNY
YLKKTISRSPG*

[81] The shaded region of the above amino acid sequence corresponds to SEQ ID NO: 20.

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

MDPKGSLSWRILLFLSLAFELSYGQVQLLQPGAELVKPGASVKLACKASGYL
FTTYWMHWLKQRPGQGLEWIGEISPTNGRAYYNARFKSEATLTVDKSSNTA
YMQLSSLTSEASAVYYCARAYGNYEFAYWGQGTLVTVSVASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPG*

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

METDTLLLWVLLLWVPGSTGDVVMTQTPLSLPVSLGDQASISCRSRQSLVN
SNGNTFLQWYLQKPGQSPKLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRV
EAEDLGLYFCSQSTHVPPTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGA
SVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTL
TKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC*

[84] The shaded region of the above amino acid sequence corresponds to SEQ ID NO: 21.

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

METDTLLLWVLLLWVPGSTGDVVMTQTPLSLPVSLGDQASISCRSRQSLVN
SNGNTFLQWYLQKPGQSPKLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRV
EAEDLGLYFCSQSTHVPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

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

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

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

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

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

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

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

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

[93] The one-letter amino acid sequence that corresponds to SEQ ID NO: 29 is MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVSCKASGYLFTTYW MHWVRQAPGQGLEWMGEISPTNGRAYYNQKFQGRVTMTVDKSTNTVYMELSSLRS EDTAVYYCARAYGNYFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPG.

[94] The DNA sequence that corresponds to SEQ ID NO: 30 is ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGCCTGGCCT TCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGA

AACCTGGCGCCTCCGTGAGGTGTCCTGCAAGGCTTCCGGCTACCTGTTCACCACC
TACTGGATGCACTGGGTGCGACAGGCCCCTGGACAGGGCCTGGAATGGATGGGC
GAGATCTCCCCTACCAACGGCAGAGCCTACTACAACAGAAATTCCAGGGCAGAGT
GACCATGACCGTGGACAAGTCCACCAACACCGTGTACATGGAACTGTCCTCCCTG
CGGAGCGAGGACACCGCCGTGTACTACTGCGCTAGAGCCTACGGCAACTACGATT
CGCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTCCTCTGCTAGCACCAAGGG
CCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGAACCGC
CGCCCTGGGCTGCCTGGGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGG
AACAGCGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCCGTGCTGCAGAGC
AGCGGCCTGTACTCCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAGCCTGGGCA
CCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAA
GAAGGTGGAGCCTAAGAGCTGCGACAAGACCCACACCTGCCCTCCCTGCCCCGC
CCCGAGCTGCTGGGCGGACCCAGCGTGTTCCTGTTCCCTCCCAAGCCCAAGGAC
ACCCTGATGATCAGCCGCACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGC
CACGAGGACCCCGAGGTGAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACA
ACGCCAAGACCAAGCCTCGGGAGGAGCAGTACAACTCCACCTACCGCGTGGTGA
GCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAGGAGTACAAGTGCAA
GGTGAGCAACAAGGCCCTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAA
GGGCCAGCCCCGGGAGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCT
GACAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACA
TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCC
CTCCCGTGCTGGACAGCGACGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGAC
AAGTCCCGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCC
CTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCGGATAGTAA.

[95] The one-letter amino acid sequence that corresponds to SEQ ID NO: 31 is
MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVSCKASGYLFTTYW
MHWVRQAPGQGLEWMGEISPTNGRAYYNAKFQGRVTMTVDKSTNTAYMELSSLRSE
DTAVYYCARAYGNYFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH

KPSNTKVDKKVEPKSCDKTHTCPPCPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPG.

[96] The DNA sequence that corresponds to SEQ ID NO: 32 is
ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGCCTGGCCT
TCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGA
AACCTGGCGCCTCCGTGAGGTGTCCTGCAAGGCTTCCGGCTACCTGTTCACCACC
TACTGGATGCACTGGGTGCGACAGGCCCCTGGACAGGGCCTGGAATGGATGGGC
GAGATCTCCCCTACCAACGGCAGAGCCTACTACAACCAAAATTCCAGGGCAGAGT
GACCATGACCGTGGACAAGTCCACCAACACCGCTTACATGGAACTGTCCTCCCTG
CGGAGCGAGGACACCGCCGTGTACTACTGCGCTAGAGCCTACGGCAACTACGATT
CGCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTCCTCTGCTAGCACCAAGGG
CCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGAACCGC
CGCCCTGGGCTGCCTGGGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGG
AACAGCGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCCGTGCTGCAGAGC
AGCGGCCTGTACTCCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAGCCTGGGCA
CCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAA
GAAGGTGGAGCCTAAGAGCTGCGACAAGACCCACACCTGCCCTCCCTGCCCCGC
CCCGAGCTGCTGGGCGGACCCAGCGTGTTCCTGTTCCCTCCCAAGCCCAAGGAC
ACCCTGATGATCAGCCGCACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGC
CACGAGGACCCCGAGGTGAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACA
ACGCCAAGACCAAGCCTCGGGAGGAGCAGTACAACTCCACCTACCGCGTGGTGA
GCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAGGAGTACAAGTGCAA
GGTGAGCAACAAGGCCCTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAA
GGGCCAGCCCCGGGAGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCT
GACAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACA
TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCC

CTCCCGTGCTGGACAGCGACGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGAC
AAGTCCCGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCC
CTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCGGATAGTAA.

[97] The one-letter amino acid sequence that corresponds to SEQ ID NO: 33 is
MDPKGSLSWRILLFLSLAFELSYGQVQLVQSGAEVKKPGASVKVSCKASGYLFTTYW
MHWVRQAPGQGLEWMGEISPTNGRAYYNAKFQGRVTMTVDKSINTAYMELSRLRSD
DTAVYYCARAYGNYFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH
KPSNTKVDKKVEPKSCDKTHTCPPCPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPG.

[98] The DNA sequence that corresponds to SEQ ID NO: 34 is
ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCTGTTCCTGAGCCTGGCCT
TCGAGCTGAGCTACGGCCAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGA
AACCTGGCGCCTCCGTGAGGTGTCCTGCAAGGCTTCCGGCTACCTGTTCACCACC
TACTGGATGCACTGGGTGCGACAGGCCCCTGGACAGGGCCTGGAATGGATGGGC
GAGATCTCCCCTACCAACGGCAGAGCCTACTACAACCAAAATTCCAGGGCAGAGT
GACCATGACCGTGGACAAGTCCATCAACACCGCTTACATGGAACTGTCCAGACTG
CGGAGCGATGACACCGCCGTGTACTACTGCGCTAGAGCCTACGGCAACTACGATT
CGCCTACTGGGGCCAGGGCACCCTCGTGACAGTGTCCTCTGCTAGCACCAAGGG
CCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGAACCGC
CGCCCTGGGCTGCCTGGGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGG
AACAGCGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCCGTGCTGCAGAGC
AGCGGCCTGTACTCCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAGCCTGGGCA
CCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAA
GAAGGTGGAGCCTAAGAGCTGCGACAAGACCCACACCTGCCCTCCCTGCCCCGC

CCCGAGCTGCTGGGCGGACCCAGCGTGTTCCTGTTCCCTCCCAAGCCCAAGGAC
ACCCTGATGATCAGCCGCACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGC
CACGAGGACCCCGAGGTGAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACA
ACGCCAAGACCAAGCCTCGGGAGGAGCAGTACAACTCCACCTACCGCGTGGTGA
GCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAGGAGTACAAGTGCAA
GGTGAGCAACAAGGCCCTGCCCGCTCCCATCGAGAAGACCATCAGCAAGGCCAA
GGGCCAGCCCCGGGAGCCTCAGGTGTACACCCTGCCCCCCAGCCGCGACGAGCT
GACAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACA
TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCC
CTCCCGTGCTGGACAGCGACGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGAC
AAGTCCCGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCC
CTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGAGCCCGGATAGTAA.

[99] The one-letter amino acid sequence that corresponds to SEQ ID NO: 35 is
METDTLLLWVLLLWVPGSTGDVVMTQSPLSLPVTLGQPASISCRSSQSLVNSNGNTFL
QWYQQRPGQSPRLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQ
STHVPPTFGGGTVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK
VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK
SFNRGEC.

[100] The DNA sequence that corresponds to SEQ ID NO: 36 is
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCC
ACCGGAGACGTCGTGATGACCCAGTCCCCTCTGTCCCTGCCTGTGACCCTGGGAC
AGCCTGCCTCCATCTCCTCAGATCCTCCCAGTCCCTCGTGAACTCCAACGGCAACA
CCTTCCTGCAGTGGTATCAGCAGCGGCCTGGCCAGAGCCCCAGACTGCTGATCTA
CAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACGATTTTCCGGCTCTGGCTCTG
GCACCGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGAGGACGTGGGCGTGT
ACTACTGCTCCCAGAGCACCCACGTGCCCCCTACATTTGGCGGAGGCACCAAGTG
GAAATCAAGCGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACG
AGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCC

CCGCGAGGCCAAGGGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAG
CCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAG
CACCCTGACCCTGAGCAAGGCCGACTACGAGAAGACAAGGTGTACGCCTGCGAG
GTGACCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAG
TGCTAA.

[101] The one-letter amino acid sequence that corresponds to SEQ ID NO: 37 is
METDTLLLWVLLLWVPGSTGDVVMTQSPLSLPVTLGQPASISCRSRQSLVNSNGNTFL
QWYQQRPGQSPRLLIYKVSLRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQ
STHVPPTFGGGTVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK
VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK
SFNRGEC.

[102] The DNA sequence that corresponds to SEQ ID NO: 38 is
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCC
ACCGGAGACGTCGTGATGACCCAGTCCCCTCTGTCCCTGCCTGTGACCCTGGGAC
AGCCTGCCTCCATCTCCTCAGATCCAGGCAGTCCCTCGTGAACTCCAACGGCAAC
ACCTTCCTGCAGTGGTATCAGCAGCGGCCTGGCCAGAGCCCCAGACTGCTGATCT
ACAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACGATTTTCCGGCTCTGGCTCT
GGCACCGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGAGGACGTGGGCGTG
TACTACTGCTCCCAGAGCACCCACGTGCCCCCTACATTTGGCGGAGGCACCAAGT
GGAAATCAAGCGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGAC
GAGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACC
CCCGCGAGGCCAAGGGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACA
GCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCA
GCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGACAAGGTGTACGCCTGCGA
GGTGACCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGA
GTGCTAA.

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

QWYHQRPGQPPRLLIYKVSLRFSGVPDRFSGSGAGKDFTLKISRVEAEDVGVYYCSQ
STHVPPTFGQGTLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC.

[104] The DNA sequence that corresponds to SEQ ID NO: 40 is
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCC
ACCGGAGACGTCGTGATGACCCAGTCCCCTCTGTCCAGTCCTGTGACCCTGGGAC
AGCCTGCCTCCATCTCCTCAGATCCTCCCAGTCCCTCGTGAACTCCAACGGCAACA
CCTTCCTGCAGTGGTATCACCAGCGGCCTGGCCAGCCTCCCAGACTGCTGATCTA
CAAGGTGTCCCTGCGGTTCTCCGGCGTGCCCGACGATTTTCCGGCTCTGGCGCTG
GCAAGGACTTCACCCTGAAGATCTCCCGGGTGGAAGCCGAGGACGTGGGCGTGT
ACTACTGCTCCCAGAGCACCCACGTGCCCCCTACATTTGGCCAGGGCACCAACTG
GAAATCAAGCGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACG
AGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCC
CCGCGAGGCCAAGGGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAG
CCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAG
CACCCTGACCCTGAGCAAGGCCGACTACGAGAAGACAAGGTGTACGCCTGCGAG
GTGACCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAG
TGCTAA.

[105] **EXAMPLES**

[106] Example 1: *In vivo* study of the administration of anti-glycation end-product antibody

[107] To examine the effects of an anti-glycation end-product antibody, the antibody was administered to the aged CD1(ICR) mouse (Charles River Laboratories), twice daily by intravenous injection, once a week, for three weeks (Days 1, 8 and 15), followed by a 10 week treatment-free period. The test antibody was a commercially available mouse anti-glycation end-product antibody raised against carboxymethyl

lysine conjugated with keyhole limpet hemocyanin, the carboxymethyl lysine MAb (Clone 318003) available from R&D Systems, Inc. (Minneapolis, MN; catalog no. MAB3247). A control reference of physiological saline was used in the control animals.

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

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

Group No.	Test Material	Mice	Dose Level (µg/gm/BID/ week)	Number of Animals	
				Main Study	Treatment-Free
				Females	Females
1	Saline	young	0	20	-
2	Saline	old	0	20	20
3	Antibody	old	2.5	20	20
4	None	old	0	20	pre
5	Antibody	old	5.0	20	20

- = Not Applicable, Pre = Subset of animals euthanized prior to treatment start for collection of adipose tissue.

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

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

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

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

[113] When results from Group 2 (Control) untreated old mice were compared to results from Group 5 (5 µg/gram) treated old mice euthanized Day 22, it was observed that $p16^{Ink4a}$ mRNA was 3.03-fold higher in Group 2 (controls) than in Group 5 (5 µg/gram). This comparison indicated that the Group 5 animals had lower levels of $p16^{Ink4a}$ mRNA expression when they were treated with 5.0 µg/gram/BID/week, providing $p16^{Ink4a}$ mRNA expression levels comparable to that of the young untreated mice (i.e. Group 1). Unlike Group 3 (2.5 µg/gram) mice that were euthanized at end of recovery Day 85, Group 5 mice were euthanized at end of treatment Day 22.

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

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

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

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

[117] Example 2: Affinity and kinetics of test antibody

[118] The affinity and kinetics of the test antibody used in Example 1 were analyzed using Nα,Nα-bis(carboxymethyl)-L-lysine trifluoroacetate salt (Sigma-Aldrich, St. Louis, MO) as a model substrate for an AGE-modified protein of a cell. Label-free interaction analysis was carried out on a BIACORE™ T200 (GE Healthcare, Pittsburgh, PA), using a Series S sensor chip CM5 (GE Healthcare, Pittsburgh, PA), with Fc1 set as blank, and Fc2 immodilized with the test antibody (molecular weigh of 150,000 Da). The running buffer was a HBS-EP buffer (10 mM HEPES, 150 mM NaCl, 3 mM EDTA and 0.05% P-20, pH of 7.4), at a temperature of 25 °C. Software was BIACORE™ T200 evaluation software, version 2.0. A double reference (Fc2-1 and only buffer injection), was used in the analysis, and the data was fitted to a Langmuir 1:1 binding model.

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

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

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

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

[122] 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.

[123] 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.

[124] The conditioned media for murine and chimeric anti-AGE antibodies were harvested and clarified from the transient transfection production runs by centrifugation and filtration. The supernatants were run over a Protein A column and eluted with a low pH buffer. Filtration using a 0.2 μm membrane filter was performed before aliquoting. After purification and filtration, the protein concentrations were calculated from the OD280 and the extinction coefficient. A summary of yields and aliquots is shown in Table 5:

[125] Table 5: Yields and aliquots

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

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

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

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

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

[130] 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.

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

Conc. (ug/mL)	1	2	3	4	5	6	7
50	0.462	0.092	0.42		1.199	0.142	1.852
16.67	0.312	0.067	0.185		0.31	0.13	0.383
5.56	0.165	0.063	0.123		0.19	0.115	0.425
1.85	0.092	0.063	0.088		0.146	0.099	0.414
0.62	0.083	0.072	0.066		0.108	0.085	0.248
0.21	0.075	0.066	0.09		0.096	0.096	0.12
0.07	0.086	0.086	0.082		0.098	0.096	0.098
0	0.09	0.085	0.12		0.111	0.083	0.582
	R&D Positive Control	Parental Anti-AGE	Chimeric Anti-AGE		R&D Positive Control	Parental Anti-AGE	Chimeric Anti-AGE
	CML-KLH Coat				CML Coat		

[132] 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.

[133] Plate map of CML-only ELISA:

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

[134] 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.

[135] Example 5: Humanized antibodies

[136] 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.

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

[138] Table 6: Antibody humanness

Antibody	Humanness (Framework + CDR)
Parental (mouse) heavy chain	63.60
Heavy chain 1 (SEQ ID NO: 29)	82.20
Heavy chain 2 (SEQ ID NO: 31)	80.76
Heavy chain 3 (SEQ ID NO: 33)	81.10
Parental (mouse) light chain	77.87

Light chain 1 (SEQ ID NO: 35)	86.74
Light chain 2 (SEQ ID NO: 37)	86.04
Light chain 3 (SEQ IN NO: 39)	83.57

[139] 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.

[140] 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).

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

[142] Table 7: Antibody titers

Antibody	Titer (mg/L)
Chimeric parental	23.00
SEQ ID NO: 29 + SEQ ID NO: 35	24.67
SEQ ID NO: 29 + SEQ ID NO: 37	41.67

SEQ ID NO: 29 + SEQ ID NO: 39	29.67
SEQ ID NO: 31 + SEQ ID NO: 35	26.00
SEQ ID NO: 31 + SEQ ID NO: 37	27.33
SEQ ID NO: 31 + SEQ ID NO: 39	35.33
SEQ ID NO: 33 + SEQ ID NO: 35	44.00
SEQ ID NO: 33 + SEQ ID NO: 37	30.33
SEQ ID NO: 33 + SEQ ID NO: 39	37.33

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

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WHAT IS CLAIMED IS:

1. An anti-AGE antibody, comprising a protein or peptide comprising at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, and SEQ ID NO: 39,

wherein the antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

2. An anti-AGE antibody, comprising a protein or peptide comprising at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28,

wherein the antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

3. An anti-AGE antibody, comprising

a heavy chain, and

a light chain,

wherein the heavy chain comprises an amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 17, SEQ ID NO: 29, SEQ ID NO: 31, and SEQ ID NO: 33, or

the light chain comprises an amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98%

sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 19, SEQ ID NO: 35, SEQ ID NO: 37, and SEQ ID NO: 39; and

the antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

4. An anti-AGE antibody, comprising

a heavy chain, and

a light chain,

wherein the heavy chain comprises an amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 17, SEQ ID NO: 29, SEQ ID NO: 31, and SEQ ID NO: 33, and

the light chain comprises an amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 19, SEQ ID NO: 35, SEQ ID NO: 37, and SEQ ID NO: 39; and

the antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification.

5. An anti-AGE antibody, comprising complementary determining region comprising at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28,

wherein the antibody binds to a protein or peptide that exhibits a carboxymethyllysine modification, and

the antibody is substantially non-immunogenic to a species selected from the group consisting of mice, rats, goats, sheep, cows, horses, dogs and cats.

6. An antibody conjugate, comprising:

an anti-AGE antibody fragment comprising a protein or peptide comprising at least one amino acid sequence having at least 90% sequence identity, preferably at least 95% sequence identity, more preferably at least 98% sequence identity, with an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, and SEQ ID NO: 39, and

an agent that causes the destruction of AGE-modified cells, conjugated to the anti-AGE antibody fragment,

wherein the anti-AGE antibody fragment binds to a protein or peptide that exhibits a carboxymethyllysine modification.

7. An anti-AGE antibody of any of the preceding claims for use in killing senescent cells.

8. An anti-AGE antibody of any of the preceding claims for use in killing partially-functional or non-functional cells.

9. An anti-AGE antibody of any of the preceding claims for use in treating sarcopenia in a subject by killing partially-functional or non-functional cells.

10. An anti-AGE antibody of any of the preceding claims for use in promoting tissue or organ regeneration in a subject by killing partially-functional or non-functional cells.

11. An anti-AGE antibody of any of the preceding claims for use in promoting regenerative processes or overcoming aging effects in a subject by killing partially-functional or non-functional cells.

12. An anti-AGE antibody of any of the preceding claims for use in treating atherosclerosis in a subject by killing partially-functional or non-functional cells.

13. An anti-AGE antibody of any of the preceding claims for use in preventing or delaying the onset of cataracts in a subject.

14. An anti-AGE antibody of any of the preceding claims for use preventing or delaying the onset of loss of adipose tissue in a subject.

15. An anti-AGE antibody of any of the preceding claims for use in preventing or delaying the onset of lordokyphosis in a subject.

16. An anti-AGE antibody of any of the preceding claims for use in treating inflammation or auto-immune disorders in a subject.

17. An anti-AGE antibody of any of the preceding claims for use in treating neurodegenerative disorders in a subject.

18. An anti-AGE antibody of any of the preceding claims for use in treating cancer in a subject.

19. Use of an anti-AGE antibody of any of the preceding claims for the manufacture of a medicament for killing senescent cells.

20. Use of an anti-AGE antibody of any of the preceding claims for the manufacture of a medicament for treating sarcopenia.

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

22. The anti-AGE antibody of any of the preceding claims, wherein the treating comprises administering the anti-AGE antibody to the central nervous system of the subject.

23. The anti-AGE antibody of any of the preceding claims, wherein the subject has ALS or MD, and

the treating comprises administering the anti-AGE antibody to muscles of the subject.

24. The anti-AGE antibody of any of the preceding claims, wherein the antibody is substantially non-immunogenic to a species selected from the group consisting of humans, mice, rats, goats, sheep, cows, horses, dogs and cats.

25. The anti-AGE antibody of any of the preceding claims, wherein the antibody is a humanized antibody.

26. The anti-AGE antibody of any of the preceding claims, wherein the antibody is monoclonal.

27. The anti-AGE antibody of any of the preceding claims, wherein the antibody is substantially non-immunogenic to humans.

28. The anti-AGE antibody of any of the preceding claims, wherein the antibody has a rate of dissociation (k_d) of at most 9×10^{-3} sec^{-1}.

29. The anti-AGE antibody of any of the preceding claims, wherein the antibody is conjugated to an agent that causes the destruction of AGE-modified cells.

30. The anti-AGE antibody of any of the preceding claims, wherein the agent is selected from the group consisting of a toxin, a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

31. The anti-AGE antibody of any of the preceding claims, wherein the antibody includes constant regions which permit destruction of targeted cells by a subject's immune system.

32. The anti-AGE antibody of any of the preceding claims, wherein the antibody is a bi-specific antibody.

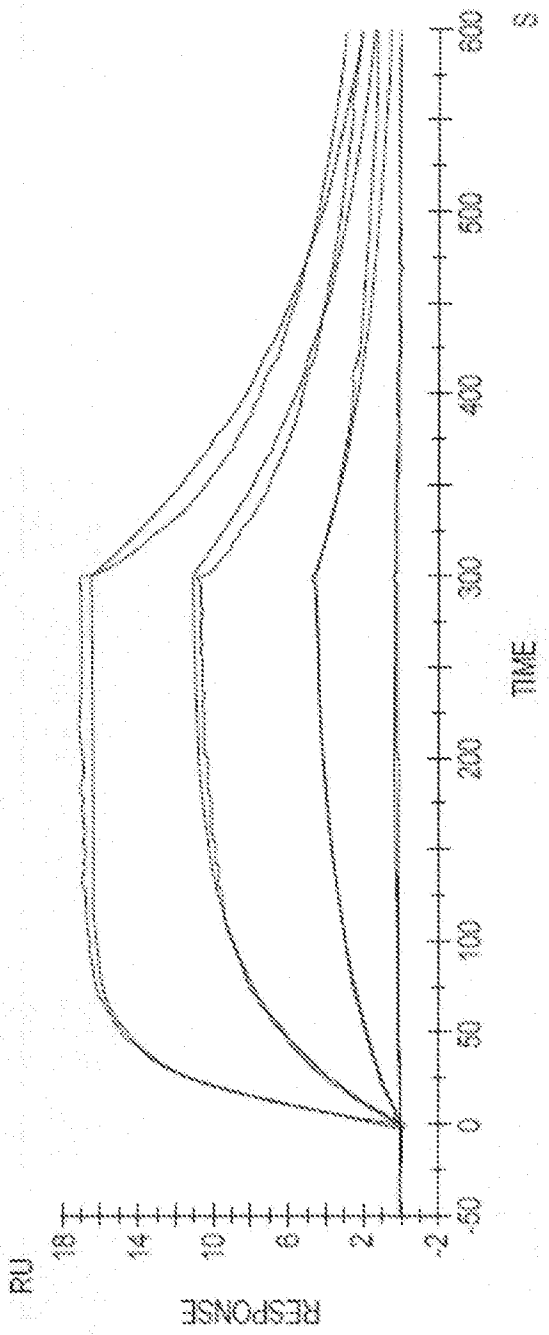

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/034880

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/44 C07K14/47
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. NI ET AL: "Plasma Protein Pentosidine and Carboxymethyllysine, Biomarkers for Age-related Macular Degeneration", MOLECULAR & CELLULAR PROTEOMICS, vol. 8, no. 8, 1 August 2009 (2009-08-01), pages 1921-1933, XP055292726, US ISSN: 1535-9476, DOI: 10.1074/mcp.M900127-MCP200 Page 1923: "Pentosidine and CML Autoantibody assay" -/--	1-32

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 August 2016	10/08/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Turri, Matteo

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	-& Anonymous: "Carboxymethyl Lysine Antibody MAB3247", , 13 October 2015 (2015-10-13), XP055292706, Retrieved from the Internet: URL:https://resources.rndsystems.com/pdfs/datasheets/mab3247.pdf [retrieved on 2016-08-02] the whole document	1-32
X	SCHALKWIJK C G ET AL: "Increased accumulation of the glycoxidation product N<e>psilon-(carboxymethyl)lysine in hearts of diabetic patients: generation and characterisation of a monoclonal anti-CML antibody", BIOCHIMICA AND BIOPHYSICA ACTA. MOLECULAR AND CELL BIOLOGY OF LIPIDS, ELSEVIER, AMSTERDAM, NL, vol. 1636, no. 2-3, 22 March 2004 (2004-03-22), pages 82-89, XP004519877, ISSN: 1388-1981, DOI: 10.1016/J.BBALIP.2003.07.002 abstract	1-32
X	JP 2003 160599 A (TRANSGENIC INC) 3 June 2003 (2003-06-03) paragraphs [0001], [0006], [0026]	1-32
A	DARREN J. BAKER ET AL: "Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders", NATURE, vol. 479, no. 7372, 1 November 2011 (2011-11-01), pages 232-236, XP055074325, ISSN: 0028-0836, DOI: 10.1038/nature10600	1-32
A	K. M. LAPAK ET AL: "The Molecular Balancing Act of p16INK4a in Cancer and Aging", MOLECULAR CANCER RESEARCH, vol. 12, no. 2, 1 February 2014 (2014-02-01), pages 167-183, XP055291091, US ISSN: 1541-7786, DOI: 10.1158/1541-7786.MCR-13-0350	1-32

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NAYLOR R M ET AL: "Senescent cells: a novel therapeutic target for aging and age-related diseases", CLINICAL PHARMACOLOGY AND THERAPEUTICS, NATURE PUBLISHING GROUP, US, vol. 93, no. 1, 1 January 2013 (2013-01-01), pages 105-116, XP002710105, ISSN: 0009-9236, DOI: 10.1038/CLPT.2012.193 [retrieved on 2012-12-05]	1-5
A	SIMON ASBJÖRN LARSEN ET AL: "Glucose metabolite glyoxal induces senescence in telomerase-immortalized human mesenchymal stem cells", CHEMISTRY CENTRAL JOURNAL, BIOMED CENTRAL LTD, LO, vol. 6, no. 1, 17 March 2012 (2012-03-17), page 18, XP021124020, ISSN: 1752-153X, DOI: 10.1186/1752-153X-6-18	1-32
A	MAHTAB U. AHMED ET AL: "N [epsilon] -(Carboxyethyl)lysine, a product of the chemical modification of proteins by methylglyoxal, increases with age in human lens proteins", BIOCHEMICAL JOURNAL, vol. 324, no. 2, 1 June 1997 (1997-06-01), pages 565-570, XP055292796, GB ISSN: 0264-6021, DOI: 10.1042/bj3240565	1-32
A	WAUTIER J-L ET AL: "ADVANCED GLYCATION END PRODUCTS (AGES) ON THE SURFACE OF DIABETIC ERYTHROCYTES BIND TO THE VESSEL WALL VIA A SPECIFIC RECEPTOR INDUCING OXIDANT STRESS IN THE VASCULATURE: A LINK BETWEEN SURFACE-ASSOCIATED AGES AND DIABETIC COMPLICATIONS", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 91, 1 August 1994 (1994-08-01), pages 7742-7746, XP002036216, ISSN: 0027-8424, DOI: 10.1073/PNAS.91.16.7742	1-32

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/034880

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DUNN J A ET AL: "AGE-DEPENDENT ACCUMULATION OF NE-CARBOXYMETHYL)LYSINE AND NE-(CARBOXYMETHYL)HYDROXYLYSINE IN HUMAN SKIN COLLAGEN", BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 30, 5 February 1991 (1991-02-05), pages 1205-1210, XP000615906, ISSN: 0006-2960, DOI: 10.1021/BI00219A007 -----	1-32

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/034880

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/034880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2003160599 A	03-06-2003	JP 4012722 B2	21-11-2007
		JP 2003160599 A	03-06-2003