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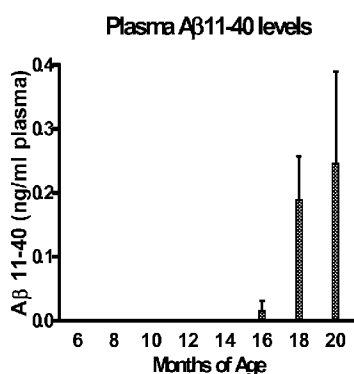
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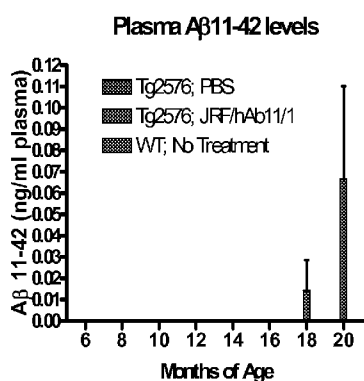
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(54) Title: ANTI-AMYLOID ANTIBODIES, COMPOSITIONS, METHODS AND USES



(57) Abstract: The present invention relates to at least one novel anti-amyloid antibody, including isolated nucleic acids that encode at least one anti-amyloid antibody, amyloid, vectors, host cells, transgenic animals or plants, and methods of making and using thereof, including therapeutic compositions, methods and devices.



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ANTI-AMYLOID ANTIBODIES, COMPOSITIONS, METHODS AND USES**BACKGROUND OF THE INVENTION****PRIOR APPLICATION**

This application claims priority to U.S. application No. 60/817,299, filed June 29,
5 2006, which is entirely incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to antibodies, including specified portions or variants,
specific for at least one beta-amyloid (amyloid) protein or fragment thereof, as well as anti-
10 idiotype antibodies, and nucleic acids encoding such anti-amyloid antibodies, complementary
nucleic acids, vectors, host cells, and methods of making and using thereof, including
therapeutic formulations, administration and devices.

RELATED ART

15 Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by
progressive loss of memory, cognition, reasoning, judgment and emotional stability that
gradually leads to profound mental deterioration and ultimately death. AD is a very common
cause of progressive mental failure (dementia) in aged humans and is believed to represent the
fourth most common medical cause of death in the United States. AD has been observed in
20 races and ethnic groups worldwide and presents a major present and future public health
problem. The disease is currently estimated to affect about two to three million individuals in
the United States alone. AD is at present incurable. No treatment that effectively prevents AD
or reverses its symptoms and course is currently known

The brains of individuals with AD exhibit characteristic lesions termed senile (or
25 amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary
tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary
tangles, are generally found in several areas of the human brain important for memory and
cognitive function in patients with AD. Smaller numbers of these lesions in a more restricted
anatomical distribution are also found in the brains of most aged humans who do not have
30 clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of
individuals with Trisomy 21 (Down's Syndrome), Diffuse Lewy Body Disease and Hereditary
Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D).

A major constituent of amyloid plaques are a variety amyloid-beta (A β) peptides which
are produced by cleavage of the β -amyloid precursor protein (APP). While in the past there

was significant scientific debate over whether the plaques and tangles are a cause or are merely the result of Alzheimer's disease, recent discoveries indicate that amyloid plaque is a causative precursor or factor. In particular, it has been discovered that the production of A β peptides can result from mutations in the gene encoding amyloid precursor protein, a protein which when normally processed will not produce the A β peptides. The identification of mutations in the amyloid precursor protein gene which cause familial, early onset Alzheimer's disease is the strongest evidence that amyloid metabolism is the central event in the pathogenic process underlying the disease. It is presently believed that a normal (non-pathogenic) processing of the APP protein occurs via cleavage by an "alpha-secretase" which cleaves between amino acids 16 and 17 of the A β peptide region within the protein. It is further believed that pathogenic processing occurs in part via "beta-secretases" which cleave at the amino-terminus of the A β peptide region within the precursor protein. Beta amyloid protein is also thought to be potentially associated with other neurological and some cardiovascular disorders.

Accordingly, there is a need to provide anti-amyloid antibodies or fragments that overcome one more of these problems, as well as improvements over known antibodies or fragments thereof.

SUMMARY OF THE INVENTION

The present invention provides isolated human, primate, rodent, mammalian, chimeric, humanized and/or CDR-grafted anti-amyloid antibodies, immunoglobulins, fragments, cleavage products and other specified portions and variants thereof, as well as anti-amyloid antibody compositions, encoding or complementary nucleic acids, vectors, host cells, compositions, formulations, devices, transgenic animals, transgenic plants, and methods of making and using thereof, as described and enabled herein, in combination with what is known in the art.

The present invention also provides at least one isolated anti-amyloid antibody as described herein. An antibody according to the present invention includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to, at least one ligand binding portion (LBP), such as but not limited to, a complementarity determining region (CDR) of a heavy or light chain (e.g., comprising at least one of SEQ ID NOS:42-47, 53-58) or a ligand binding portion thereof, a heavy chain or light chain variable region (e.g., comprising at least one of 10-125 contiguous amino acids of at least one of SEQ ID NOS:1-30, or at least one FR1, FR2, FR3, FR4 or fragment thereof as described in Table 1, further optionally comprising at least one substitution, insertion or deletion as provided in Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004), a heavy chain or light chain constant region (e.g., comprising at least one of 10-384 contiguous amino acids of at

least one of SEQ ID NOS:31-41, or at least one CH1, hinge1, hinge2, hinge 3, hinge4, CH2, CH3 or fragment thereof as described in Table 1, further optionally comprising at least one substitution, insertion or deletion as provided in Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004), a framework region, or any portion thereof, that can be incorporated into an antibody of the present invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, or any combination thereof, and the like.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding specific anti-amyloid antibodies, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said anti-amyloid antibody nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such antibody nucleic acids, vectors and/or host cells.

The present invention also provides at least one anti-amyloid antibody or specified portion or variant, comprising at least one amyloid binding sequence and at least 10-384 contiguous amino acids of at least one of SEQ ID NOS:1-41, or at least one FR1, FR2, FR3, FR4, CH1, hinge1, hinge2, hinge 3, hinge4, CH2, CH3 or fragment thereof as described in Table 1, further optionally comprising at least one substitution, insertion or deletion as provided in Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, or as known in the art.

At least one antibody of the invention binds at least one specified epitope specific to at least one amyloid protein, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of said protein, which epitope is preferably comprised of at least 1-5 amino acids of at least one portion thereof, such as but not limited to, at least one functional, extracellular, soluble, hydrophilic, external or cytoplasmic domain of said protein, or any portion thereof.

The at least one antibody can optionally comprise at least one specified portion of at least one complementarity determining region (CDR) (e.g., CDR1, CDR2 or CDR3 of the heavy or light chain variable region) and optionally further comprising at least one constant or variable framework region or any portion thereof. The at least one antibody amino acid sequence can further optionally comprise at least one specified substitution, insertion or deletion as described herein or as known in the art.

The present invention also provides at least one isolated anti-amyloid antibody as described herein, wherein the antibody has at least one activity, such as, but not limited to one known amyloid protein assay. An anti-amyloid antibody can thus be screened for a

corresponding activity according to known methods, such as but not limited to, at least one biological activity towards an amyloid protein.

The present invention further provides at least one amyloid anti-idiotypic antibody to at least one amyloid antibody of the present invention. The anti-idiotypic antibody includes any
5 protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one ligand binding portion (LBP), such as but not limited to a complementarity determining region (CDR) of a heavy or light chain, or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, that can be incorporated into
10 an antibody of the present invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, and the like.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding at least one amyloid
15 anti-idiotypic antibody, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said amyloid anti-idiotypic antibody encoding nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such anti-idiotypic antibody nucleic acids, vectors and/or host cells.

20 The present invention also provides at least one method for expressing at least one anti-amyloid antibody, or amyloid anti-idiotypic antibody, in a host cell, comprising culturing a host cell as described herein under conditions wherein at least one anti-amyloid antibody is expressed in detectable and/or recoverable amounts.

The present invention also provides at least one composition comprising (a) an isolated
25 anti-amyloid antibody encoding nucleic acid and/or antibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known carriers or diluents. The composition can optionally further comprise at least one further compound, protein or composition.

The present invention further provides at least one anti-amyloid antibody method or
30 composition, for administering a therapeutically effective amount to modulate or treat at least one amyloid related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery of a therapeutically or prophylactically effective amount of at least one anti-amyloid
35 antibody, according to the present invention.

The present invention further provides at least one anti-amyloid antibody method or

composition, for diagnosing at least one amyloid related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery for diagnosing of at least one anti-amyloid antibody, according to the present invention.

In one aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one variable region comprising SEQ ID NO:48 or 49.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising either (i) all of the heavy chain complementarity determining regions (CDR) amino acid sequences of SEQ ID NOS:42-44; or (ii) all of the light chain CDR amino acids sequences of SEQ ID NOS:45-47.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS: 42-47.

In one aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one variable region comprising SEQ ID NO:59 or 60.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising either (i) all of the heavy chain complementarity determining regions (CDR) amino acid sequences of SEQ ID NOS:53-55; or (ii) all of the light chain CDR amino acids sequences of SEQ ID NOS:56-58.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:53-58.

In one aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one human CDR, wherein the antibody specifically binds at least one epitope selected from amino acids 2-7, 3-8, 33-42, or 34-40 of SEQ ID NO:50.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one human CDR, wherein the antibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:50.

The at least one antibody can optionally further comprise at least one characteristic selected from: (i) bind amyloid with an affinity of at least one selected from at least 10^{-9} M, at

least 10^{-10} M, at least 10^{-11} M, or at least 10^{-12} M; and/or (ii) substantially neutralize at least one activity of at least one amyloid protein. Also provided is an isolated nucleic acid encoding at least one isolated mammalian anti-amyloid antibody; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can optionally be at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell thereof. Also provided is a method for producing at least one anti-amyloid antibody, comprising translating the antibody encoding nucleic acid under conditions in vitro, in vivo or in situ, such that the amyloid antibody is expressed in detectable or recoverable amounts.

Also provided is a composition comprising at least one isolated mammalian anti-amyloid antibody and at least one pharmaceutically acceptable carrier or diluent. The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

The present invention further provides an anti-idiotypic antibody or fragment that specifically binds at least one isolated mammalian anti-amyloid antibody of the present invention.

Also provided is a method for diagnosing or treating an amyloid related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one isolated mammalian anti-amyloid antibody of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.001-50 mg/kilogram per: 1-24 hours, 1-7 days, 1-52 weeks, 1-24 months, 1-30 years (or any range or value therein), of the cells, tissue, organ or animal. The method can optionally

further comprise using the contacting or the administering by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or protein selected from at least one of a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is a medical device, comprising at least one isolated mammalian anti-amyloid antibody of the invention, wherein the device is suitable to contacting or administering the at least one anti-amyloid antibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of

at least one isolated mammalian anti-amyloid antibody of the present invention. The article of manufacture can optionally comprise having the container as a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated mammalian anti-amyloid antibody of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the antibody. Further provided in the present invention is at least one anti-amyloid antibody produced by the above method.

The present invention further provides any invention described herein.

DESCRIPTION OF THE FIGURES

Figure 1A-B. Measurement of b-Amyloid 11-40/42 in plasma samples taken from Tg2576 study animals or wild-type littermates. Mice were dosed weekly i.p., and plasma samples collected at 2-month intervals. Plasma levels of peptide were determined by ELISA using biotinylated JRF/hAb11/1 for detection. No peptide was detected in any group until 16 months of age, after which increasing levels of both Ab11-40 (left) and Ab11-42 (right) were found only in the antibody treated group.

Figure 2. Measurement of b-Amyloid 11-40/42 in brain homogenate samples taken from 20-month old Tg2576 study animals or wild-type littermates. Brains were homogenized in diethylamine to measure soluble Ab levels and formic acid to measure insoluble (plaque) Ab. Levels of Ab11-40/42 peptide were determined by ELISA using biotinylated JRF/hAb11/1 for detection. No differences were observed between vehicle control and antibody treated groups.

Figure 3A-F. Holeboard test – At 6 months of age, Tg2576 animals in the antibody-treatment group demonstrated some improvement in time to complete task (latency). By 18-months of age, a slight trend in improvement of number of correct responses was observed in the JRF/hAb11/1 antibody-treated animals although not statistically significant over vehicle-treated animals.

Figure 4A-B. Novel Object Recognition test – a slight improvement over vehicle control was observed in JRF/hAb11/1-treated Tg2576 animals at 8 months of age, but not at any other time points tested

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Figure 5. Y-maze test – a trend in improvement in correct choices is observed in Tg2576 mice treated with JRF/hAb11/1 antibody, as well as in time taken to complete task (latency).

DESCRIPTION OF THE INVENTION

10 The present invention provides isolated, recombinant and/or synthetic anti-amyloid human, primate, rodent, mammalian, chimeric, humanized or CDR-grafted, antibodies and amyloid anti-idiotypic antibodies thereto, as well as compositions and encoding nucleic acid molecules comprising at least one polynucleotide encoding at least one anti-amyloid antibody or anti-idiotypic antibody. The present invention further includes, but is not limited to, methods
15 of making and using such nucleic acids and antibodies and anti-idiotypic antibodies, including diagnostic and therapeutic compositions, methods and devices.

As used herein, an "anti-beta-amyloid antibody," "anti-amyloid antibody," "anti-amyloid antibody portion," or "anti-amyloid antibody fragment" and/or "anti-amyloid antibody variant" and the like include any protein or peptide containing molecule that comprises at least
20 a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, or at least one portion of an amyloid receptor or binding protein, which can be incorporated into an antibody of the present
25 invention. Such antibody optionally further affects a specific ligand, such as but not limited to where such antibody modulates, decreases, increases, antagonizes, antagonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one amyloid activity or binding, or with amyloid receptor activity or binding, *in vitro*, *in situ* and/or *in vivo*. As a non-limiting example, a suitable anti-amyloid antibody, specified portion or variant of the present
30 invention can bind at least one amyloid, or specified portions, variants or domains thereof. A suitable anti-amyloid antibody, specified portion, or variant can also optionally affect at least one of amyloid activity or function, such as but not limited to, RNA, DNA or protein synthesis, amyloid release, amyloid receptor signaling, membrane amyloid cleavage, amyloid activity, amyloid production and/or synthesis.

Antibodies can include one or more of at least one CDR, at least one variable region, at least one constant region, at least one heavy chain (e.g., γ_1 , γ_2 , γ_3 , γ_4 , μ , α_1 , α_2 , δ , ϵ), at least one light chain (e.g., κ and λ), or any portion or fragment thereof, and can further comprise interchain and intrachain disulfide bonds, hinge regions, glycosylation sites that can be separated by a hinge region, as well as heavy chains and light chains. Light chains typically have a molecular weight of about 25Kd and heavy chains typically range from 50K-77Kd. Light chains can exist in two distinct forms or isotypes, kappa (κ) and lambda (λ), which can combine with any of the heavy chain types. All light chains have at least one variable region and at least one constant region. The IgG antibody is considered a typical antibody structure and has two intrachain disulfide bonds in the light chain (one in variable region and one in the constant region), with four in the heavy chain, and such bond encompassing a peptide loop of about 60-70 amino acids comprising a "domain" of about 110 amino acids in the chain. IgG antibodies can be characterized into four classes, IgG1, IgG2, IgG3 and IgG4. Each immunoglobulin class has a different set of functions. The following table summarizes the reported examples of the physicochemical properties of each of the immunoglobulin classes and subclasses.

Property	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	SIgA	IgD	IgE
Heavy Chain	γ_1	γ_1	γ_1	γ_1	μ	α_1	α_2	α_1 / α_2	δ	E
Mean Serum conc. (mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.05	0.03	0.00005
Sedimentation constant	7s	7s	7s	7s	19s	7s	7s	11s	7s	8s
Mol. Wt. ($\times 10^3$)	146	146	170	146	970	160	160	385	184	188
Half Life (days)	5-30	5-30	2-10	5-30	5-15	2-10	2-10	1-10	1-10	1-10
% intravascular distribution	45	45	45	45	80	42	42	Trace	75	50
Carbohydrate (%)	2-3	2-3	2-3	2-3	12	7-11	7-11	7-11	9-14	12

The following table summarizes non-limiting examples of antibody effector functions for human antibody classes and subclasses.

Effector function	IgG1	IgG2	IgG3	IgG4	IgM	IgA	IgD	IgE
Complement fixation	++	+	+++	-	+++	-	-	-
Placental transfer	+	+	+	+	-	-	-	-
Binding to Staph A	+++	+++	-	+++	-	-	-	-
Binding to Strep G	+++	+++	+++	+++	-	-	-	-

Accordingly, the type of antibody or fragment thereof can be selected for use according to the present invention based on the desired characteristics and functions that are desired for a particular therapeutic or diagnostic use, such as but not limited to serum half life, intravascular distribution, complement fixation, etc.

Antibody diversity is generated by at least 5 mechanisms, including (1) the use of multiple genes encoding parts of the antibody; (2) somatic mutation, e.g., primordial V gene mutation during B-cell ontogeny to produce different V genes in different B-cell clones; (3) somatic recombination, e.g., gene segments J1-Jn recombine to join the main part of the V-region gene during B-cell ontogeny; (4) gene conversion where sections of DNA from a number of pseudo V region can be copied into the V region to alter the DNA sequence; and (5) nucleotide addition, e.g., when V and J regions are cut, before joining, and extra nucleotides may be inserted to code for additional amino acids. Non-limiting examples include, but are not limited to, (i) the selection/recombination of V κ , J, and C κ regions from germ line to B-cell clones to generate kappa chains; (ii) selection/recombination of V λ , J, and C λ regions from germ line to B-cell clones to generate lambda chains; (iii) selection/recombination of V $_H$, D1-D30 and J $_H$ 1-J $_H$ 6 genes to form a functional VDJ gene encoding a heavy chain variable region. The above mechanisms work in a coordinated fashion to generate antibody diversity and specificity.

The term "antibody" is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian amyloid. For example, antibody fragments capable of binding to amyloid or portions thereof, including, but not limited to Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and F(ab')₂ (e.g., by pepsin digestion), facb (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, Immunology, supra).

Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a F(ab')₂ heavy chain portion can be designed to include DNA sequences encoding the CH₁ domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques.

As used herein, the term "human antibody" refers to an antibody in which substantially every part of the protein (e.g., CDR, framework, C_L, C_H domains (e.g., C_H1, C_H2, C_H3), hinge, (V_L, V_H)) is substantially non-immunogenic in humans, with only minor sequence changes or

variations. Similarly, antibodies designated primate (monkey, baboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pig, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies of the invention can include any combination of the above. Such changes or variations
5 optionally and preferably retain or reduce the immunogenicity in humans or other species relative to non-modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human
10 antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies. For example, an Fv can comprise a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

15 Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for at least one amyloid protein, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific
20 antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule,
25 which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, US Patent Nos, 6210668, 6193967, 6132992, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 5807706, 5643759, 5601819, 5582996, 5496549, 4676980, WO 91/00360, WO 92/00373, EP 03089, Traunecker et al., EMBO J. 10:3655
30 (1991), Suresh et al., Methods in Enzymology 121:210 (1986), as well known in the art.

Anti-amyloid antibodies (also termed amyloid antibodies) useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to amyloid and optionally and preferably having low toxicity. In particular, an antibody,
35 specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low immunogenicity, is useful in the present invention. The antibodies that

can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as
5 raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double antigen enzyme immunoassay) (Elliott *et al.*, *Lancet* 344:1125-1127 (1994), and as well known in the art).

Utility

10 The isolated nucleic acids of the present invention can be used for production of at least one anti-amyloid antibody or specified variant thereof, which can be used to measure or effect in an cell, tissue, organ or animal (including mammals and humans), to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one amyloid condition, selected from, but not limited to, at least one of an immune disorder or
15 disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified amyloid related condition.

Such a method can comprise administering an effective amount of a composition or a pharmaceutical composition comprising at least one anti-amyloid antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation, prevention, or
20 reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.001 to 500 mg/kg per single (e.g., bolus), multiple or continuous administration, or to achieve a serum concentration of 0.01-5000 µg/ml serum concentration per single, multiple, or continuous administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

Citations

25 All publications or patents cited herein are and as well known in the art as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or
30 printed formats. The following references are and as well known in the art: Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY

(1994-2001); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001).

Antibodies of the Present Invention

At least one anti-amyloid antibody of the present invention can be optionally produced
5 by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells,
as well known in the art. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology,
John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A
Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies,
a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols
10 in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols
in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), as well known in the art.

Human antibodies that are specific for human amyloid proteins or fragments thereof
can be raised against an appropriate immunogenic antigen, such as isolated and/or amyloid
protein or a portion thereof (including synthetic molecules, such as synthetic peptides), e.g., but
15 not limited to at least one of amino acid 1-7, 1-40, 31-42 and 36-40 of SEQ ID NO:50. Other
specific or general mammalian antibodies can be similarly raised. Preparation of immunogenic
antigens, and monoclonal antibody production can be performed using any suitable technique.

In one approach, a hybridoma is produced by fusing a suitable immortal cell line (e.g.,
a myeloma cell line such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1,
20 L.5, >243, P3X63Ag8.653, Sp2 SA3, Sp2 MAI, Sp2 SS1, Sp2 SA5, U937, MLA 144, ACT IV,
MOLT4, DA-1, JURKAT, WEHI, K-562, COS, RAJI, NIH 3T3, HL-60, MLA 144,
NAMAIWA, NEURO 2A, or the like, or heteromyelomas, fusion products thereof, or any cell or
fusion cell derived therefrom, or any other suitable cell line as known in the art. See, e.g.,
www.atcc.org, www.lifetech.com., and the like, with antibody producing cells, such as, but not
25 limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell
containing cells, or any other cells expressing heavy or light chain constant or variable or
framework or CDR sequences, either as endogenous or heterologous nucleic acid, as
recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian,
fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA,
30 cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA,
tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof.
See, e.g., Ausubel, supra, and Colligan, Immunology, supra, chapter 2, and as well known in
the art.

Antibody producing cells can also be obtained from the peripheral blood or, preferably
35 the spleen or lymph nodes, of humans or other suitable animals that have been immunized with
the antigen of interest. Any other suitable host cell can also be used for expressing

heterologous or endogenous nucleic acid encoding an antibody, specified fragment or variant thereof, of the present invention. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).

Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a peptide or protein library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, RNA, cDNA, or the like, display library; e.g., as available from Cambridge antibody Technologies, Cambridgeshire, UK; MorphoSys, Martinsreid/Planegg, DE; Biovation, Aberdeen, Scotland, UK; BioInvent, Lund, Sweden; Dyax Corp., Enzon, Affymax/Biosite; Xoma, Berkeley, CA; Ixsys. See, e.g., EP 368,684, PCT/GB91/01134; PCT/GB92/01755; PCT/GB92/002240; PCT/GB92/00883; PCT/GB93/00605; US 08/350260(5/12/94); PCT/GB94/01422; PCT/GB94/02662; PCT/GB97/01835; (CAT/MRC); WO90/14443; WO90/14424; WO90/14430; PCT/US94/1234; WO92/18619; WO96/07754; (Scripps); WO96/13583, WO97/08320 (MorphoSys); WO95/16027 (BioInvent); WO88/06630; WO90/3809 (Dyax); US 4,704,692 (Enzon); PCT/US91/02989 (Affymax); WO89/06283; EP 371 998; EP 550 400; (Xoma); EP 229 046; PCT/US91/07149 (Ixsys); or stochastically generated peptides or proteins - US 5723323, 5763192, 5814476, 5817483, 5824514, 5976862, WO 86/05803, EP 590 689 (Ixsys, now Applied Molecular Evolution (AME), as well known in the art) or that rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al., Microbiol. Immunol. 41:901-907 (1997); Sandhu et al., Crit. Rev. Biotechnol. 16:95-118 (1996); Eren et al., Immunol. 93:154-161 (1998), and as well known in the art as well as related patents and applications) that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein. Such techniques, include, but are not limited to, ribosome display (Hanes et al., Proc. Natl. Acad. Sci. USA, 94:4937-4942 (May 1997); Hanes et al., Proc. Natl. Acad. Sci. USA, 95:14130-14135 (Nov. 1998)); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (US pat. No. 5,627,052, Wen et al., J. Immunol. 17:887-892 (1987); Babcook et al., Proc. Natl. Acad. Sci. USA 93:7843-7848 (1996)); gel microdroplet and flow cytometry (Powell et al., Biotechnol. 8:333-337 (1990); One Cell Systems, Cambridge, MA; Gray et al., J. Imm. Meth. 182:155-163 (1995); Kenny et al., Bio/Technol. 13:787-790 (1995)); B-cell selection (Steenbakkers et al., Molec. Biol. Reports 19:125-134 (1994); Jonak et al., Progress Biotech, Vol. 5, In Vitro Immunization in Hybridoma Technology, Borrebaeck, ed., Elsevier Science Publishers B.V., Amsterdam, Netherlands (1988)).

Methods for engineering or humanizing non-human or human antibodies can also be used and are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid residues from a source which is non-human, e.g., but not limited to mouse, rat, rabbit, non-human primate or other mammal. These human amino acid residues are often
5 referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence.

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10 rabbit, non-human primate or other mammal. These human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence.

By "humanized antibody" is meant an antibody that is composed partially or fully of amino acid sequences derived from a human antibody germline by altering the sequence of an
15 antibody having non-human complementarity determining regions (CDR). The simplest such alteration may consist simply of substituting the constant region of a human antibody for the murine constant region, thus resulting in a human/murine chimera which may have sufficiently low immunogenicity to be acceptable for pharmaceutical use.

Preferably, however, the variable region of the antibody and even the CDR is also
20 humanized by techniques that are by now well known in the art. The framework regions of the variable regions are substituted by the corresponding human framework regions leaving the non-human CDR substantially intact, or even replacing the CDR with sequences derived from a human genome. Fully human antibodies are produced in genetically modified mice whose immune systems have been altered to correspond to human immune systems. As mentioned
25 above, it is sufficient for use in the methods of the invention, to employ an immunologically specific fragment of the antibody, including fragments representing single chain forms.

A humanized antibody again refers to an antibody comprising a human framework, at least one CDR from a non-human antibody, and in which any constant region present is substantially identical to a human immunoglobulin constant region, i.e., at least about 85-90%,
30 preferably at least 95% identical. Hence, all parts of a humanized antibody, except possibly the CDRs, are substantially identical to corresponding parts of one or more native human immunoglobulin sequences. For example, a humanized immunoglobulin would typically not encompass a chimeric mouse variable region/human constant region antibody.

Humanized antibodies have at least three potential advantages over non- human and
35 chimeric antibodies for use in human therapy:

1) Because the effector portion is human, it may interact better with the other parts of the human immune system (e.g., destroy the target cells more efficiently by complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC)).

2) The human immune system should not recognize the framework or C region of the humanized antibody as foreign, and therefore the antibody response against such an injected antibody should be less than against a totally foreign non-human antibody or a partially foreign chimeric antibody.

3) Injected non-human antibodies have been reported to have a half-life in the human circulation much shorter than the half-life of human antibodies. Injected humanized antibodies will have a half-life essentially identical to naturally occurring human antibodies, allowing smaller and less frequent doses to be given.

Known human Ig sequences are disclosed, e.g.,
www.ncbi.nlm.nih.gov/entrez/query.fcgi; www.atcc.org/phage/hdb.html; www.sciquest.com/;
www.abcam.com/; www.antibodyresource.com/onlinecomp.html;
www.public.iastate.edu/~pedro/research_tools.html; www.mgen.uni-heidelberg.de/SD/IT/IT.html; www.whfreeman.com/immunology/CH05/kuby05.htm;
www.library.thinkquest.org/12429/Immune/Antibody.html;
www.hhmi.org/grants/lectures/1996/vlab/; www.path.cam.ac.uk/~mrc7/mikeimages.html;
www.antibodyresource.com/;
mcb.harvard.edu/BioLinks/Immunology.html; www.immunologylink.com/;
pathbox.wustl.edu/~hcenter/index.html; www.biotech.ufl.edu/~hcl/;
www.pebio.com/pa/340913/340913.html; www.nal.usda.gov/awic/pubs/antibody/;
www.m.ehime-u.ac.jp/~yasuhito/Elisa.html; www.biodesign.com/table.asp;
www.icnet.uk/axp/facs/davies/links.html; www.biotech.ufl.edu/~fccl/protocol.html; www.isac-net.org/sites_geo.html; aximt1.imt.uni-marburg.de/~rek/AEPStart.html;
baserv.uci.kun.nl/~jraats/links1.html; www.recab.uni-hd.de/immuno.bme.nwu.edu/; www.mrc-cpe.cam.ac.uk/imt-doc/public/INTRO.html; www.ibt.unam.mx/vir/V_mice.html;
imgt.cnusc.fr:8104/; www.biochem.ucl.ac.uk/~martin/abs/index.html; antibody.bath.ac.uk/;
abgen.cvm.tamu.edu/lab/wwwabgen.html;
www.unizh.ch/~honegger/AHOseminar/Slide01.html; www.cryst.bbk.ac.uk/~ubcg07s/;
www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm;
www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html;
www.ibt.unam.mx/vir/structure/stat_aim.html; www.biosci.missouri.edu/smithgp/index.html;
www.cryst.bioc.cam.ac.uk/~fmolina/Web-pages/Pept/spottech.html;
www.jerini.de/fr_products.htm; www.patents.ibm.com/ibm.html. Kabat et al., Sequences of

Proteins of Immunological Interest, U.S. Dept. Health (1983), as well known in the art.

Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art. Generally part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions are replaced with human or other amino acids. Antibodies can also optionally be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, humanized antibodies can be optionally prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the consensus and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding. Humanization or engineering of antibodies of the present invention can be performed using any known method, such as but not limited to those described in, Winter (Jones et al., Nature 321:522 (1986); Riechmann et al., Nature 332:323 (1988); Verhoeven et al., Science 239:1534 (1988)), Sims et al., J. Immunol. 151: 2296 (1993); Chothia and Lesk, J. Mol. Biol. 196:901 (1987), Carter et al., Proc. Natl. Acad. Sci. U.S.A. 89:4285 (1992); Presta et al., J. Immunol. 151:2623 (1993), US patent Nos: 5723323, 5976862, 5824514, 5817483, 5814476, 5763192, 5723323, 5,766886, 5714352, 6204023, 6180370, 5693762, 5530101, 5585089, 5225539; 4816567, PCT/: US98/16280, US96/18978, US91/09630, US91/05939, US94/01234, GB89/01334, GB91/01134, GB92/01755; WO90/14443, WO90/14424, WO90/14430, EP 229246, as well known in the art, included references cited therein.

The anti-amyloid antibody can also be optionally generated by immunization of a transgenic animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of producing a repertoire of human antibodies, as described herein and/or as known in the art. Cells that produce a human anti-amyloid antibody can be isolated from such animals and immortalized using suitable methods, such as the methods described herein.

Transgenic mice that can produce a repertoire of human antibodies that bind to human antigens can be produced by known methods (e.g., but not limited to, U.S. Pat. Nos: 5,770,428,

5,569,825, 5,545,806, 5,625,126, 5,625,825, 5,633,425, 5,661,016 and 5,789,650 issued to Lonberg *et al.*; Jakobovits *et al.* WO 98/50433, Jakobovits *et al.* WO 98/24893, Lonberg *et al.* WO 98/24884, Lonberg *et al.* WO 97/13852, Lonberg *et al.* WO 94/25585, Kucherlapate *et al.* WO 96/34096, Kucherlapate *et al.* EP 0463 151 B1, Kucherlapate *et al.* EP 0710 719 A1, Surani *et al.* US. Pat. No. 5,545,807, Bruggemann *et al.* WO 90/04036, Bruggemann *et al.* EP 0438 474 B1, Lonberg *et al.* EP 0814 259 A2, Lonberg *et al.* GB 2 272 440 A, Lonberg *et al.* *Nature* 368:856-859 (1994), Taylor *et al.*, *Int. Immunol.* 6(4):579-591 (1994), Green *et al.*, *Nature Genetics* 7:13-21 (1994), Mendez *et al.*, *Nature Genetics* 15:146-156 (1997), Taylor *et al.*, *Nucleic Acids Research* 20(23):6287-6295 (1992), Tuaillon *et al.*, *Proc Natl Acad Sci USA* 90(8):3720-3724 (1993), Lonberg *et al.*, *Int Rev Immunol* 13(1):65-93 (1995) and Fishwald *et al.*, *Nat Biotechnol* 14(7):845-851 (1996), which are as well known in the art). Generally, these mice comprise at least one transgene comprising DNA from at least one human immunoglobulin locus that is functionally rearranged, or which can undergo functional rearrangement. The endogenous immunoglobulin loci in such mice can be disrupted or deleted to eliminate the capacity of the animal to produce antibodies encoded by endogenous genes.

Screening antibodies for specific binding to similar proteins or fragments can be conveniently achieved using peptide display libraries. This method involves the screening of large collections of peptides for individual members having the desired function or structure. Antibody screening of peptide display libraries is well known in the art. The displayed peptide sequences can be from 3 to 5000 or more amino acids in length, frequently from 5-100 amino acids long, and often from about 8 to 25 amino acids long. In addition to direct chemical synthetic methods for generating peptide libraries, several recombinant DNA methods have been described. One type involves the display of a peptide sequence on the surface of a bacteriophage or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular displayed peptide sequence. Such methods are described in PCT Patent Publication Nos. 91/17271, 91/18980, 91/19818, and 93/08278. Other systems for generating libraries of peptides have aspects of both in vitro chemical synthesis and recombinant methods. See, PCT Patent Publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754; and 5,643,768. Peptide display libraries, vector, and screening kits are commercially available from such suppliers as Invitrogen (Carlsbad, CA), and Cambridge antibody Technologies (Cambridgeshire, UK). See, e.g., U.S. Pat. Nos. 4704692, 4939666, 4946778, 5260203, 5455030, 5518889, 5534621, 5656730, 5763733, 5767260, 5856456, assigned to Enzon; 5223409, 5403484, 5571698, 5837500, assigned to Dyax, 5427908, 5580717, assigned to Affymax; 5885793, assigned to Cambridge antibody Technologies; 5750373, assigned to Genentech, 5618920, 5595898, 5576195, 5698435, 5693493, 5698417, assigned to Xoma, Colligan, *supra*; Ausubel, *supra*; or Sambrook, *supra*, each of the above patents and publications and as well known in the art.

Antibodies of the present invention can also be prepared using at least one anti-amyloid antibody encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, sheep, and the like, that produce such antibodies in their milk. Such animals can be provided using known methods. See, e.g., but not limited to, US patent nos. 5,827,690;
5 5,849,992; 4,873,316; 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is and as well known in the art.

Antibodies of the present invention can additionally be prepared using at least one anti-amyloid antibody encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to tobacco and maize) that produce such antibodies, specified portions or
10 variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves expressing recombinant proteins have been successfully used to provide large amounts of recombinant proteins, e.g., using an inducible promoter. See, e.g., Cramer et al., Curr. Top. Microbiol. Immunol. 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian proteins at commercial production
15 levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al., Adv. Exp. Med. Biol. 464:127-147 (1999) and references cited therein. antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al., Plant Mol. Biol. 38:101-109
20 (1998) and reference cited therein. Thus, antibodies of the present invention can also be produced using transgenic plants, according to know methods. See also, e.g., Fischer et al., Biotechnol. Appl. Biochem. 30:99-108 (Oct., 1999), Ma et al., Trends Biotechnol. 13:522-7 (1995); Ma et al., Plant Physiol. 109:341-6 (1995); Whitelam et al., Biochem. Soc. Trans. 22:940-944 (1994); and references cited therein. See, also generally for plant expression of
25 antibodies, but not limited to, Each of the above references is and as well known in the art.

The antibodies of the invention can bind human amyloid with a wide range of affinities (K_D). In a preferred embodiment, at least one human mAb of the present invention can optionally bind human amyloid with high affinity. For example, a human mAb can bind human amyloid with a K_D equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9
30 (or any range or value therein) $\times 10^{-7}$, 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} , 10^{-12} , 10^{-13} or any range or value therein.

The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, *et al.*, "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY
35 (1984); Kuby, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction

can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., K_D , K_a , K_d) are preferably made with standardized solutions of antibody and antigen, and a standardized buffer, such as the buffer described herein.

5 Nucleic Acid Molecules

Using the information provided herein, such as the nucleotide sequences encoding at least 70-100% of the contiguous amino acids of at least one of SEQ ID NOS:42-49, 53-60, 63-70, 73-80, specified fragments, variants or consensus sequences thereof, or a deposited vector comprising at least one of these sequences, a nucleic acid molecule of the present invention
10 encoding at least one anti-amyloid antibody can be obtained using methods described herein or as known in the art.

Nucleic acid molecules of the present invention can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations
15 thereof. The DNA can be triple-stranded, double-stranded or single-stranded, or any combination thereof. Any portion of at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as the anti-sense strand.

Isolated nucleic acid molecules of the present invention can include nucleic acid
20 molecules comprising an open reading frame (ORF), optionally with one or more introns, e.g., but not limited to, at least one specified portion of at least one CDR, as CDR1, CDR2 and/or CDR3 of at least one heavy chain (e.g., SEQ ID NOS:42-44, 53-55) or light chain (e.g., SEQ ID NOS:45-47, 56-58); nucleic acid molecules comprising the coding sequence for an anti-amyloid antibody or variable region (e.g., SEQ ID NOS:48, 49, 59, 60), such as but not limited
25 to SEQ ID NOS:51, 52, 61, and 62; and nucleic acid molecules which comprise a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least one anti-amyloid antibody as described herein and/or as known in the art. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate nucleic acid variants that code for
30 specific anti-amyloid antibodies of the present invention. See, e.g., Ausubel, et al., *supra*, and such nucleic acid variants are included in the present invention.

As indicated herein, nucleic acid molecules of the present invention which comprise a nucleic acid encoding an anti-amyloid antibody can include, but are not limited to, those encoding the amino acid sequence of an antibody fragment, by itself; the coding sequence for
35 the entire antibody or a portion thereof; the coding sequence for an antibody, fragment or portion, as well as additional sequences, such as the coding sequence of at least one signal

leader or fusion peptide, with or without the aforementioned additional coding sequences, such as at least one intron, together with additional, non-coding sequences, including but not limited to, non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals (for example, ribosome binding and stability of mRNA); an additional coding sequence that codes for additional amino acids, such as those that provide additional functionalities. Thus, the sequence encoding an antibody can be fused to a marker sequence, such as a sequence encoding a peptide that facilitates purification of the fused antibody comprising an antibody fragment or portion.

10 **Polynucleotides Which Selectively Hybridize to a Polynucleotide as Described Herein**

The present invention provides isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides of the present invention can be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library.

Preferably, the cDNA library comprises at least 80% full-length sequences, preferably at least 85% or 90% full-length sequences, and more preferably at least 95% full-length sequences. The cDNA libraries can be normalized to increase the representation of rare sequences. Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and can be employed to identify orthologous or paralogous sequences.

Optionally, polynucleotides of this invention will encode at least a portion of an antibody encoded by the polynucleotides described herein. The polynucleotides of this invention embrace nucleic acid sequences that can be employed for selective hybridization to a polynucleotide encoding an antibody of the present invention. See, e.g., Ausubel, supra; Colligan, supra, as well known in the art.

Construction of Nucleic Acids

The isolated nucleic acids of the present invention can be made using (a) recombinant methods, (b) synthetic techniques, (c) purification techniques, or combinations thereof, as well known in the art.

The nucleic acids can conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide of the present invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the proteins of the present invention. The nucleic acid of the present invention - excluding the coding sequence - is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention.

Additional sequences can be added to such cloning and/or expression sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Recombinant Methods for Constructing Nucleic Acids

The isolated nucleic acid compositions of this invention, such as RNA, cDNA, genomic DNA, or any combination thereof, can be obtained from biological sources using any number of cloning methodologies known to those of skill in the art. In some embodiments, oligonucleotide probes that selectively hybridize, under stringent conditions, to the polynucleotides of the present invention are used to identify the desired sequence in a cDNA or genomic DNA library. The isolation of RNA, and construction of cDNA and genomic libraries, is well known to those of ordinary skill in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Nucleic Acid Screening and Isolation Methods

A cDNA or genomic library can be screened using a probe based upon the sequence of a polynucleotide of the present invention, such as those disclosed herein. Probes can be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different organisms. Those of skill in the art will appreciate that various degrees of stringency of hybridization can be employed in the assay; and either the hybridization or the wash medium can be stringent. As the conditions for hybridization become more stringent, there must be a greater degree of complementarity between the probe and the target for duplex formation to occur. The degree of stringency can be controlled by one or more of temperature, ionic strength, pH and the presence of a partially denaturing solvent such as formamide. For example, the stringency of hybridization is conveniently varied by changing the polarity of the reactant solution through, for example, manipulation of the concentration of formamide within the range of 0% to 50%. The degree of complementarity (sequence identity) required for detectable binding will vary in accordance with the stringency of the hybridization medium and/or wash medium. The degree of complementarity will optimally be 100%, or 70-100%, or any range or value therein. However, it

should be understood that minor sequence variations in the probes and primers can be compensated for by reducing the stringency of the hybridization and/or wash medium.

Methods of amplification of RNA or DNA are well known in the art and can be used according to the present invention without undue experimentation, based on the teaching and guidance presented herein.

Known methods of DNA or RNA amplification include, but are not limited to, polymerase chain reaction (PCR) and related amplification processes (see, e.g., U.S. Patent Nos. 4,683,195, 4,683,202, 4,800,159, 4,965,188, to Mullis, et al.; 4,795,699 and 4,921,794 to Tabor, et al; 5,142,033 to Innis; 5,122,464 to Wilson, et al.; 5,091,310 to Innis; 5,066,584 to Gyllensten, et al; 4,889,818 to Gelfand, et al; 4,994,370 to Silver, et al; 4,766,067 to Biswas; 4,656,134 to Ringold) and RNA mediated amplification that uses anti-sense RNA to the target sequence as a template for double-stranded DNA synthesis (U.S. Patent No. 5,130,238 to Malek, et al, with the tradename NASBA), the entire contents of which references are incorporated herein by reference. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*.)

For instance, polymerase chain reaction (PCR) technology can be used to amplify the sequences of polynucleotides of the present invention and related genes directly from genomic DNA or cDNA libraries. PCR and other in vitro amplification methods can also be useful, for example, to clone nucleic acid sequences that code for proteins to be expressed, to make nucleic acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes. Examples of techniques sufficient to direct persons of skill through in vitro amplification methods are found in Berger, *supra*, Sambrook, *supra*, and Ausubel, *supra*, as well as Mullis, et al., U.S. Patent No. 4,683,202 (1987); and Innis, et al., PCR Protocols A Guide to Methods and Applications, Eds., Academic Press Inc., San Diego, CA (1990). Commercially available kits for genomic PCR amplification are known in the art. See, e.g., Advantage-GC Genomic PCR Kit (Clontech). Additionally, e.g., the T4 gene 32 protein (Boehringer Mannheim) can be used to improve yield of long PCR products.

Synthetic Methods for Constructing Nucleic Acids

The isolated nucleic acids of the present invention can also be prepared by direct chemical synthesis by known methods (see, e.g., Ausubel, et al., *supra*). Chemical synthesis generally produces a single-stranded oligonucleotide, which can be converted into double-stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. One of skill in the art will recognize that while chemical synthesis of DNA can be limited to sequences of about 100 or more bases, longer sequences can be obtained by the ligation of shorter sequences.

Recombinant Expression Cassettes

The present invention further provides recombinant expression cassettes comprising a nucleic acid of the present invention. A nucleic acid sequence of the present invention, for example a cDNA or a genomic sequence encoding an antibody of the present invention, can be used to construct a recombinant expression cassette that can be introduced into at least one desired host cell. A recombinant expression cassette will typically comprise a polynucleotide of the present invention operably linked to transcriptional initiation regulatory sequences that will direct the transcription of the polynucleotide in the intended host cell. Both heterologous and non-heterologous (i.e., endogenous) promoters can be employed to direct expression of the nucleic acids of the present invention.

In some embodiments, isolated nucleic acids that serve as promoter, enhancer, or other elements can be introduced in the appropriate position (upstream, downstream or in intron) of a non-heterologous form of a polynucleotide of the present invention so as to up or down regulate expression of a polynucleotide of the present invention. For example, endogenous promoters can be altered *in vivo* or *in vitro* by mutation, deletion and/or substitution.

Vectors And Host Cells

The present invention also relates to vectors that include isolated nucleic acid molecules of the present invention, host cells that are genetically engineered with the recombinant vectors, and the production of at least one anti-amyloid antibody by recombinant techniques, as is well known in the art. See, e.g., Sambrook, et al., supra; Ausubel, et al., supra, as well known in the art.

The polynucleotides can optionally be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it can be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

The DNA insert should be operatively linked to an appropriate promoter. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating at the beginning and a termination codon (e.g., UAA, UGA or UAG) appropriately positioned at the end of the mRNA to be translated, with UAA and UAG preferred for mammalian or eukaryotic cell expression.

Expression vectors will preferably but optionally include at least one selectable marker. Such markers include, e.g., but not limited to, methotrexate (MTX), dihydrofolate reductase (DHFR, US Pat.Nos. 4,399,216; 4,634,665; 4,656,134; 4,956,288; 5,149,636; 5,179,017, ampicillin, neomycin (G418), mycophenolic acid, or glutamine synthetase (GS, US Pat.Nos.

5,122,464; 5,770,359; 5,827,739) resistance for eukaryotic cell culture, and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria or prokaryotics (the above patents are entirely incorporated hereby by reference). Appropriate culture mediums and conditions for the above-described host cells are known in the art. Suitable vectors will be readily apparent to the skilled artisan. Introduction of a vector construct into a host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other known methods. Such methods are described in the art, such as Sambrook, supra, Chapters 1-4 and 16-18; Ausubel, supra, Chapters 1, 9, 13, 15, 16.

At least one antibody of the present invention can be expressed in a modified form, such as a fusion protein, and can include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of an antibody to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties can be added to an antibody of the present invention to facilitate purification. Such regions can be removed prior to final preparation of an antibody or at least one fragment thereof. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Chapters 17.29-17.42 and 18.1-18.74; Ausubel, supra, Chapters 16, 17 and 18.

Those of ordinary skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a protein of the present invention.

Alternatively, nucleic acids of the present invention can be expressed in a host cell by turning on (by manipulation) in a host cell that contains endogenous DNA encoding an antibody of the present invention. Such methods are well known in the art, e.g., as described in US patent Nos. 5,580,734, 5,641,670, 5,733,746, and 5,733,761, and as well known in the art.

Illustrative of cell cultures useful for the production of the antibodies, specified portions or variants thereof, are mammalian cells. Mammalian cell systems often will be in the form of monolayers of cells although mammalian cell suspensions or bioreactors can also be used. A number of suitable host cell lines capable of expressing intact glycosylated proteins have been developed in the art, and include the COS-1 (e.g., ATCC CRL 1650), COS-7 (e.g., ATCC CRL-1651), HEK293, BHK21 (e.g., ATCC CRL-10), CHO (e.g., ATCC CRL 1610) and BSC-1 (e.g., ATCC CRL-26) cell lines, Cos-7 cells, CHO cells, hep G2 cells, P3X63Ag8.653, SP2/0-Ag14, 293 cells, HeLa cells and the like, which are readily available from, for example, American Type Culture Collection, Manassas, Va (www.atcc.org). Host cells include cells of lymphoid origin such as myeloma and lymphoma cells. Host cells are P3X63Ag8.653 cells (ATCC Accession Number CRL-1580) and SP2/0-Ag14 cells (ATCC Accession Number CRL-1851).

In a particularly preferred embodiment, the recombinant cell is a P3X63Ab8.653 or an SP2/0-Ag14 cell.

Expression vectors for these cells can include one or more of the following expression control sequences, such as, but not limited to an origin of replication; a promoter (e.g., late or early SV40 promoters, the CMV promoter (US Pat.Nos. 5,168,062; 5,385,839), an HSV tk promoter, a pgk (phosphoglycerate kinase) promoter, an EF-1 alpha promoter (US Pat.No. 5,266,491), at least one human immunoglobulin promoter; an enhancer, and/or processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites (e.g., an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. See, e.g., Ausubel et al., supra; Sambrook, et al., supra. Other cells useful for production of nucleic acids or proteins of the present invention are known and/or available, for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas (www.atcc.org) or other known or commercial sources.

When eukaryotic host cells are employed, polyadenylation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenylation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript can also be included. An example of a splicing sequence is the VP1 intron from SV40 (Sprague, et al., J. Virol. 45:773-781 (1983)). Additionally, gene sequences to control replication in the host cell can be incorporated into the vector, as known in the art.

Purification of an Antibody

An anti-amyloid antibody can be recovered and purified from recombinant cell cultures by well-known methods including, but not limited to, protein A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, Current Protocols in Immunology, or Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), e.g., Chapters 1, 4, 6, 8, 9, 10, as well known in the art.

Antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the antibody of the present invention can be glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Sections 17.37-17.42; Ausubel, supra, Chapters 10, 12, 13, 16, 18 and 20, Colligan, Protein Science, supra, Chapters 12-14, all and as well known in the art.

Anti-amyloid Antibodies

The isolated antibodies of the present invention comprise an antibody amino acid sequences disclosed herein encoded by any suitable polynucleotide, or any isolated or prepared antibody. Preferably, the human antibody or antigen-binding fragment binds human amyloid and, thereby partially or substantially neutralizes at least one biological activity of the protein. An antibody, or specified portion or variant thereof, that partially or preferably substantially neutralizes at least one biological activity of at least one amyloid protein or fragment can bind the protein or fragment and thereby inhibit activities mediated through the binding of amyloid to the amyloid receptor or through other amyloid-dependent or mediated mechanisms. As used herein, the term “neutralizing antibody” refers to an antibody that can inhibit an amyloid-dependent activity by about 20-120%, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% or more depending on the assay. The capacity of an anti-amyloid antibody to inhibit an amyloid-dependent activity is preferably assessed by at least one suitable amyloid protein or receptor assay, as described herein and/or as known in the art. A human antibody of the invention can be of any class (IgG, IgA, IgM, IgE, IgD, etc.) or isotype and can comprise a kappa or lambda light chain. In one embodiment, the human antibody comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. Antibodies of this type can be prepared by employing a transgenic mouse or other transgenic non-human mammal comprising at least one human light chain (e.g., IgG, IgA and IgM (e.g., $\gamma 1$, $\gamma 2$, $\gamma 3$, $\gamma 4$) transgenes as described herein and/or as known in the art. In another embodiment, the anti-human amyloid human antibody comprises an IgG1 heavy chain and an IgG1 light chain.

At least one antibody of the invention binds at least one specified epitope specific to at least one amyloid protein, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of the protein, which epitope is preferably comprised of at least one extracellular, soluble, hydrophilic, external or cytoplasmic portion of the protein. The at least one specified epitope can comprise any combination of at least one amino acid sequence of at least 1-3 amino acids to the entire specified portion of contiguous amino acids of the SEQ ID NO:50. As non-limiting examples, antibodies of the present invention showed binding of amino acids 2-7, 3-8, 33-42, and/or 34-40 of SEQ ID NO:50.

Generally, the human antibody or antigen-binding fragment of the present invention will comprise an antigen-binding region that comprises at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one heavy chain variable region and at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one light chain variable region. As a non-limiting example, the antibody or

antigen-binding portion or variant can comprise at least one of the heavy chain CDR3 having the amino acid sequence of SEQ ID NO:44, and/or a light chain CDR3 having the amino acid sequence of SEQ ID NO:47. In a particular embodiment, the antibody or antigen-binding fragment can have an antigen-binding region that comprises at least a portion of at least one heavy chain CDR (i.e., CDR1, CDR2 and/or CDR3) having the amino acid sequence of the corresponding CDRs 1, 2 and/or 3 (e.g., SEQ ID NOS:42, 43 and/or 44; 53, 54 and/or 55; 63, 64 and/or 65; 73, 74 and/or 75). In another particular embodiment, the antibody or antigen-binding portion or variant can have an antigen-binding region that comprises at least a portion of at least one light chain CDR (i.e., CDR1, CDR2 and/or CDR3) having the amino acid sequence of the corresponding CDRs 1, 2 and/or 3 (e.g., SEQ ID NOS:45, 46 and/or 47; 56, 57 and/or 58; 66, 67 and/or 68; 76, 77 and/or 78). In a preferred embodiment the three heavy chain CDRs and the three light chain CDRs of the antibody or antigen-binding fragment have the amino acid sequence of the corresponding CDRs of at least one of mAb C701, C705, C706, and C707, as described herein. Such antibodies can be prepared by chemically joining together the various portions (e.g., CDRs, framework) of the antibody using conventional techniques, by preparing and expressing a (i.e., one or more) nucleic acid molecule that encodes the antibody using conventional techniques of recombinant DNA technology or by using any other suitable method.

The anti-amyloid antibody can comprise at least one of a heavy or light chain variable region having a defined amino acid sequence. Any suitable Ig variable sequence can be used, e.g., from any subclass or any combination or fragment thereof. Such sequences are well known in the art.

As a non-limiting example, representative variable sequences include those from IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, and the like, e.g., HC and LC, FR1, FR2, and/or FR3 sequences from any combination of Ig subclasses, e.g., as presented in SEQ ID NOS: 48-49, and 59-60.

As a further non-limiting example, in a preferred embodiment, the anti-amyloid antibody comprises at least one of at least one heavy chain variable region, optionally having the amino acid sequence of SEQ ID NO:48 and/or at least one light chain variable region, optionally having the amino acid sequence of SEQ ID NO:49. In another preferred embodiment, the anti-amyloid antibody comprises at least one of at least one heavy chain variable region, optionally having the amino acid sequence of SEQ ID NO:59 and/or at least one light chain variable region, optionally having the amino acid sequence of SEQ ID NO:60.

Antibodies that bind to human amyloid and that comprise a defined heavy or light chain variable region can be prepared using suitable methods, such as phage display (Katsube, Y., *et al.*, *Int J Mol. Med*, 1(5):863-868 (1998)) or methods that employ transgenic animals, as

known in the art and/or as described herein. For example, a transgenic mouse, comprising a functionally rearranged human immunoglobulin heavy chain transgene and a transgene comprising DNA from a human immunoglobulin light chain locus that can undergo functional rearrangement, can be immunized with human amyloid or a fragment thereof to elicit the
5 production of antibodies. If desired, the antibody producing cells can be isolated and hybridomas or other immortalized antibody-producing cells can be prepared as described herein and/or as known in the art. Alternatively, the antibody, specified portion or variant can be expressed using the encoding nucleic acid or portion thereof in a suitable host cell.

The invention also relates to antibodies, antigen-binding fragments, immunoglobulin
10 chains and CDRs comprising amino acids in a sequence that is substantially the same as an amino acid sequence described herein. Preferably, such antibodies or antigen-binding fragments and antibodies comprising such chains or CDRs can bind human amyloid with high affinity (e.g., K_D less than or equal to about 10^{-9} M). Amino acid sequences that are substantially the same as the sequences described herein include sequences comprising
15 conservative amino acid substitutions, as well as amino acid deletions and/or insertions. A conservative amino acid substitution refers to the replacement of a first amino acid by a second amino acid that has chemical and/or physical properties (e.g, charge, structure, polarity, hydrophobicity/ hydrophilicity) that are similar to those of the first amino acid. Conservative substitutions include replacement of one amino acid by another within the following groups:
20 lysine (K), arginine (R) and histidine (H); aspartate (D) and glutamate (E); asparagine (N), glutamine (Q), serine (S), threonine (T), tyrosine (Y), K, R, H, D and E; alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), tryptophan (W), methionine (M), cysteine (C) and glycine (G); F, W and Y; C, S and T.

Amino Acid Codes

25 The amino acids that make up anti-amyloid antibodies of the present invention are often abbreviated. The amino acid designations can be indicated by designating the amino acid by its single letter code, its three letter code, name, or three nucleotide codon(s) as is well understood in

the art (see Alberts, B., et al., Molecular Biology of The Cell, Third Ed., Garland Publishing, Inc., New York, 1994):

SINGLE LETTER CODE	THREE LETTER CODE	NAME	THREE NUCLEOTIDE CODON(S)
A	Ala	Alanine	GCA, GCC, GCG, GCU
C	Cys	Cysteine	UGC, UGU
D	Asp	Aspartic acid	GAC, GAU
E	Glu	Glutamic acid	GAA, GAG
F	Phe	Phenylalanine	UUC, UUU
G	Gly	Glycine	GGA, GGC, GGG, GGU
H	His	Histidine	CAC, CAU
I	Ile	Isoleucine	AUA, AUC, AUU
K	Lys	Lysine	AAA, AAG
L	Leu	Leucine	UUA, UUG, CUA, CUC, CUG, CUU
M	Met	Methionine	AUG
N	Asn	Asparagine	AAC, AAU
P	Pro	Proline	CCA, CCC, CCG, CCU
Q	Gln	Glutamine	CAA, CAG
R	Arg	Arginine	AGA, AGG, CGA, CGC, CGG, CGU
S	Ser	Serine	AGC, AGU, UCA, UCC, UCG, UCU
T	Thr	Threonine	ACA, ACC, ACG, ACU
V	Val	Valine	GUA, GUC, GUG, GUU
W	Trp	Tryptophan	UGG
Y	Tyr	Tyrosine	UAC, UAU

5 An anti-amyloid antibody of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein.

Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid substitutions, insertions or deletions for any given anti-amyloid antibody, fragment
 10 or variant will not be more than 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, such as 1-30 or any range or value therein, as specified herein.

Amino acids in an anti-amyloid antibody of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, supra, Chapters 8, 15; Cunningham and Wells, Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at
 15 every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to at least one amyloid neutralizing activity. Sites that are

critical for antibody binding can also be identified by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., J. Mol. Biol. 224:899-904 (1992) and de Vos, et al., Science 255:306-312 (1992)).

Anti-amyloid antibodies of the present invention can include, but are not limited to, at least one portion, sequence or combination selected from 5 to all of the contiguous amino acids of at least one of SEQ ID NOS:42-47 or 53-58.

An anti-amyloid antibody can further optionally comprise a polypeptide of at least one of 70-100% of the contiguous amino acids of at least one of SEQ ID NOS:48, 49, 59, and 60.

In one embodiment, the amino acid sequence of an immunoglobulin chain, or portion thereof (e.g., variable region, CDR) has about 70-100% identity (e.g., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) to the amino acid sequence of the corresponding chain of at least one of SEQ ID NOS:48, 49, 59 and 60. For example, the amino acid sequence of a light chain variable region can be compared with the sequence of SEQ ID NO:49, 60, 70 or 80, or the amino acid sequence of a heavy chain CDR3 can be compared with SEQ ID NO:48 or 59. Preferably, 70-100% amino acid identity (i.e., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) is determined using a suitable computer algorithm, as known in the art.

Exemplary heavy chain and light chain variable regions sequences are provided in SEQ ID NOS:48, 49, 59, and 60. The antibodies of the present invention, or specified variants thereof, can comprise any number of contiguous amino acid residues from an antibody of the present invention, wherein that number is selected from the group of integers consisting of from 10-100% of the number of contiguous residues in an anti-amyloid antibody. Optionally, this subsequence of contiguous amino acids is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 or more amino acids in length, or any range or value therein. Further, the number of such subsequences can be any integer selected from the group consisting of from 1 to 20, such as at least 2, 3, 4, or 5.

As those of skill will appreciate, the present invention includes at least one biologically active antibody of the present invention. Biologically active antibodies have a specific activity at least 20%, 30%, or 40%, and preferably at least 50%, 60%, or 70%, and most preferably at least 80%, 90%, or 95%-1000% of that of the native (non-synthetic), endogenous or related and known antibody. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity, are well known to those of skill in the art.

MODIFIED ANTIBODIES

In another aspect, the invention relates to human antibodies and antigen-binding fragments, as described herein, which are modified by the covalent attachment of an organic

moiety. Such modification can produce an antibody or antigen-binding fragment with improved pharmacokinetic properties (e.g., increased *in vivo* serum half-life). The organic moiety can be a linear or branched hydrophilic polymeric group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g.,
5 polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrrolidone, and the fatty acid or fatty acid ester group can comprise from about eight to about forty carbon atoms.

The modified antibodies and antigen-binding fragments of the invention can comprise
10 one or more organic moieties that are covalently bonded, directly or indirectly, to the antibody.

Each organic moiety that is bonded to an antibody or antigen-binding fragment of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an
15 organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, an antibody modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like),
20 carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine, polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrrolidone. Preferably, the hydrophilic polymer that modifies the antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For
25 example PEG₅₀₀₀ and PEG_{20,000}, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate
30 of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for
35 modifying antibodies of the invention include, for example, n-dodecanoate (C₁₂, laurate), n-tetradecanoate (C₁₄, myristate), n-octadecanoate (C₁₈, stearate), n-eicosanoate (C₂₀, arachidate),

n-docosanoate (C₂₂, behenate), n-triacontanoate (C₃₀), n-tetracontanoate (C₄₀), *cis*-Δ⁹-octadecanoate (C₁₈, oleate), all *cis*-Δ^{5,8,11,14}-eicosatetraenoate (C₂₀, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or
5 branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably one to about six, carbon atoms.

The modified human antibodies and antigen-binding fragments can be prepared using suitable methods, such as by reaction with one or more modifying agents. A "modifying agent" as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty
10 acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS),
15 and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acryloyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups
20 into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example a divalent C₁-C₁₂ group wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include,
25 for example, tetraethylene glycol, -(CH₂)₃-, -NH-(CH₂)₆-NH-, -(CH₂)₂-NH- and -CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH-NH-. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and
30 the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for example, Thompson, *et al.*, WO 92/16221 the entire teachings of which are incorporated herein
35 by reference.)

The modified antibodies of the invention can be produced by reacting a human antibody or antigen-binding fragment with a modifying agent. For example, the organic moieties can be bonded to the antibody in a non-site specific manner by employing an amine-reactive modifying agent, for example, an NHS ester of PEG. Modified human antibodies or antigen-binding fragments can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of an antibody or antigen-binding fragment. The reduced antibody or antigen-binding fragment can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified human antibodies and antigen-binding fragments comprising an organic moiety that is bonded to specific sites of an antibody of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch *et al.*, *Bioconjugate Chem.*, 3:147-153 (1992); Werlen *et al.*, *Bioconjugate Chem.*, 5:411-417 (1994); Kumaran *et al.*, *Protein Sci.* 6(10):2233-2241 (1997); Itoh *et al.*, *Bioorg. Chem.*, 24(1): 59-68 (1996); Capellas *et al.*, *Biotechnol. Bioeng.*, 56(4):456-463 (1997)), and the methods described in Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).

ANTI-IDIOTYPE ANTIBODIES TO ANTI-AMYLOID ANTIBODY COMPOSITIONS

In addition to monoclonal or chimeric anti-amyloid antibodies, the present invention is also directed to an anti-idiotypic (anti-Id) antibody specific for such antibodies of the invention. An anti-Id antibody is an antibody which recognizes unique determinants generally associated with the antigen-binding region of another antibody. The anti-Id can be prepared by immunizing an animal of the same species and genetic type (e.g. mouse strain) as the source of the Id antibody with the antibody or a CDR containing region thereof. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody and produce an anti-Id antibody. The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody.

AMYLOID ANTIBODY COMPOSITIONS

The present invention also provides at least one anti-amyloid antibody composition comprising at least one, at least two, at least three, at least four, at least five, at least six or more anti-amyloid antibodies thereof, as described herein and/or as known in the art that are provided in a non-naturally occurring composition, mixture or form. Such compositions comprise non-naturally occurring compositions comprising at least one or two full length, C- and/or N-terminally deleted variants, domains, fragments, or specified variants, of the anti-amyloid antibody amino acid sequence selected from the group consisting of 70-100% of the contiguous amino acids of SEQ ID NOS:42-49, 53-60, or specified fragments, domains or variants thereof. Preferred anti-amyloid antibody compositions include at least one or two full length, fragments, domains or variants as at least one CDR or LBP containing portions of the anti-

amyloid antibody sequence of 70-100% of SEQ ID NOS:42-47, 53-58, or specified fragments, domains or variants thereof. Further preferred compositions comprise 40-99% of at least one of 70-100% of SEQ ID NOS:42-47, 53-58, or specified fragments, domains or variants thereof. Such composition percentages are by weight, volume, concentration, molarity, or molality as
5 liquid or dry solutions, mixtures, suspension, emulsions, particles, powder, or colloids, as known in the art or as described herein.

The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug,
10 a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a statin, or the like. Such drugs are well known in the art, including formulations, indications, dosing and administration for each presented herein (see, e.g., Nursing 2001 Handbook of Drugs, 21st edition, Springhouse
15 Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; Pharmacotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, as well known in the art).

The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opioid
20 analgesics, sedative-hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous system stimulants, antiparkinsonians, miscellaneous central nervous system drugs. The ANS drug can be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, neuromuscular blockers. The at least one
25 nonnarcotic analgesic or antipyretic can be at least one selected from acetaminophen, aspirin, choline magnesium trisalicylate, diflunisal, magnesium salicylate. The at least one nonsteroidal anti-inflammatory drug can be at least one selected from celecoxib, diclofenac potassium, diclofenac sodium, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, indomethacin sodium trihydrate, ketoprofen, ketorolac tromethamine, nabumetone, naproxen,
30 naproxen sodium, oxaprozin, piroxicam, rofecoxib, sulindac. The at least one narcotic or opioid analgesic can be at least one selected from alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, codeine phosphate, codeine sulfate, fentanyl citrate, fentanyl transdermal system, fentanyl transmucosal, hydromorphone hydrochloride, meperidine hydrochloride, methadone hydrochloride, morphine hydrochloride, morphine sulfate, morphine
35 tartrate, nalbuphine hydrochloride, oxycodone hydrochloride, oxycodone pectinate, oxymorphone hydrochloride, pentazocine hydrochloride, pentazocine hydrochloride and

naloxone hydrochloride, pentazocine lactate, propoxyphene hydrochloride, propoxyphene napsylate, remifentanyl hydrochloride, sufentanyl citrate, tramadol hydrochloride. The at least one sedative-hypnotic can be at least one selected from chloral hydrate, estazolam, flurazepam hydrochloride, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, 5 temazepam, triazolam, zaleplon, zolpidem tartrate. The at least one anticonvulsant can be at least one selected from acetazolamide sodium, carbamazepine, clonazepam, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximide, fosphenytoin sodium, gabapentin, lamotrigine, magnesium sulfate, phenobarbital, phenobarbital sodium, phenytoin, phenytoin sodium, phenytoin sodium (extended), primidone, tiagabine hydrochloride, topiramate, 10 valproate sodium, valproic acid. The at least one antidepressant can be at least one selected from amitriptyline hydrochloride, amitriptyline pamoate, amoxapine, bupropion hydrochloride, citalopram hydrobromide, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, imipramine hydrochloride, imipramine pamoate, mirtazapine, nefazodone hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride, 15 phenelzine sulfate, sertraline hydrochloride, transylcypromine sulfate, trimipramine maleate, venlafaxine hydrochloride. The at least one antianxiety drug can be at least one selected from alprazolam, buspirone hydrochloride, chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, doxepin hydrochloride, hydroxyzine embonate, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, mephrobamate, midazolam 20 hydrochloride, oxazepam. The at least one antipsychotic drug can be at least one selected from chlorpromazine hydrochloride, clozapine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, haloperidol, haloperidol decanoate, haloperidol lactate, loxapine hydrochloride, loxapine succinate, mesoridazine besylate, molindone hydrochloride, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine fumarate, risperidone, 25 thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine hydrochloride. The at least one central nervous system stimulant can be at least one selected from amphetamine sulfate, caffeine, dextroamphetamine sulfate, doxapram hydrochloride, methamphetamine hydrochloride, methylphenidate hydrochloride, modafinil, pemoline, phentermine hydrochloride. The at least one antiparkinsonian can be at least one selected from 30 amantadine hydrochloride, benzotropine mesylate, biperiden hydrochloride, biperiden lactate, bromocriptine mesylate, carbidopa-levodopa, entacapone, levodopa, pergolide mesylate, pramipexole dihydrochloride, ropinirole hydrochloride, selegiline hydrochloride, tolcapone, trihexyphenidyl hydrochloride. The at least one miscellaneous central nervous system drug can be at least one selected from riluzole, bupropion hydrochloride, donepezil hydrochloride, 35 droperidol, fluvoxamine maleate, lithium carbonate, lithium citrate, naratriptan hydrochloride, nicotine polacrilex, nicotine transdermal system, propofol, rizatriptan benzoate, sibutramine

hydrochloride monohydrate, sumatriptan succinate, tacrine hydrochloride, zolmitriptan. (See, e.g., pp. 337-530 of *Nursing 2001 Drug Handbook*.)

The at least one cholinergic (e.g., parasympathomimetic) can be at least one selected from bethanechol chloride, edrophonium chloride, neostigmine bromide, neostigmine
5 methylsulfate, physostigmine salicylate, pyridostigmine bromide. The at least one anticholinergics can be at least one selected from atropine sulfate, dicyclomine hydrochloride, glycopyrrolate, hyoscyamine, hyoscyamine sulfate, propantheline bromide, scopolamine, scopolamine butylbromide, scopolamine hydrobromide. The at least one adrenergics (sympathomimetics) can be at least one selected from dobutamine hydrochloride, dopamine
10 hydrochloride, metaraminol bitartrate, norepinephrine bitartrate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate. The at least one adrenergic blocker (sympatholytic) can be at least one selected from dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, propranolol hydrochloride. The at least one skeletal muscle relaxant can be at least one selected from baclofen, carisoprodol, chlorzoxazone,
15 cyclobenzaprine hydrochloride, dantrolene sodium, methocarbamol, tizanidine hydrochloride. The at least one neuromuscular blockers can be at least one selected from atracurium besylate, cisatracurium besylate, doxacurium chloride, mivacurium chloride, pancuronium bromide, pipecuronium bromide, rapacuronium bromide, rocuronium bromide, succinylcholine chloride, tubocurarine chloride, vecuronium bromide. (See, e.g., pp. 531-84 of *Nursing 2001 Drug
20 Handbook*.)

The anti-infective drug can be at least one selected from amebicides or at least one antiprotozoals, anthelmintics, antifungals, antimalarials, antituberculotics or at least one antileprotics, aminoglycosides, penicillins, cephalosporins, tetracyclines, sulfonamides, fluoroquinolones, antivirals, macrolide anti-infectives, miscellaneous anti-infectives. The CV
25 drug can be at least one selected from inotropics, antiarrhythmics, antianginals, antihypertensives, antilipemics, miscellaneous cardiovascular drugs. The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opioid analgesics, sedative-hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous
30 system stimulants, antiparkinsonians, miscellaneous central nervous system drugs. The ANS drug can be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, neuromuscular blockers. The respiratory tract drug can be at least one selected from antihistamines, bronchodilators, expectorants or at least one antitussives, miscellaneous
35 respiratory drugs. The GI tract drug can be at least one selected from antacids or at least one adsorbents or at least one antiflatulents, digestive enzymes or at least one gallstone solubilizers,

antidiarrheals, laxatives, antiemetics, antiulcer drugs. The hormonal drug can be at least one selected from corticosteroids, androgens or at least one anabolic steroids, estrogens or at least one progestins, gonadotropins, antidiabetic drugs or at least one glucagon, thyroid hormones, thyroid hormone antagonists, pituitary hormones, parathyroid-like drugs. The drug for fluid and electrolyte balance can be at least one selected from diuretics, electrolytes or at least one replacement solutions, acidifiers or at least one alkalinizers. The hematologic drug can be at least one selected from hematinics, anticoagulants, blood derivatives, thrombolytic enzymes. The antineoplastics can be at least one selected from alkylating drugs, antimetabolites, antibiotic antineoplastics, antineoplastics that alter hormone balance, miscellaneous antineoplastics. The immunomodulation drug can be at least one selected from immunosuppressants, vaccines or at least one toxoids, antitoxins or at least one antivenins, immune serums, biological response modifiers. The ophthalmic, otic, and nasal drugs can be at least one selected from ophthalmic anti-infectives, ophthalmic anti-inflammatories, miotics, mydriatics, ophthalmic vasoconstrictors, miscellaneous ophthalmics, otics, nasal drugs. The topical drug can be at least one selected from local anti-infectives, scabicides or at least one pediculicides, topical corticosteroids. The nutritional drug can be at least one selected from vitamins, minerals, or calories. See, e.g., contents of *Nursing 2001 Drug Handbook, supra*.

The at least one amebicide or antiprotozoal can be at least one selected from atovaquone, chloroquine hydrochloride, chloroquine phosphate, metronidazole, metronidazole hydrochloride, pentamidine isethionate. The at least one anthelmintic can be at least one selected from mebendazole, pyrantel pamoate, thiabendazole. The at least one antifungal can be at least one selected from amphotericin B, amphotericin B cholesteryl sulfate complex, amphotericin B lipid complex, amphotericin B liposomal, fluconazole, flucytosine, griseofulvin microsize, griseofulvin ultramicrosize, itraconazole, ketoconazole, nystatin, terbinafine hydrochloride. The at least one antimalarial can be at least one selected from chloroquine hydrochloride, chloroquine phosphate, doxycycline, hydroxychloroquine sulfate, mefloquine hydrochloride, primaquine phosphate, pyrimethamine, pyrimethamine with sulfadoxine. The at least one antituberculous or antileprotic can be at least one selected from clofazimine, cycloserine, dapsone, ethambutol hydrochloride, isoniazid, pyrazinamide, rifabutin, rifampin, rifapentine, streptomycin sulfate. The at least one aminoglycoside can be at least one selected from amikacin sulfate, gentamicin sulfate, neomycin sulfate, streptomycin sulfate, tobramycin sulfate. The at least one penicillin can be at least one selected from amoxicillin/clavulanate potassium, amoxicillin trihydrate, ampicillin, ampicillin sodium, ampicillin trihydrate, ampicillin sodium/sulbactam sodium, cloxacillin sodium, dicloxacillin sodium, mezlocillin sodium, nafcillin sodium, oxacillin sodium, penicillin G benzathine, penicillin G potassium, penicillin G procaine, penicillin G sodium, penicillin V potassium, piperacillin sodium,

piperacillin sodium/tazobactam sodium, ticarcillin disodium, ticarcillin disodium/clavulanate potassium. The at least one cephalosporin can be at least one selected from at least one of cefaclor, cefadroxil, cefazolin sodium, cefdinir, cefepime hydrochloride, cefixime, cefmetazole sodium, cefonicid sodium, cefoperazone sodium, cefotaxime sodium, cefotetan disodium, 5 cefoxitin sodium, cefpodoxime proxetil, cefprozil, ceftazidime, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuroxime sodium, cephalixin hydrochloride, cephalixin monohydrate, cephradine, loracarbef. The at least one tetracycline can be at least one selected from demeclocycline hydrochloride, doxycycline calcium, doxycycline hyclate, doxycycline hydrochloride, doxycycline monohydrate, minocycline hydrochloride, tetracycline 10 hydrochloride. The at least one sulfonamide can be at least one selected from co-trimoxazole, sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfisoxazole acetyl. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin mesylate. The at least one fluoroquinolone can be at least one 15 selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin mesylate. The at least one antiviral can be at least one selected from abacavir sulfate, acyclovir sodium, amantadine hydrochloride, amprenavir, cidofovir, delavirdine mesylate, didanosine, efavirenz, famciclovir, fomivirsen sodium, foscarnet sodium, ganciclovir, indinavir sulfate, lamivudine, 20 lamivudine/zidovudine, nelfinavir mesylate, nevirapine, oseltamivir phosphate, ribavirin, rimantadine hydrochloride, ritonavir, saquinavir, saquinavir mesylate, stavudine, valacyclovir hydrochloride, zalcitabine, zanamivir, zidovudine. The at least one macrolide anti-infective can be at least one selected from azithromycin, clarithromycin, dirithromycin, erythromycin base, erythromycin estolate, erythromycin ethylsuccinate, erythromycin lactobionate, erythromycin 25 stearate. The at least one miscellaneous anti-infective can be at least one selected from aztreonam, bacitracin, chloramphenicol sodium succinate, clindamycin hydrochloride, clindamycin palmitate hydrochloride, clindamycin phosphate, imipenem and cilastatin sodium, meropenem, nitrofurantoin macrocrystals, nitrofurantoin microcrystals, quinupristin/dalfopristin, spectinomycin hydrochloride, trimethoprim, vancomycin 30 hydrochloride. (See, e.g., pp. 24-214 of *Nursing 2001 Drug Handbook*.)

The at least one inotropic can be at least one selected from amrinone lactate, digoxin, milrinone lactate. The at least one antiarrhythmic can be at least one selected from adenosine, amiodarone hydrochloride, atropine sulfate, bretylium tosylate, diltiazem hydrochloride, disopyramide, disopyramide phosphate, esmolol hydrochloride, flecainide acetate, ibutilide 35 fumarate, lidocaine hydrochloride, mexiletine hydrochloride, moricizine hydrochloride, phenytoin, phenytoin sodium, procainamide hydrochloride, propafenone hydrochloride,

propranolol hydrochloride, quinidine bisulfate, quinidine gluconate, quinidine polygalacturonate, quinidine sulfate, sotalol, tocainide hydrochloride, verapamil hydrochloride.

The at least one antianginal can be at least one selected from amlodipine besylate, amyl nitrite, bepridil hydrochloride, diltiazem hydrochloride, isosorbide dinitrate, isosorbide mononitrate, nadolol, nicardipine hydrochloride, nifedipine, nitroglycerin, propranolol hydrochloride, verapamil, verapamil hydrochloride. The at least one antihypertensive can be at least one selected from acebutolol hydrochloride, amlodipine besylate, atenolol, benazepril hydrochloride, betaxolol hydrochloride, bisoprolol fumarate, candesartan cilexetil, captopril, carteolol hydrochloride, carvedilol, clonidine, clonidine hydrochloride, diazoxide, diltiazem hydrochloride, doxazosin mesylate, enalaprilat, enalapril maleate, eprosartan mesylate, felodipine, fenoldopam mesylate, fosinopril sodium, guanabenz acetate, guanadrel sulfate, guanfacine hydrochloride, hydralazine hydrochloride, irbesartan, isradipine, labetalol hydrochloride, lisinopril, losartan potassium, methyldopa, methyldopate hydrochloride, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril hydrochloride, nadolol, nicardipine hydrochloride, nifedipine, nisoldipine, nitroprusside sodium, penbutolol sulfate, perindopril erbumine, phentolamine mesylate, pindolol, prazosin hydrochloride, propranolol hydrochloride, quinapril hydrochloride, ramipril, telmisartan, terazosin hydrochloride, timolol maleate, trandolapril, valsartan, verapamil hydrochloride. The at least one antilipemic can be at least one selected from atorvastatin calcium, cerivastatin sodium, cholestyramine, colestipol hydrochloride, fenofibrate (micronized), fluvastatin sodium, gemfibrozil, lovastatin, niacin, pravastatin sodium, simvastatin. The at least one miscellaneous CV drug can be at least one selected from abciximab, alprostadil, arbutamine hydrochloride, cilostazol, clopidogrel bisulfate, dipyridamole, eptifibatide, midodrine hydrochloride, pentoxifylline, ticlopidine hydrochloride, tirofiban hydrochloride. (See, e.g., pp. 215-336 of *Nursing 2001 Drug Handbook*.)

The at least one antihistamine can be at least one selected from brompheniramine maleate, cetirizine hydrochloride, chlorpheniramine maleate, clemastine fumarate, cypheptadine hydrochloride, diphenhydramine hydrochloride, fexofenadine hydrochloride, loratadine, promethazine hydrochloride, promethazine theoclate, triprolidine hydrochloride.

The at least one bronchodilators can be at least one selected from albuterol, albuterol sulfate, aminophylline, atropine sulfate, ephedrine sulfate, epinephrine, epinephrine bitartrate, epinephrine hydrochloride, ipratropium bromide, isoproterenol, isoproterenol hydrochloride, isoproterenol sulfate, levalbuterol hydrochloride, metaproterenol sulfate, oxtriphylline, pirbuterol acetate, salmeterol xinafoate, terbutaline sulfate, theophylline. The at least one expectorants or antitussives can be at least one selected from benzonatate, codeine phosphate, codeine sulfate, dextromethorphan hydrobromide, diphenhydramine hydrochloride,

guaifenesin, hydromorphone hydrochloride. The at least one miscellaneous respiratory drug can be at least one selected from acetylcysteine, beclomethasone dipropionate, beractant, budesonide, calfactant, cromolyn sodium, dornase alfa, epoprostenol sodium, flunisolide, fluticasone propionate, montelukast sodium, nedocromil sodium, palivizumab, triamcinolone acetate, zafirlukast, zileuton. (See, e.g., pp. 585-642 of *Nursing 2001 Drug Handbook*.)

The at least one antacid, adsorbents, or antiflatulents can be at least one selected from aluminum carbonate, aluminum hydroxide, calcium carbonate, magaldrate, magnesium hydroxide, magnesium oxide, simethicone, sodium bicarbonate. The at least one digestive enzymes or gallstone solubilizers can be at least one selected from pancreatin, pancrelipase, ursodiol. The at least one antidiarrheal can be at least one selected from attapulgite, bismuth subsalicylate, calcium polycarbophil, diphenoxylate hydrochloride or atropine sulfate, loperamide, octreotide acetate, opium tincture, opium tincture (camphorated). The at least one laxative can be at least one selected from bisacodyl, calcium polycarbophil, cascara sagrada, cascara sagrada aromatic fluidextract, cascara sagrada fluidextract, castor oil, docusate calcium, docusate sodium, glycerin, lactulose, magnesium citrate, magnesium hydroxide, magnesium sulfate, methylcellulose, mineral oil, polyethylene glycol or electrolyte solution, psyllium, senna, sodium phosphates. The at least one antiemetic can be at least one selected from chlorpromazine hydrochloride, dimenhydrinate, dolasetron mesylate, dronabinol, granisetron hydrochloride, meclizine hydrochloride, metoclopramide hydrochloride, ondansetron hydrochloride, perphenazine, prochlorperazine, prochlorperazine edisylate, prochlorperazine maleate, promethazine hydrochloride, scopolamine, thiethylperazine maleate, trimethobenzamide hydrochloride. The at least one antiulcer drug can be at least one selected from cimetidine, cimetidine hydrochloride, famotidine, lansoprazole, misoprostol, nizatidine, omeprazole, rabeprazole sodium, ranitidine bismuth citrate, ranitidine hydrochloride, sucralfate. (See, e.g., pp. 643-95 of *Nursing 2001 Drug Handbook*.) The at least one corticosteroids can be at least one selected from betamethasone, betamethasone acetate or betamethasone sodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetate, triamcinolone diacetate.

The at least one androgen or anabolic steroids can be at least one selected from danazol, fluoxymesterone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, testosterone, testosterone cypionate, testosterone enanthate, testosterone

propionate, testosterone transdermal system. The at least one estrogen or progestin can be at least one selected from esterified estrogens, estradiol, estradiol cypionate, estradiol/norethindrone acetate transdermal system, estradiol valerate, estrogens (conjugated), estropipate, ethinyl estradiol, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and levonorgestrel, ethinyl estradiol and norethindrone, ethinyl estradiol and norethindrone acetate, ethinyl estradiol and norgestimate, ethinyl estradiol and norgestrel, ethinyl estradiol and norethindrone and acetate and ferrous fumarate, levonorgestrel, medroxyprogesterone acetate, mestranol and norethindrone, norethindrone, norethindrone acetate, norgestrel, progesterone. The at least one gonadotropin can be at least one selected from ganirelix acetate, gonadoreline acetate, histrelin acetate, menotropins. The at least one antidiabetic or glucagon can be at least one selected from acarbose, chlorpropamide, glimepiride, glipizide, glucagon, glyburide, insulins, metformin hydrochloride, miglitol, pioglitazone hydrochloride, repaglinide, rosiglitazone maleate, troglitazone. The at least one thyroid hormone can be at least one selected from levothyroxine sodium, liothyronine sodium, liotrix, thyroid. The at least one thyroid hormone antagonist can be at least one selected from methimazole, potassium iodide, potassium iodide (saturated solution), propylthiouracil, radioactive iodine (sodium iodide ^{131}I), strong iodine solution. The at least one pituitary hormone can be at least one selected from corticotropin, cosyntropin, desmopressin acetate, leuprolide acetate, repository corticotropin, somatrem, somatropin, vasopressin. The at least one parathyroid-like drug can be at least one selected from calcifediol, calcitonin (human), calcitonin (salmon), calcitriol, dihydrotachysterol, etidronate disodium. (See, e.g., pp. 696-796 of *Nursing 2001 Drug Handbook*.)

The at least one diuretic can be at least one selected from acetazolamide, acetazolamide sodium, amiloride hydrochloride, bumetanide, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, mannitol, metolazone, spironolactone, torsemide, triamterene, urea. The at least one electrolyte or replacement solution can be at least one selected from calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, calcium lactate, calcium phosphate (dibasic), calcium phosphate (tribasic), dextran (high-molecular-weight), dextran (low-molecular-weight), hetastarch, magnesium chloride, magnesium sulfate, potassium acetate, potassium bicarbonate, potassium chloride, potassium gluconate, Ringer's injection, Ringer's injection (lactated), sodium chloride. The at least one acidifier or alkalinizer can be at least one selected from sodium bicarbonate, sodium lactate, tromethamine. (See, e.g., pp. 797-833 of *Nursing 2001 Drug Handbook*.)

The at least one hematinic can be at least one selected from ferrous fumarate, ferrous

gluconate, ferrous sulfate, ferrous sulfate (dried), iron dextran, iron sorbitol, polysaccharide-iron complex, sodium ferric gluconate complex. The at least one anticoagulant can be at least one selected from ardeparin sodium, dalteparin sodium, danaparoid sodium, enoxaparin sodium, heparin calcium, heparin sodium, warfarin sodium. The at least one blood derivative
 5 can be at least one selected from albumin 5%, albumin 25%, antihemophilic factor, anti-inhibitor coagulant complex, antithrombin III (human), factor IX (human), factor IX complex, plasma protein fractions. The at least one thrombolytic enzyme can be at least one selected from alteplase, anistreplase, reteplase (recombinant), streptokinase, urokinase. (See, e.g., pp. 834-66 of *Nursing 2001 Drug Handbook*.)

10 The at least one alkylating drug can be at least one selected from busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, ifosfamide, lomustine, mechlorethamine hydrochloride, melphalan, melphalan hydrochloride, streptozocin, temozolomide, thiotepa. The at least one antimetabolite can be at least one selected from capecitabine, cladribine, cytarabine, floxuridine, fludarabine phosphate, fluorouracil,
 15 hydroxyurea, mercaptopurine, methotrexate, methotrexate sodium, thioguanine. The at least one antibiotic antineoplastic can be at least one selected from bleomycin sulfate, dactinomycin, daunorubicin citrate liposomal, daunorubicin hydrochloride, doxorubicin hydrochloride, doxorubicin hydrochloride liposomal, epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, pentostatin, plicamycin, valrubicin. The at least one antineoplastics that alter
 20 hormone balance can be at least one selected from anastrozole, bicalutamide, estramustine phosphate sodium, exemestane, flutamide, goserelin acetate, letrozole, leuprolide acetate, megestrol acetate, nilutamide, tamoxifen citrate, testolactone, toremifene citrate. The at least one miscellaneous antineoplastic can be at least one selected from asparaginase, bacillus Calmette-Guerin (BCG) (live intravesical), dacarbazine, docetaxel, etoposide, etoposide
 25 phosphate, gemcitabine hydrochloride, irinotecan hydrochloride, mitotane, mitoxantrone hydrochloride, paclitaxel, pegaspargase, porfimer sodium, procarbazine hydrochloride, rituximab, teniposide, topotecan hydrochloride, trastuzumab, tretinoin, vinblastine sulfate, vincristine sulfate, vinorelbine tartrate. (See, e.g., pp. 867-963 of *Nursing 2001 Drug Handbook*.)

30 The at least one immunosuppressant can be at least one selected from azathioprine, basiliximab, cyclosporine, daclizumab, lymphocyte immune globulin, muromonab-CD3, mycophenolate mofetil, mycophenolate mofetil hydrochloride, sirolimus, tacrolimus. The at least one vaccine or toxoid can be at least one selected from BCG vaccine, cholera vaccine, diphtheria and tetanus toxoids (adsorbed), diphtheria and tetanus toxoids and acellular pertussis
 35 vaccine adsorbed, diphtheria and tetanus toxoids and whole-cell pertussis vaccine, *Haemophilus b* conjugate vaccines, hepatitis A vaccine (inactivated), hepatitis B vaccine

(recombinant), influenza virus vaccine 1999-2000 trivalent types A & B (purified surface antigen), influenza virus vaccine 1999-2000 trivalent types A & B (subvirion or purified subvirion), influenza virus vaccine 1999-2000 trivalent types A & B (whole virion), Japanese encephalitis virus vaccine (inactivated), Lyme disease vaccine (recombinant OspA), measles and mumps and rubella virus vaccine (live), measles and mumps and rubella virus vaccine (live attenuated), measles virus vaccine (live attenuated), meningococcal polysaccharide vaccine, mumps virus vaccine (live), plague vaccine, pneumococcal vaccine (polyvalent), poliovirus vaccine (inactivated), poliovirus vaccine (live, oral, trivalent), rabies vaccine (adsorbed), rabies vaccine (human diploid cell), rubella and mumps virus vaccine (live), rubella virus vaccine (live, attenuated), tetanus toxoid (adsorbed), tetanus toxoid (fluid), typhoid vaccine (oral), typhoid vaccine (parenteral), typhoid Vi polysaccharide vaccine, varicella virus vaccine, yellow fever vaccine. The at least one antitoxin or antivenin can be at least one selected from black widow spider antivenin, Crotalidae antivenom (polyvalent), diphtheria antitoxin (equine), *Micrurus fulvius* antivenin). The at least one immune serum can be at least one selected from cytomegalovirus immune globulin (intravenous), hepatitis B immune globulin (human), immune globulin intramuscular, immune globulin intravenous, rabies immune globulin (human), respiratory syncytial virus immune globulin intravenous (human), Rh₀(D) immune globulin (human), Rh₀(D) immune globulin intravenous (human), tetanus immune globulin (human), varicella-zoster immune globulin. The at least one biological response modifiers can be at least one selected from aldesleukin, epoetin alfa, filgrastim, glatiramer acetate for injection, interferon alfacon-1, interferon alfa-2a (recombinant), interferon alfa-2b (recombinant), interferon beta-1a, interferon beta-1b (recombinant), interferon gamma-1b, levamisole hydrochloride, oprelvekin, sargramostim. (See, e.g., pp. 964-1040 of *Nursing 2001 Drug Handbook*.)

The at least one ophthalmic anti-infectives can be selected from bacitracin, chloramphenicol, ciprofloxacin hydrochloride, erythromycin, gentamicin sulfate, ofloxacin 0.3%, polymyxin B sulfate, sulfacetamide sodium 10%, sulfacetamide sodium 15%, sulfacetamide sodium 30%, tobramycin, vidarabine. The at least one ophthalmic anti-inflammatories can be at least one selected from dexamethasone, dexamethasone sodium phosphate, diclofenac sodium 0.1%, fluorometholone, flurbiprofen sodium, ketorolac tromethamine, prednisolone acetate (suspension) prednisolone sodium phosphate (solution). The at least one miotic can be at least one selected from acetylcholine chloride, carbachol (intraocular), carbachol (topical), echothiophate iodide, pilocarpine, pilocarpine hydrochloride, pilocarpine nitrate. The at least one mydriatic can be at least one selected from atropine sulfate, cyclopentolate hydrochloride, epinephrine hydrochloride, epinephryl borate, homatropine hydrobromide, phenylephrine hydrochloride, scopolamine hydrobromide, tropicamide. The at

least one ophthalmic vasoconstrictors can be at least one selected from naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride. The at least one miscellaneous ophthalmics can be at least one selected from apraclonidine hydrochloride, betaxolol hydrochloride, brimonidine tartrate, carteolol hydrochloride, dipivefrin
5 hydrochloride, dorzolamide hydrochloride, emedastine difumarate, fluorescein sodium, ketotifen fumarate, latanoprost, levobunolol hydrochloride, metipranolol hydrochloride, sodium chloride (hypertonic), timolol maleate. The at least one otic can be at least one selected from boric acid, carbamide peroxide, chloramphenicol, triethanolamine polypeptide oleate-condensate. The at least one nasal drug can be at least one selected from beclomethasone
10 dipropionate, budesonide, ephedrine sulfate, epinephrine hydrochloride, flunisolide, fluticasone propionate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, triamcinolone acetonide, xylometazoline hydrochloride. (See, e.g., pp. 1041-97 of *Nursing 2001 Drug Handbook*.)

The at least one local anti-infectives can be at least one selected from acyclovir,
15 amphotericin B, azelaic acid cream, bacitracin, butoconazole nitrate, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamicin sulfate, ketoconazole, mafenide acetate, metronidazole (topical), miconazole nitrate, mupirocin, naftifine hydrochloride, neomycin sulfate, nitrofurazone, nystatin, silver sulfadiazine, terbinafine hydrochloride, terconazole, tetracycline hydrochloride, tioconazole, tolnaftate. The at least one scabicide or
20 pediculicide can be at least one selected from crotamiton, lindane, permethrin, pyrethrins. The at least one topical corticosteroid can be at least one selected from betamethasone dipropionate, betamethasone valerate, clobetasol propionate, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, diflorasone diacetate, fluocinolone acetonide, fluocinonide, flurandrenolide, fluticasone propionate, halcionide, hydrocortisone, hydrocortisone acetate,
25 hydrocortisone butyrate, hydrocortisone valerate, mometasone furoate, triamcinolone acetonide. (See, e.g., pp. 1098-1136 of *Nursing 2001 Drug Handbook*.)

The at least one vitamin or mineral can be at least one selected from vitamin A, vitamin B complex, cyanocobalamin, folic acid, hydroxocobalamin, leucovorin calcium, niacin, niacinamide, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, vitamin C, vitamin
30 D, cholecalciferol, ergocalciferol, vitamin D analogue, doxercalciferol, paricalcitol, vitamin E, vitamin K analogue, phytonadione, sodium fluoride, sodium fluoride (topical), trace elements, chromium, copper, iodine, manganese, selenium, zinc. The at least one calorics can be at least one selected from amino acid infusions (crystalline), amino acid infusions in dextrose, amino acid infusions with electrolytes, amino acid infusions with electrolytes in dextrose, amino acid
35 infusions for hepatic failure, amino acid infusions for high metabolic stress, amino acid infusions for renal failure, dextrose, fat emulsions, medium-chain triglycerides. (See, e.g., pp.

1137-63 of *Nursing 2001 Drug Handbook*.)

Anti-amyloid antibody compositions of the present invention can further comprise at least one of any suitable and effective amount of a composition or pharmaceutical composition comprising at least one anti-amyloid antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-I or TBP-II), nerelimonmab, infliximab, entercept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limited to, any of IL-1 to IL-23. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., *Pharmacotherapy Handbook*, 2nd Edition, Appleton and Lange, Stamford, CT (2000); *PDR Pharmacopoeia*, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are and as well known in the art.

Such anti-cancer or anti-infectives can also include toxin molecules that are associated, bound, co-formulated or co-administered with at least one antibody of the present invention. The toxin can optionally act to selectively kill the pathologic cell or tissue. The pathologic cell can be a cancer or other cell. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g.,

selected from at least one of ricin, diphtheria toxin, a venom toxin, or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal enterotoxin A (SEA), B (SEB), or C (SEC), Streptococcal enterotoxins and the like. Such bacteria include, but are not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype 0157:H7), Staphylococcus species (e.g., *Staphylococcus aureus*, *Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi*, *Salmonella cholera-suis*, *Salmonella enteritidis*), *Clostridium* species (e.g., *Clostridium perfringens*, *Clostridium difficile*, *Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni*, *Camphlobacter fetus*), *Heliobacter* species, (e.g., *Heliobacter pylori*), *Aeromonas* species (e.g., *Aeromonas sobria*, *Aeromonas hydrophila*, *Aeromonas caviae*), *Pleisomonas shigelloides*, *Yersina enterocolitica*, *Vibrios* species (e.g., *Vibrios cholerae*, *Vibrios parahemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp 239-254, Plenum Medical Book Co., New York (1991); Mandell et al, Principles and Practice of Infectious Diseases, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, FEMS Microbiology Immunology, 76:121-134 (1991); Marrack et al, Science, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference.

Anti-amyloid antibody compounds, compositions or combinations of the present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co. (Easton, PA) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the anti-amyloid antibody, fragment or variant composition as well known in the art or as described herein.

Pharmaceutical excipients and additives useful in the present composition include but

are not limited to proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like.

One preferred amino acid is glycine.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate excipients for use in the present invention are mannitol, trehalose, and raffinose.

Anti-amyloid antibody compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts such as citrate.

Additionally, anti-amyloid antibody compositions of the invention can include polymeric excipients/additives such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrans (e.g., cyclodextrins, such as 2-hydroxypropyl- β -cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as "TWEEN 20" and "TWEEN 80"), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

These and additional known pharmaceutical excipients and/or additives suitable for use in the anti-amyloid antibody, portion or variant compositions according to the invention are known in the art, e.g., as listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are and as well known in the art.

Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and

buffers (e.g., citrate) or polymeric agents.

Formulations

As noted above, the invention provides for stable formulations, which is preferably a phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one anti-amyloid antibody in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol (e.g., 0.2, 0.3, 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0, 2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

As noted above, the invention provides an article of manufacture, comprising packaging material and at least one vial comprising a solution of at least one anti-amyloid antibody with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein said packaging material comprises a label that indicates that such solution can be held over a period of 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further comprises an article of manufacture, comprising packaging material, a first vial comprising lyophilized at least one anti-amyloid antibody, and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a patient to reconstitute the at least one anti-amyloid antibody in the aqueous diluent to form a solution that can be held over a period of twenty-four hours or greater.

The at least one anti-amyloid antibody used in accordance with the present invention can be produced by recombinant means, including from mammalian cell or transgenic preparations, or can be purified from other biological sources, as described herein or as known

in the art.

The range of at least one anti-amyloid antibody in the product of the present invention includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 µg/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an anti-microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

Other excipients, e.g. isotonicity agents, buffers, antioxidants, preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably the formulations of the present invention have pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably sodium phosphate, particularly phosphate buffered saline (PBS).

Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyols, other block co-polymers, and chelators such as EDTA and EGTA can optionally be added to the formulations or compositions to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the protein to aggregate.

The formulations of the present invention can be prepared by a process which comprises mixing at least one anti-amyloid antibody and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at

least one anti-amyloid antibody and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one anti-amyloid antibody in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide
5 the protein and preservative at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

10 The claimed formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-amyloid antibody that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a
15 single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

The present claimed articles of manufacture are useful for administration over a period of immediately to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the
20 invention can optionally be safely stored at temperatures of from about 2 to about 40°C and retain the biological activity of the protein for extended periods of time, thus, allowing a package label indicating that the solution can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to 1-12 months, one-half, one and a half, and/or two years.

25 The solutions of at least one anti-amyloid antibody in the invention can be prepared by a process that comprises mixing at least one antibody in an aqueous diluent. Mixing is carried out using conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one antibody in water or buffer is combined in quantities sufficient to provide the protein and optionally a preservative or buffer
30 at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed products can be provided to patients as clear solutions or as dual
35 vials comprising a vial of lyophilized at least one anti-amyloid antibody that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial

requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

5 The claimed products can be provided indirectly to patients by providing to pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized at least one anti-amyloid antibody that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger in size, providing a large reservoir from which smaller portions of the at least one antibody solution can be retrieved one or multiple times for transfer into smaller vials and
10 provided by the pharmacy or clinic to their customers and/or patients.

Recognized devices comprising these single vial systems include those pen-injector devices for delivery of a solution such as BD Pens, BD Autojector[®], Humaject[®], NovoPen[®], B-D[®] Pen, AutoPen[®], and OptiPen[®], GenotropinPen[®], Genotronorm Pen[®], Humatro Pen[®], Reco-Pen[®], Roferon Pen[®], Biojector[®], Iject[®], J-tip Needle-Free Injector[®], Intraject[®],
15 Medi-Ject[®], e.g., as made or developed by Becton Dickensen (Franklin Lakes, NJ, www.bectondickenson.com), Disetronic (Burgdorf, Switzerland, www.disetronic.com; Bioject, Portland, Oregon (www.bioject.com); National Medical Products, Weston Medical (Peterborough, UK, www.weston-medical.com), Medi-Ject Corp (Minneapolis, MN, www.mediject.com). Recognized devices comprising a dual vial system include those pen-injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the reconstituted solution such as the HumatroPen[®].
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The products presently claimed include packaging material. The packaging material provides, in addition to the information required by the regulatory agencies, the conditions under which the product can be used. The packaging material of the present invention provides instructions to the patient to reconstitute the at least one anti-amyloid antibody in the aqueous diluent to form a solution and to use the solution over a period of 2-24 hours or greater for the two vial, wet/dry, product. For the single vial, solution product, the label indicates that such solution can be used over a period of 2-24 hours or greater. The presently claimed products are useful for human pharmaceutical product use.
25

30 The formulations of the present invention can be prepared by a process that comprises mixing at least one anti-amyloid antibody and a selected buffer, preferably a phosphate buffer containing saline or a chosen salt. Mixing the at least one anti-amyloid antibody and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one antibody in water or buffer is combined with the desired buffering agent in water in
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quantities sufficient to provide the protein and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed stable or preserved formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-amyloid antibody that is reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

Other formulations or methods of stabilizing the anti-amyloid antibody may result in other than a clear solution of lyophilized powder comprising said antibody. Among non-clear solutions are formulations comprising particulate suspensions, said particulates being a composition containing the anti-amyloid antibody in a structure of variable dimension and known variously as a microsphere, microparticle, nanoparticle, nanosphere, or liposome. Such relatively homogenous essentially spherical particulate formulations containing an active agent can be formed by contacting an aqueous phase containing the active and a polymer and a nonaqueous phase followed by evaporation of the nonaqueous phase to cause the coalescence of particles from the aqueous phase as taught in U.S. 4,589,330. Porous microparticles can be prepared using a first phase containing active and a polymer dispersed in a continuous solvent and removing said solvent from the suspension by freeze-drying or dilution-extraction-precipitation as taught in U.S. 4,818,542. Preferred polymers for such preparations are natural or synthetic copolymers or polymer selected from the group consisting of gleatin agar, starch, arabinogalactan, albumin, collagen, polyglycolic acid, polylactic acid, glycolide-L(-) lactide poly(epsilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), poly(epsilon-caprolactone-CO-glycolic acid), poly(beta-hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), poly(hydroxyethyl methacrylate), polyamides, poly(amino acids), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane) and poly(methyl methacrylate). Particularly preferred polymers are polyesters such as polyglycolic acid, polylactic acid, glycolide-L(-) lactide poly(epsilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), and poly(epsilon-caprolactone-CO-glycolic acid. Solvents useful for dissolving the polymer and/or the active include: water, hexafluoroisopropanol, methylenechloride, tetrahydrofuran, hexane, benzene, or hexafluoroacetone sesquihydrate. The process of dispersing the active

containing phase with a second phase may include pressure forcing said first phase through an orifice in a nozzle to affect droplet formation.

Dry powder formulations may result from processes other than lyophilization such as by spray drying or solvent extraction by evaporation or by precipitation of a crystalline composition followed by one or more steps to remove aqueous or nonaqueous solvent. Preparation of a spray-dried antibody preparation is taught in U.S. 6,019,968. The antibody-based dry powder compositions may be produced by spray drying solutions or slurries of the antibody and, optionally, excipients, in a solvent under conditions to provide a respirable dry powder. Solvents may include polar compounds such as water and ethanol, which may be readily dried. Antibody stability may be enhanced by performing the spray drying procedures in the absence of oxygen, such as under a nitrogen blanket or by using nitrogen as the drying gas. Another relatively dry formulation is a dispersion of a plurality of perforated microstructures dispersed in a suspension medium that typically comprises a hydrofluoroalkane propellant as taught in WO 9916419. The stabilized dispersions may be administered to the lung of a patient using a metered dose inhaler. Equipment useful in the commercial manufacture of spray dried medicaments are manufactured by Buchi Ltd. or Niro Corp.

At least one anti-amyloid antibody in either the stable or preserved formulations or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means appreciated by the skilled artisan, as well-known in the art.

Therapeutic Applications

The present invention also provides a method for modulating or treating at least one amyloid related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one amyloid antibody of the present invention.

The present invention also provides a method for modulating or treating at least one amyloid related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of obesity, an immune related disease, a cardiovascular disease, an infectious disease, a malignant disease or a neurologic disease. Such amyloid related diseases can include, but are not limited to, any amyloidosis, systemic amyloidosis, Alzheimer's disease (AD), sporadic Alzheimer's disease, familial Alzheimer's disease, Lewy body variant Alzheimer's disease, prion diseases, primary systemic amyloidosis, secondary systemic amyloidosis, dense systemic amyloidosis, monoclonal protein systemic amyloidosis, reactive systemic amyloidosis, hereditary apoA1 amyloidosis, hereditary lysozyme amyloidosis, insulin related amyloid, familial amyloidosis Finnish type, familial subepithelial corneal amyloid,

5 familial amyloid polyneuropathy, familial non-neuropathic amyloidosis, familial British dementia, hereditary cerebral amyloid angiopathy, hemodialysis related amyloidosis, familial amyloid polyneuropathy, familial amyloidotic polyneuropathy, maturity onset diabetes, type II diabetes, hereditary renal amyloidosis, pituitary gland amyloidosis, injection-localization amyloidosis, medullary carcinoma, medullary carcinoma of the thyroid, atrial amyloidosis,
10 isolated atrial amyloidosis, hereditary cerebral amyloid angiopathy, hereditary fibrinogen alpha-chain amyloidosis, Parkinson's disease, Huntington's disease, spongiform encephalopathies, prion related spongiform encephalopathies, prion related transmissible spongiform encephalopathies, amyotrophic lateral sclerosis (ALS), familial amyotrophic lateral sclerosis, chronic obstructive pulmonary disease, and the like.

The present invention also provides a method for modulating or treating at least one neurologic or amyloid related disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and
15 acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranuclear Palsy; structural
20 lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoproteinemia, ataxia, telangiectasia, and mitochondrial multi-system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and
25 disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis,
30 Hallerorden-Spatz disease; and Dementia pugilistica, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one TNF antibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. See, e.g., the Merck Manual, 16th Edition, Merck & Company, Rahway, NJ (1992).

The present invention also provides a method for modulating or treating at least one immune or amyloid related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitivity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic disease, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynaud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-mediated cytotoxicity, type III hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary biliary cirrhosis, vitiligo, vasculitis, post-MI cardiomyopathy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hemophagocytic

lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, okt3 therapy, anti-cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited to asthenia, anemia, cachexia, and the like), chronic
5 salicylate intoxication, and the like. See, e.g., the Merck Manual, 12th-17th Editions, Merck & Company, Rahway, NJ (1972, 1977, 1982, 1987, 1992, 1999), Pharmacotherapy Handbook, Wells et al., eds., Second Edition, Appleton and Lange, Stamford, Conn. (1998, 2000), and as well known in the art.

The present invention also provides a method for modulating or treating at least one
10 cardiovascular or amyloid related disease in a cell, tissue, organ, animal, or patient, including, but not limited to, at least one of cardiac stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic arteriosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, syncope, shock, syphilis of the cardiovascular system, heart failure, cor pulmonale, primary
15 pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial fibrillation (sustained or paroxysmal), post perfusion syndrome, cardiopulmonary bypass inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrhythmias, ventricular fibrillation, His bundle arrhythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina
20 pectoris, myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aortic and peripheral aneurysms, aortic dissection, inflammation of the aorta, occlusion of the abdominal aorta and its branches, peripheral vascular disorders, occlusive arterial disorders, peripheral atherosclerotic disease, thromboangitis obliterans, functional peripheral arterial
25 disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphedema, lipedema, unstable angina, reperfusion injury, post pump syndrome, ischemia-reperfusion injury, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one anti-amyloid antibody to a cell, tissue,
30 organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one infectious or amyloid related disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: acute or chronic bacterial infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection/HIV
35 neuropathy, meningitis, hepatitis (e.g., A,B or C, or the like), septic arthritis, peritonitis,

pneumonia, epiglottitis, e. coli 0157:h7, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, pelvic inflammatory disease, orchitis/epididymitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemaphagocytic syndrome, vital encephalitis/aseptic meningitis, and the like.

The present invention also provides a method for modulating or treating at least one malignant or amyloid related disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, Hodgkin's lymphoma, liver cancer, lung cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, testicular cancer, adenocarcinomas, sarcomas, malignant melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, and the like. Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one anti-amyloid antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such diseases or disorders, wherein the administering of said at least one anti-amyloid antibody, specified portion or variant thereof, further comprises administering, before concurrently, and/or after, at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-I or TBP-II), nerelimonmab, infliximab, etanercept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluorquinolone, a

macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g.,
5 G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a
10 sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket
15 Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000); Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ. each of which references are and as well known in the art.

TNF antagonists suitable for compositions, combination therapy, co-administration,
20 devices and/or methods of the present invention (further comprising at least one anti body, specified portion and variant thereof, of the present invention), include, but are not limited to, anti-TNF antibodies, antigen-binding fragments thereof, and receptor molecules which bind specifically to TNF; compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g.,
25 pentoxifylline and rolipram), A2b adenosine receptor agonists and A2b adenosine receptor enhancers; compounds which prevent and/or inhibit TNF receptor signalling, such as mitogen activated protein (MAP) kinase inhibitors; compounds which block and/or inhibit membrane TNF cleavage, such as metalloproteinase inhibitors; compounds which block and/or inhibit TNF activity, such as angiotensin converting enzyme (ACE) inhibitors (e.g., captopril); and
30 compounds which block and/or inhibit TNF production and/or synthesis, such as MAP kinase inhibitors.

As used herein, a "tumor necrosis factor antibody," "TNF antibody," "TNF α antibody," or fragment and the like decreases, blocks, inhibits, abrogates or interferes with TNF α activity *in vitro*, *in situ* and/or preferably *in vivo*. For example, a suitable TNF human
35 antibody of the present invention can bind TNF α and includes anti-TNF antibodies, antigen-

binding fragments thereof, and specified mutants or domains thereof that bind specifically to TNF α . A suitable TNF antibody or fragment can also decrease block, abrogate, interfere, prevent and/or inhibit TNF RNA, DNA or protein synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.

5 Chimeric antibody cA2 consists of the antigen binding variable region of the high-affinity neutralizing mouse anti-human TNF α IgG1 antibody, designated A2, and the constant regions of a human IgG1, kappa immunoglobulin. The human IgG1 Fc region improves allogeneic antibody effector function, increases the circulating serum half-life and decreases the immunogenicity of the antibody. The avidity and epitope specificity of the chimeric antibody
10 cA2 is derived from the variable region of the murine antibody A2. In a particular embodiment, a preferred source for nucleic acids encoding the variable region of the murine antibody A2 is the A2 hybridoma cell line.

Chimeric A2 (cA2) neutralizes the cytotoxic effect of both natural and recombinant human TNF α in a dose dependent manner. From binding assays of chimeric antibody cA2 and
15 recombinant human TNF α , the affinity constant of chimeric antibody cA2 was calculated to be $1.04 \times 10^{10} \text{M}^{-1}$. Preferred methods for determining monoclonal antibody specificity and affinity by competitive inhibition can be found in Harlow, *et al.*, *antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1988; Colligan *et al.*, eds., *Current Protocols in Immunology*, Greene Publishing Assoc. and Wiley Interscience, New
20 York, (1992-2000); Kozbor *et al.*, *Immunol. Today*, 4:72-79 (1983); Ausubel *et al.*, eds. *Current Protocols in Molecular Biology*, Wiley Interscience, New York (1987-2000); and Muller, *Meth. Enzymol.*, 92:589-601 (1983), which references are and as well known in the art.

In a particular embodiment, murine monoclonal antibody A2 is produced by a cell line designated c134A. Chimeric antibody cA2 is produced by a cell line designated c168A.

25 Additional examples of monoclonal anti-TNF antibodies that can be used in the present invention are described in the art (see, e.g., U.S. Patent No. 5,231,024; Möller, A. *et al.*, *Cytokine* 2(3):162-169 (1990); U.S. Application No. 07/943,852 (filed September 11, 1992); Rathjen *et al.*, International Publication No. WO 91/02078 (published February 21, 1991); Rubin *et al.*, EPO Patent Publication No. 0 218 868 (published April 22, 1987); Yone *et al.*,
30 EPO Patent Publication No. 0 288 088 (October 26, 1988); Liang, *et al.*, *Biochem. Biophys. Res. Comm.* 137:847-854 (1986); Meager, *et al.*, *Hybridoma* 6:305-311 (1987); Fendly *et al.*, *Hybridoma* 6:359-369 (1987); Bringman, *et al.*, *Hybridoma* 6:489-507 (1987); and Hirai, *et al.*, *J. Immunol. Meth.* 96:57-62 (1987), which references are and as well known in the art).

TNF Receptor Molecules

Preferred TNF receptor molecules useful in the present invention are those that bind TNF α with high affinity (see, e.g., Feldmann *et al.*, International Publication No. WO 92/07076 (published April 30, 1992); Schall *et al.*, *Cell* 61:361-370 (1990); and Loetscher *et al.*, *Cell* 61:351-359 (1990), which references are and as well known in the art) and optionally
5 possess low immunogenicity. In particular, the 55 kDa (p55 TNF-R) and the 75 kDa (p75 TNF-R) TNF cell surface receptors are useful in the present invention. Truncated forms of these receptors, comprising the extracellular domains (ECD) of the receptors or functional portions thereof (see, e.g., Corcoran *et al.*, *Eur. J. Biochem.* 223:831-840 (1994)), are also useful in the present invention. Truncated forms of the TNF receptors, comprising the ECD,
10 have been detected in urine and serum as 30 kDa and 40 kDa TNF α inhibitory binding proteins (Engelmann, H. *et al.*, *J. Biol. Chem.* 265:1531-1536 (1990)). TNF receptor multimeric molecules and TNF immunoreceptor fusion molecules, and derivatives and fragments or portions thereof, are additional examples of TNF receptor molecules which are useful in the methods and compositions of the present invention. The TNF receptor molecules which can be
15 used in the invention are characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, can contribute to the therapeutic results achieved.

TNF receptor multimeric molecules useful in the present invention comprise all or a
20 functional portion of the ECD of two or more TNF receptors linked via one or more polypeptide linkers or other nonpeptide linkers, such as polyethylene glycol (PEG). The multimeric molecules can further comprise a signal peptide of a secreted protein to direct expression of the multimeric molecule. These multimeric molecules and methods for their production have been described in U.S. Application No. 08/437,533 (filed May 9, 1995), the
25 content of which is and as well known in the art.

TNF immunoreceptor fusion molecules useful in the methods and compositions of the present invention comprise at least one portion of one or more immunoglobulin molecules and all or a functional portion of one or more TNF receptors. These immunoreceptor fusion
30 molecules can be assembled as monomers, or hetero- or homo-multimers. The immunoreceptor fusion molecules can also be monovalent or multivalent. An example of such a TNF immunoreceptor fusion molecule is TNF receptor/IgG fusion protein. TNF immunoreceptor fusion molecules and methods for their production have been described in the art (Lesslauer *et al.*, *Eur. J. Immunol.* 21:2883-2886 (1991); Ashkenazi *et al.*, *Proc. Natl. Acad. Sci. USA* 88:10535-10539 (1991); Peppel *et al.*, *J. Exp. Med.* 174:1483-1489 (1991); Kolls *et al.*, *Proc. Natl. Acad. Sci. USA* 91:215-219 (1994); Butler *et al.*, *Cytokine* 6(6):616-623 (1994); Baker *et al.*, *Eur. J. Immunol.* 24:2040-2048 (1994); Beutler *et al.*, U.S. Patent No. 5,447,851; and U.S.

Application No. 08/442,133 (filed May 16, 1995), each of which references are and as well known in the art). Methods for producing immunoreceptor fusion molecules can also be found in Capon *et al.*, U.S. Patent No. 5,116,964; Capon *et al.*, U.S. Patent No. 5,225,538; and Capon *et al.*, *Nature* 337:525-531 (1989), which references are and as well known in the art.

5 A functional equivalent, derivative, fragment or region of TNF receptor molecule refers to the portion of the TNF receptor molecule, or the portion of the TNF receptor molecule sequence which encodes TNF receptor molecule, that is of sufficient size and sequences to functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF α with high affinity and possess low immunogenicity). A functional equivalent of
10 TNF receptor molecule also includes modified TNF receptor molecules that functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF α with high affinity and possess low immunogenicity). For example, a functional equivalent of TNF receptor molecule can contain a "SILENT" codon or one or more amino acid
15 substitutions, deletions or additions (e.g., substitution of one acidic amino acid for another acidic amino acid; or substitution of one codon encoding the same or different hydrophobic amino acid for another codon encoding a hydrophobic amino acid). See Ausubel *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Assoc. and Wiley-Interscience, New York (1987-2000).

 Cytokines include any known cytokine. See, e.g., CopewithCytokines.com. Cytokine
20 antagonists include, but are not limited to, any antibody, fragment or mimetic, any soluble receptor, fragment or mimetic, any small molecule antagonist, or any combination thereof.

Therapeutic Treatments. Any method of the present invention can comprise a method for treating an amyloid mediated disorder, comprising administering an effective amount of a composition or pharmaceutical composition comprising at least one anti-amyloid
25 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

 Such a method can optionally further comprise co-administration or combination therapy for treating such diseases or disorders, wherein the administering of said at least one anti-amyloid antibody, specified portion or variant thereof, further comprises administering,
30 before concurrently, and/or after, at least one selected from an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or
35 the like, at least one TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF

antagonist), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Such drugs are well known in the art, including formulations, indications, dosing and administration for each presented herein (see., e.g., Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; Pharmacotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, as well known in the art).

Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one anti-amyloid antibody composition that total, on average, a range from at least about 0.01 to 500 milligrams of at least one anti-amyloid antibody per kilogram of patient per dose, and preferably from at least about 0.1 to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition. Alternatively, the effective serum concentration can comprise 0.1-5000 µg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

Preferred doses can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33,

34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 mg/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5., 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 µg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.1 to 50, and preferably 0.1 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.001 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.

For parenteral administration, the antibody can be formulated as a solution, suspension, emulsion, particle, powder, or lyophilized powder in association, or separately provided, with a

pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 1-10% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical
5 stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Alternative Administration

10 Many known and developed modes of can be used according to the present invention for administering pharmaceutically effective amounts of at least one anti-amyloid antibody according to the present invention. While pulmonary administration is used in the following description, other modes of administration can be used according to the present invention with suitable results.

15 Amyloid antibodies of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a dry powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or known in the art.

Parenteral Formulations and Administration

20 Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting
25 agent such as aqueous solution or a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent, or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthetic mono- or di- or tri-
30 glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446 and as well known in the art.

Alternative Delivery

35 The invention further relates to the administration of at least one anti-amyloid antibody by parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial,

intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, 5 intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. At least one anti-amyloid antibody composition can be prepared for use for parenteral (subcutaneous, intramuscular or intravenous) or any other administration particularly in the form of liquid solutions or suspensions; for use in vaginal or rectal administration particularly in semisolid forms such as, but not limited to, creams and suppositories; for buccal, 10 or sublingual administration such as, but not limited to, in the form of tablets or capsules; or intranasally such as, but not limited to, the form of powders, nasal drops or aerosols or certain agents; or transdermally such as not limited to a gel, ointment, lotion, suspension or patch delivery system with chemical enhancers such as dimethyl sulfoxide to either modify the skin structure or to increase the drug concentration in the transdermal patch (Junginger, et al. In 15 "Drug Permeation Enhancement"; Hsieh, D. S., Eds., pp. 59-90 (Marcel Dekker, Inc. New York 1994, and as well known in the art), or with oxidizing agents that enable the application of formulations containing proteins and peptides onto the skin (WO 98/53847), or applications of electric fields to create transient transport pathways such as electroporation, or to increase the mobility of charged drugs through the skin such as iontophoresis, or application of ultrasound 20 such as sonophoresis (U.S. Pat. Nos. 4,309,989 and 4,767,402) (the above publications and patents being and as well known in the art).

Pulmonary/Nasal Administration

For pulmonary administration, preferably at least one anti-amyloid antibody composition is delivered in a particle size effective for reaching the lower airways of the lung or sinuses. According to the invention, at least one anti-amyloid antibody can be delivered by 25 any of a variety of inhalation or nasal devices known in the art for administration of a therapeutic agent by inhalation. These devices capable of depositing aerosolized formulations in the sinus cavity or alveoli of a patient include metered dose inhalers, nebulizers, dry powder generators, sprayers, and the like. Other devices suitable for directing the pulmonary or nasal 30 administration of antibodies are also known in the art. All such devices can use of formulations suitable for the administration for the dispensing of antibody in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non aqueous) or solid particles. Metered dose inhalers like the Ventolin[®] metered dose inhaler, typically use a propellant gas and require actuation during inspiration (See, e.g., WO 94/16970, WO 98/35888). Dry powder inhalers 35 like Turbuhaler[™] (Astra), Rotahaler[®] (Glaxo), Diskus[®] (Glaxo), Spiros[™] inhaler (Dura), devices marketed by Inhale Therapeutics, and the Spinhaler[®] powder inhaler (Fisons), use

breath-actuation of a mixed powder (US 4668218 Astra, EP 237507 Astra, WO 97/25086 Glaxo, WO 94/08552 Dura, US 5458135 Inhale, WO 94/06498 Fisons, and as well known in the art). Nebulizers like AERx™ Aradigm, the Ultravent® nebulizer (Mallinckrodt), and the Acorn II® nebulizer (Marquest Medical Products) (US 5404871 Aradigm, WO 97/22376), the
5 above references and as well known in the art, produce aerosols from solutions, while metered dose inhalers, dry powder inhalers, etc. generate small particle aerosols. These specific examples of commercially available inhalation devices are intended to be a representative of specific devices suitable for the practice of this invention, and are not intended as limiting the scope of the invention. Preferably, a composition comprising at least one anti-amyloid
10 antibody is delivered by a dry powder inhaler or a sprayer. There are a several desirable features of an inhalation device for administering at least one antibody of the present invention. For example, delivery by the inhalation device is advantageously reliable, reproducible, and accurate. The inhalation device can optionally deliver small dry particles, e.g. less than about 10 µm, preferably about 1-5 µm, for good respirability.

15 **Administration of amyloid antibody Compositions as a Spray**

A spray including amyloid antibody composition can be produced by forcing a suspension or solution of at least one anti-amyloid antibody through a nozzle under pressure. The nozzle size and configuration, the applied pressure, and the liquid feed rate can be chosen to achieve the desired output and particle size. An electrospray can be produced, for example,
20 by an electric field in connection with a capillary or nozzle feed. Advantageously, particles of at least one anti-amyloid antibody composition delivered by a sprayer have a particle size less than about 10 µm, preferably in the range of about 1 µm to about 5 µm, and most preferably about 2 µm to about 3 µm.

Formulations of at least one anti-amyloid antibody composition suitable for use with a
25 sprayer typically include antibody composition in an aqueous solution at a concentration of about 0.1 mg to about 100 mg of at least one anti-amyloid antibody composition per ml of solution or mg/gm, or any range or value therein, e.g., but not limited to, .1, .2, .3, .4, .5, .6, .7, .8, .9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/ml or mg/gm. The formulation can include
30 agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the antibody composition, such as a buffer, a reducing agent, a bulk protein, or a carbohydrate. Bulk proteins useful in formulating antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating antibody compositions include sucrose,
35 mannitol, lactose, trehalose, glucose, or the like. The antibody composition formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the

antibody composition caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters. Amounts will generally range between 0.001 and 14% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan monooleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a protein such as amyloid antibodies, or specified portions or variants, can also be included in the formulation.

Administration of amyloid antibody compositions by a Nebulizer

Antibody composition can be administered by a nebulizer, such as jet nebulizer or an ultrasonic nebulizer. Typically, in a jet nebulizer, a compressed air source is used to create a high-velocity air jet through an orifice. As the gas expands beyond the nozzle, a low-pressure region is created, which draws a solution of antibody composition through a capillary tube connected to a liquid reservoir. The liquid stream from the capillary tube is sheared into unstable filaments and droplets as it exits the tube, creating the aerosol. A range of configurations, flow rates, and baffle types can be employed to achieve the desired performance characteristics from a given jet nebulizer. In an ultrasonic nebulizer, high-frequency electrical energy is used to create vibrational, mechanical energy, typically employing a piezoelectric transducer. This energy is transmitted to the formulation of antibody composition either directly or through a coupling fluid, creating an aerosol including the antibody composition. Advantageously, particles of antibody composition delivered by a nebulizer have a particle size less than about 10 μm , preferably in the range of about 1 μm to about 5 μm , and most preferably about 2 μm to about 3 μm .

Formulations of at least one anti-amyloid antibody suitable for use with a nebulizer, either jet or ultrasonic, typically include a concentration of about 0.1 mg to about 100 mg of at least one anti-amyloid antibody protein per ml of solution. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the at least one anti-amyloid antibody composition, such as a buffer, a reducing agent, a bulk protein, or a carbohydrate. Bulk proteins useful in formulating at least one anti-amyloid antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating at least one anti-amyloid antibody include sucrose, mannitol, lactose, trehalose, glucose, or the like. The at least one anti-amyloid antibody formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the at least one anti-amyloid antibody caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters. Amounts will generally range between

0.001 and 4% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan mono-oleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a protein such as antibody protein can also be included in the formulation.

5 **Administration of amyloid antibody compositions By A Metered Dose Inhaler**

In a metered dose inhaler (MDI), a propellant, at least one anti-amyloid antibody, and any excipients or other additives are contained in a canister as a mixture including a liquefied compressed gas. Actuation of the metering valve releases the mixture as an aerosol, preferably
10 containing particles in the size range of less than about 10 μm , preferably about 1 μm to about 5 μm , and most preferably about 2 μm to about 3 μm . The desired aerosol particle size can be obtained by employing a formulation of antibody composition produced by various methods known to those of skill in the art, including jet-milling, spray drying, critical point
15 condensation, or the like. Preferred metered dose inhalers include those manufactured by 3M or Glaxo and employing a hydrofluorocarbon propellant.

Formulations of at least one anti-amyloid antibody for use with a metered-dose inhaler device will generally include a finely divided powder containing at least one anti-amyloid antibody as a suspension in a non-aqueous medium, for example, suspended in a propellant with the aid of a surfactant. The propellant can be any conventional material employed for this
20 purpose, such as chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol and 1,1,1,2-tetrafluoroethane, HFA-134a (hydrofluoroalkane-134a), HFA-227 (hydrofluoroalkane-227), or the like. Preferably the propellant is a hydrofluorocarbon. The surfactant can be chosen to stabilize the at least one anti-amyloid antibody as a suspension
25 in the propellant, to protect the active agent against chemical degradation, and the like. Suitable surfactants include sorbitan trioleate, soya lecithin, oleic acid, or the like. In some cases solution aerosols are preferred using solvents such as ethanol. Additional agents known in the art for formulation of a protein such as protein can also be included in the formulation.

One of ordinary skill in the art will recognize that the methods of the current invention
30 can be achieved by pulmonary administration of at least one anti-amyloid antibody compositions via devices not described herein.

Oral Formulations and Administration

Formulations for oral rely on the co-administration of adjuvants (e.g., resorcinols and nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to
35 increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and

trasyol) to inhibit enzymatic degradation. Formulations for delivery of hydrophilic agents including proteins and antibodies and a combination of at least two surfactants intended for oral, buccal, mucosal, nasal, pulmonary, vaginal transmembrane, or rectal administration are taught in U.S. 6,309,663. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant such as magnesium stearate, paraben, preserving agent such as sorbic acid, ascorbic acid, alpha-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.

Tablets and pills can be further processed into enteric-coated preparations. The liquid preparations for oral administration include emulsion, syrup, elixir, suspension and solution preparations allowable for medical use. These preparations can contain inactive diluting agents ordinarily used in said field, e.g., water. Liposomes have also been described as drug delivery systems for insulin and heparin (U.S. Pat. No. 4,239,754). More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals (U.S. Pat. No. 4,925,673). Furthermore, carrier compounds described in U.S. Pat. No. 5,879,681 and U.S. Pat. No. 5,587,753 are used to deliver biologically active agents orally are known in the art.

Mucosal Formulations and Administration

A formulation for orally administering a bioactive agent encapsulated in one or more biocompatible polymer or copolymer excipients, preferably a biodegradable polymer or copolymer, affording microcapsules which due to the proper size of the resultant microcapsules results in the agent reaching and being taken up by the folliculi lymphatic aggregati, otherwise known as the "Peyer's patch," or "GALT" of the animal without loss of effectiveness due to the agent having passed through the gastrointestinal tract. Similar folliculi lymphatic aggregati can be found in the bronchei tubes (BALT) and the large intestine. The above-described tissues are referred to in general as mucosally associated lymphoreticular tissues (MALT). For absorption through mucosal surfaces, compositions and methods of administering at least one anti-amyloid antibody include an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption through mucosal surfaces by achieving mucoadhesion of the emulsion particles (U.S. Pat. No. 5,514,670). Mucous surfaces suitable for application of the emulsions of the

present invention can include corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration. Formulations for vaginal or rectal administration, e.g. suppositories, can contain as excipients, for example, polyalkyleneglycols, vaseline, cocoa butter, and the like. Formulations for intranasal administration can be solid and contain as excipients, for example, lactose or can be aqueous or oily solutions of nasal drops. For buccal administration excipients include sugars, calcium stearate, magnesium stearate, pregelatinated starch, and the like (U.S. Pat. No. 5,849,695).

Transdermal Formulations and Administration

For transdermal administration, the at least one anti-amyloid antibody is encapsulated in a delivery device such as a liposome or polymeric nanoparticles, microparticle, microcapsule, or microspheres (referred to collectively as microparticles unless otherwise stated). A number of suitable devices are known, including microparticles made of synthetic polymers such as polyhydroxy acids such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, and polyphosphazenes, and natural polymers such as collagen, polyamino acids, albumin and other proteins, alginate and other polysaccharides, and combinations thereof (U.S. Pat. No. 5,814,599).

Prolonged Administration and Formulations

It can be sometimes desirable to deliver the compounds of the present invention to the subject over prolonged periods of time, for example, for periods of one week to one year from a single administration. Various slow release, depot or implant dosage forms can be utilized. For example, a dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b) e.g. a zinc tannate salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel with, e.g. sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, pamoate salts, and the like. Another type of slow release depot formulation for injection would contain the compound or salt dispersed for encapsulated in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. Pat. No. 3,773,919. The compounds or, preferably, relatively insoluble salts such as those described above can also be formulated in cholesterol matrix silastic pellets, particularly for use in

animals. Additional slow release, depot or implant formulations, e.g. gas or liquid liposomes are known in the literature (U.S. Pat. No. 5,770,222 and "Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson ed., Marcel Dekker, Inc., N.Y., 1978).

5 Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

10 **Example 1: Cloning and Expression of amyloid antibody in Mammalian Cells**

A typical mammalian expression vector contains at least one promoter element, which mediates the initiation of transcription of the antibody coding sequences, encoding heavy and light chain variable regions adjacent to coding sequences of known constant regions, and signals required for the termination of transcription and polyadenylation of the transcript. Additional
15 elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRS) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use
20 in practicing the present invention include, for example, vectors such as pIRESneo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clontech Labs, Palo Alto, CA), pcDNA3.1 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Mammalian host cells that could be used include human Hela 293, H9 and Jurkat cells,
25 mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the gene can be expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

30 The transfected gene can also be amplified to express large amounts of the encoded antibody. The DHFR (dihydrofolate reductase) marker is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy, et al., Biochem. J. 227:277-279 (1991); Bebbington, et al., Bio/Technology 10:169-175 (1992)). Using these markers, the
35 mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese

hamster ovary (CHO) and NSO cells are often used for the production of antibodies.

The expression vectors pC1 and pC4 contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen, et al., *Molec. Cell. Biol.* 5:438-447 (1985)) plus a fragment of the CMV-enhancer (Boshart, et al., *Cell* 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

Cloning and Expression in CHO Cells

The vector pC4 is used for the expression of amyloid antibody. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary- or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (e.g., alpha minus MEM, Life Technologies, Gaithersburg, MD) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented (see, e.g., F. W. Alt, et al., *J. Biol. Chem.* 253:1357-1370 (1978); J. L. Hamlin and C. Ma, *Biochem. et Biophys. Acta* 1097:107-143 (1990); and M. J. Page and M. A. Sydenham, *Biotechnology* 9:64-68 (1991)). Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained that contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains for expressing the gene of interest the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus (Cullen, et al., *Molec. Cell. Biol.* 5:438-447 (1985)) plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV) (Boshart, et al., *Cell* 41:521-530 (1985)). Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human b-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLV. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the amyloid in a regulated way in mammalian cells (M. Gossen, and H. Bujard, *Proc. Natl. Acad. Sci. USA* 89: 5547-5551 (1992)). For the polyadenylation of the mRNA other signals, e.g., from the human growth

hormone or globin genes can be used as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It is advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

5 The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

 In one set of experiments, the DNA sequence encoding the complete amyloid antibody is used, e.g., as presented in SEQ ID NOS:51 or 52, corresponding to HC and LC variable
10 regions of the amyloid antibody of the present invention as presented in SEQ ID NOS:48 or 49, according to known method steps. Isolated nucleic acid encoding a suitable human constant region (i.e., HC and LC regions) is also used in this construct. In another set of experiments, the DNA sequence as presented in SEQ ID NOS:61 or 62, corresponding to HC and LC variable regions as presented in SEQ ID NOS:59 or 60, is used.

15 The isolated variable and constant region encoding DNA and the dephosphorylated vector are then ligated with T4 DNA ligase. E. coli HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

 Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for
20 transfection. 5 µg of the expression plasmid pC4 is cotransfected with 0.5 µg of the plasmid pSV2-neo using lipofectin. The plasmid pSV2neo contains a dominant selectable marker, the neo gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 µg /ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner,
25 Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 µg /ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate
30 (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained that grow at a concentration of 100 - 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reverse phase HPLC analysis.

Binding Kinetics of Human Anti-Human amyloid antibodies

 ELISA analysis confirms that purified antibody from these host cells bind amyloid in a
35 concentration-dependent manner. In this case, the avidity of the antibody for its cognate antigen (epitope) is measured. Quantitative binding constants are obtained using BIAcore

analysis of the human antibodies and reveals that several of the human monoclonal antibodies are very high affinity with K_D in the range of 1×10^{-9} to 9×10^{-12} .

Conclusions

Human amyloid reactive IgG monoclonal antibodies of the invention are generated.

5 The human anti-amyloid antibodies are further characterized. Several of generated antibodies have affinity constants between 1×10^8 and 9×10^{12} . The high affinities of these fully human monoclonal antibodies make them suitable for therapeutic applications in amyloid-dependent diseases, pathologies or related conditions.

10 Example 2: Expression and Purification of an amyloid Protein or Antibody in *E. coli*

The bacterial expression vector pQE60 is used for bacterial expression in this example. (QIAGEN, Inc., Chatsworth, CA). pQE60 encodes ampicillin antibiotic resistance ("Ampr") and contains a bacterial origin of replication ("ori"), an IPTG inducible promoter, a ribosome
15 binding site ("RBS"), six codons encoding histidine residues that allow affinity purification using nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin sold by QIAGEN, Inc., and suitable single restriction enzyme cleavage sites. These elements are arranged such that a DNA fragment encoding a protein or antibody can be inserted in such a way as to produce that protein or antibody with the six His residues (i.e., a "6 X His tag") covalently linked to the
20 carboxyl terminus of that protein or antibody. However, a protein or antibody coding sequence can optionally be inserted such that translation of the six His codons is prevented and, therefore, a protein or antibody is produced with no 6 X His tag.

The nucleic acid sequence encoding the desired portion of an amyloid antibody, e.g., the HC and LC variable region as represented in SEQ ID NOS:48, 49, 59, and 60, the HC
25 CDRs as represented in SEQ ID NOS:42-44, and 53-55, the LC CDRs as represented in SEQ ID NOS:45-47, and 56-58, optionally further comprising part or all of the coding sequence for a known human constant region optionally and preferably lacking the hydrophobic leader sequence is amplified from the deposited cDNA clone using PCR oligonucleotide primers (based on the sequences presented, which anneal to the amino terminal encoding DNA
30 sequences of the desired portion of an amyloid protein or antibody and to sequences in the deposited construct 3' to the cDNA coding sequence. Additional nucleotides containing restriction sites to facilitate cloning in the pQE60 vector are added to the 5' and 3' sequences, respectively.

For cloning an amyloid protein or antibody, the 5' and 3' primers have nucleotides
35 corresponding or complementary to a portion of the coding sequence of an amyloid protein or antibody, according to known method steps. One of ordinary skill in the art would appreciate,

of course, that the point in a protein or antibody coding sequence where the 5' primer begins can be varied to amplify a desired portion of the complete protein or antibody shorter or longer than the mature form.

The amplified amyloid nucleic acid fragments and the vector pQE60 are digested with appropriate restriction enzymes and the digested DNAs are then ligated together. Insertion of the amyloid DNA into the restricted pQE60 vector places an amyloid protein or antibody coding region including its associated stop codon downstream from the IPTG-inducible promoter and in-frame with an initiating AUG codon. The associated stop codon prevents translation of the six histidine codons downstream of the insertion point.

The ligation mixture is transformed into competent *E. coli* cells using standard procedures such as those described in Sambrook, et al., 1989; Ausubel, 1987-1998. *E. coli* strain M15/rep4, containing multiple copies of the plasmid pREP4, which expresses the lac repressor and confers kanamycin resistance ("Kan"), is used in carrying out the illustrative example described herein. This strain, which is only one of many that are suitable for expressing amyloid protein or antibody, is available commercially from QIAGEN, Inc. Transformants are identified by their ability to grow on LB plates in the presence of ampicillin and kanamycin. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

Clones containing the desired constructs are grown overnight ("O/N") in liquid culture in LB media supplemented with both ampicillin (100 µg/ml) and kanamycin (25 µg/ml). The O/N culture is used to inoculate a large culture, at a dilution of approximately 1:25 to 1:250. The cells are grown to an optical density at 600 nm ("OD600") of between 0.4 and 0.6. Isopropyl-b-D-thiogalactopyranoside ("IPTG") is then added to a final concentration of 1 mM to induce transcription from the lac repressor sensitive promoter, by inactivating the lacI repressor. Cells subsequently are incubated further for 3 to 4 hours. Cells then are harvested by centrifugation.

The cells are then stirred for 3-4 hours at 4°C in 6M guanidine-HCl, pH8. The cell debris is removed by centrifugation, and the supernatant containing the amyloid is dialyzed against 50 mM Na-acetate buffer pH6, supplemented with 200 mM NaCl. Alternatively, a protein or antibody can be successfully refolded by dialyzing it against 500 mM NaCl, 20% glycerol, 25 mM Tris/HCl pH7.4, containing protease inhibitors.

If insoluble protein is generated, the protein is made soluble according to known method steps. After renaturation the protein or antibody is purified by ion exchange, hydrophobic interaction and size exclusion chromatography. Alternatively, an affinity chromatography step such as an antibody column is used to obtain pure amyloid protein or

antibody. The purified protein or antibody is stored at 4°C or frozen at -40°C to -120°C.

Example 3: Cloning and Expression of an amyloid Polypeptide in a Baculovirus Expression System

5 In this illustrative example, the plasmid shuttle vector pA2 GP is used to insert the cloned DNA encoding the antibody (e.g., comprising the variable regions of SEQ ID NOS:51-52, or 61-62) into a baculovirus to express an amyloid antibody, using a baculovirus leader and standard methods as described in Summers, et al., A Manual of Methods for Baculovirus
10 Vectors and Insect Cell Culture Procedures, Texas Agricultural Experimental Station Bulletin No. 1555 (1987). This expression vector contains the strong polyhedrin promoter of the Autographa californica nuclear polyhedrosis virus (AcMNPV) followed by the secretory signal peptide (leader) of the baculovirus gp67 protein or antibody and convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is
15 used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from E. coli under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate viable virus that expresses the cloned
20 polynucleotide.

Other baculovirus vectors are used in place of the vector above, such as pAc373, pVL941 and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for
25 instance, in Luckow, et al., Virology 170:31-39.

The cDNA sequence encoding the amyloid antibody in the deposited or other clone, lacking the AUG initiation codon and the naturally associated nucleotide binding site, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. Non-limiting examples include 5' and 3' primers having nucleotides corresponding or
30 complementary to a portion of the coding sequence of an amyloid protein or antibody, e.g., as presented in SEQ ID NOS:48-49 for C889A, SEQ ID NOS:59-60 for C890A, according to known method steps.

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit (e.g., "Geneclean," BIO 101 Inc., La Jolla, CA). The fragment then is then
35 digested with the appropriate restriction enzyme and again is purified on a 1% agarose gel. This fragment is designated herein "F1".

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, CA). This vector DNA is designated herein "V1".

5 Fragment F1 and the dephosphorylated plasmid V1 are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria are identified that contain the plasmid with the human amyloid gene using the PCR method, in which one of the primers that is used to amplify the gene and the second
10 primer is from well within the vector so that only those bacterial colonies containing the amyloid gene fragment will show amplification of the DNA. The sequence of the cloned fragment is confirmed by DNA sequencing. This plasmid is designated herein pBac amyloid .

Five µg of the plasmid pBacamyloid is co-transfected with 1.0 µg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San
15 Diego, CA), using the lipofection method described by Felgner, et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). 1 µg of BaculoGold™ virus DNA and 5 µg of the plasmid pBac amyloid are mixed in a sterile well of a microtiter plate containing 50 µl of serum-free Grace's medium (Life Technologies, Inc., Rockville, MD). Afterwards, 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the
20 transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is rocked back and forth to mix the newly added solution. The plate is then incubated for 5 hours at 27°C. After 5 hours the transfection solution is removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. The plate is put back into an incubator and
25 cultivation is continued at 27°C for four days.

After four days the supernatant is collected and a plaque assay is performed, according to known methods. An agarose gel with "Blue Gal" (Life Technologies, Inc., Rockville, MD) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in
30 the user's guide for insect cell culture and baculovirology distributed by Life Technologies, Inc., Rockville, MD, page 9-10). After appropriate incubation, blue stained plaques are picked with a micropipettor tip (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes.

Four days later the supernatants of these culture dishes are harvested and then they are stored at 4°C. The recombinant virus is called V-amyloid.

To verify the expression of the amyloid gene, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus V-amyloid at a multiplicity of infection ("MOI") of about 2. Six hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available, e.g., from Life Technologies, Inc., Rockville, MD). If radiolabeled protein or antibody is desired, 42 hours later, 5 mCi of 35S-methionine and 5 mCi 35S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then they are harvested by centrifugation. The protein or antibody in the supernatant as well as the intracellular protein or antibody are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled). Microsequencing of the amino acid sequence of the amino terminus of purified protein or antibody can be used to determine the amino terminal sequence of the mature protein or antibody and thus the cleavage point and length of the secretory signal peptide.

Example 4: Characterization of linear epitopes of anti-human beta amyloid antibodies

Introduction

Alzheimer's Disease (AD) is a progressive dementia with pathology that can be characterized by hyperphosphorylated tau in neurons and extracellular deposits of beta-amyloid (A β) plaques in the brain. A β plaques form as a result of over-production, or inefficient clearance, of a highly self-aggregating 42 amino acid peptide of amyloid precursor protein (APP). The normal function of APP or the A β_{42} peptide is unknown, but it is the A β_{42} species that is believed to be related to AD. A β_{42} can quickly self-aggregate to form oligomeric structures that progress to fibrils, and eventually plaques. These plaques are a hallmark of AD pathology.

Therapeutic intervention directed towards interrupting the amyloid cascade has been demonstrated in transgenic AD animal models using active vaccination with A β peptide or peripheral administration of A β -specific monoclonal antibodies. The rationale for these approaches relied upon immune system mediated plaque and/or A β clearance. The mechanism of plaque clearance was proposed to occur via direct binding of antibody to plaques within the brain, thus activating microglial cells via Fc receptors to phagocytose the deposited A β . Alternatively, peripherally administered antibodies may bind circulating A β moieties, thus changing the dynamic equilibrium of A β concentrations between the central nervous system and plasma and promoting A β efflux from the brain.

Methods

Peptide synthesis on cellulose membranes

Membranes were purchased from Intavis (Bergisch Gladbach, Germany).

Fluorenylmethoxycarbonyl (Fmoc) amino acids and N-hydroxybenzotriazole (HBOT) were from Novabiochem (Meudon, France). N,N'-diisopropylcarbodiimide (DIC) was from Fluka
5 (Germany). N,N'-dimethylformamide (DMF) and N-methylpyrrolidone-2 (NMP), were obtained from Applied Biosystems. The Rink resin was purchased from Advanced Chem Tech.

The peptide synthesis of A β ,

KMDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVVIAITVIVITLVML (SEQ
ID NO:50), was performed according to Frank R. (2002) using an Auto Spot Robot ASP 222
10 (Abimed GmbH, Germany), as previously described (Kramer et al., 1994). The membranes used were derivatized with polyethylene glycol spacer of a length of 8 to 10 ethylene glycol units (Amino-PEG₅₀₀-UC Sheet, loading: 400 nmol/cm²) (Intavis AG, Lot AC112050900). The grid was generated by spotting the C-terminal β -alanine. All peptides were N-acetylated and approximately 20 nmol of peptide per single spot was generated.

15 Membrane probing and regeneration

After an overnight saturation step in SuperBlock Blocking Buffer (Pierce), protein G purified antibodies were added to the membrane (1 μ g/ml, 2 hrs incubation at room temperature). After washing the membrane, a 1:10,000 dilution of a Horse Radish Peroxidase-conjugated goat anti-mouse IgG (Jackson ImmunoResearch Laboratory Inc.) was incubated for
20 1 hour at room temperature. Bound antibody was detected by the ECL plus kit (Amersham), which gives a positive indicative of the antibody binding on the spots.

Conclusion

In summary, epitope mapping of anti-A β monoclonal antibodies using Spot membranes showed these antibodies recognized linear epitopes. Two mAbs, C889A and C890A, are
25 specific for at least 2-5 amino acids of SEQ ID NO:50 of one of the sequences of A β .

Example 5: Ligand binding of Anti-human beta amyloid antibodies

Methods

BIAcore 3000, CM5 sensor surface, amine coupling kit, HEPES buffered saline (HBS, 10 mM HEPES 150 mM NaCl, pH7.4 with 3 mM EDTA and 0.005% Tween-20) and 10 mM
30 sodium acetate pH 4.5 were purchased from Biacore, Inc. (Piscataway, NJ). Anti-A β monoclonal antibodies (100 μ g/mL) were dialyzed against HBS diluted 1:10 with water. Then, the dialyzed mAb solution was diluted 1:10 into 10 mM sodium acetate pH 4.5. The CM5 sensor surface was equilibrated in the BIAcore 3000 with HBS. Each antibody was immobilized onto a flow cell using the immobilization wizard provided in the operating
35 software and the protocols supplied with the amine coupling kit. The wizard was set to

immobilize 2500 RU of antibody. Typically 2000 – 3000 RU were actually immobilized.

Results

For each mAb response, data as a function of time were collected (Figure 46). From the sensorgram, report points are taken 10 seconds prior to the injection of the peptide, 10
5 seconds prior to the completion of the association phase, and 60 seconds into the dissociation phase. This data was then used to determine the binding stoichiometry, and a measure of stability (Fraction of bound peptide remaining on the sensor surface after 60 seconds). These calculations are made possible by assuming that 1 RU = 1 pg of peptide (or protein)/ mm².

Due to the potentially multiple aggregation states of the 1-38 and 1-42 peptides, a
10 quantitative analysis of the binding constants is not possible. However, a qualitative analysis is possible. Figure 47 ranks the mAbs as a function of binding ratio and fraction remaining on the surface after 60 seconds reflecting the stability of the complex. From this analysis C889A and C890A are expected to be capable of binding to “monomeric” peptide and/or aggregated peptide.

15 Example 5: Oligomer neutralization of Anti-human beta amyloid antibodies

Methods

A β ₁₋₄₂ oligomer preparations were generated according to published protocols (Klein, 2002). Briefly, 1mg of human A β ₁₋₄₂ (California peptide, catalog #641-15) was monomerized in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 0.45mg was aliquoted to non-siliconized
20 microcentrifuge tubes. The HFIP was allowed to evaporate overnight in a hood at room temperature. If any HFIP remained, it was removed in a speed-vac for 10 minutes. A 5mM A β stock was then prepared by adding 20 μ l of anhydrous DMSO (Hybri-Max, Sigma) to 0.45mg of monomerized peptide film. Then, 980 μ l of Ham's F12 medium (BioSource, Inc) was added to create a 100 μ M oligomer solution. The resulting solution was incubated at 4°C for 24 hr.
25 Following incubation, the oligomer solution was centrifuged at 14,000 x g for 10 minutes at 4°C. The resulting supernatant was carefully recovered and used as the 100 μ M oligomer solution for cell toxicity studies.

Rat PC12 cells (ATCC) were plated at 20,000 cells/well in collagen-coated 96 well plates in F12K media (1% Horse serum, 1% Pen/Strep) and allowed to adhere overnight at
30 37°C and 5%CO₂. Media was refreshed with F12K just before the assay commenced. All A β antibodies (C889A and C890A) and a commercially available mouse anti- A β antibody, 6E10, (Signet, catalog #9320-05) were diluted to 5.6 μ g/10 μ l in sterile water. Then, 5 μ M of A β ₁₋₄₂ oligomers were pre-incubated with each of the antibodies for 2 hours at 4°C. Then, the oligomer and antibody combinations were added to the cells and incubated for 24 hr at 37°C.
35 In this experiment, 5% ethanol was used as a positive control for cell toxicity. Cell viability

was assessed by adding 10µl of MTT reagent (Roche, #1-465-007) to each well and allowed to incubate for 4hrs. Viable cells will reduce the MTT reagent to a formazan salt crystal. The crystals are solubilized overnight in the supplied buffer (Roche) and then read on a spectrophotometer at 550nm-690nm.

5 Results

The ability of the Aβ mAbs to inhibit Aβ₄₂ oligomer toxicity was tested using the rat PC12 cell line. Toxicity was measured using an MTT assay that determines cellular proliferation and viability. The MTT assay also represents a measure of cellular mitochondrial function since mitochondrial dehydrogenase activity is required to reduce the MTT dye to a formazan salt crystal, read on a spectrophotometer. There is typically a 40-50% decrease in MTT reduction following Aβ₄₂ oligomer exposure, as shown in Figure 48 upon comparison of Vehicle treated PC12 cells to those treated with 5 µM Aβ oligomers. The anti-human Aβ antibodies were tested for their ability to prevent of Aβ₄₂ oligomer toxicity. Aβ oligomers were pre-incubated with anti-human Aβ antibodies before they were exposed to the neuron-like PC12 cells.

Cellular exposure to 5µM oligomers alone resulted in a 27.3% decrease in cell viability compared to the vehicle control. All anti-human Aβ antibodies were able to impart neuroprotection on the PC12 cells following a 2 hr pre-incubation with the oligomers. Both C89A and C890A are expected to completely prevent Aβ₄₂ oligomer-induced toxicity in PC12 cells. The commercially available mouse monoclonal Ab antibody, 6E10, did not protect the cells at the concentration tested (560µg/ml).

Example 6: Animal Model Studies for Beta Amyloid Antibodies

ABSTRACT: Background: Although the role of full-length peptides Ab1-40 and Ab1-42 has been extensively studied, the role of various truncated forms is less understood in Alzheimer's disease. One particular truncated form of Ab, Ab11-40/42, results from the further cleavage of the Ab by BACE1 at position 11 and is found to be increased in biological samples from AD patients with the Swedish mutation in APP (APP670/671KMàNL). It has been demonstrated that oligomeric forms of full-length Ab1-40/42 have a greater toxic effect on neurons than monomeric species. Due to increased hydrophobicity, Ab11-40/42 fragments may aggregate even more readily, and hence be a potentially toxic form of Ab. **Objective:** Using a novel monoclonal antibody specific to Ab11-40/42 (JRF/hAb11/1), we examined whether targeting this fragment specifically would have any therapeutic effect in Tg2576 mice. **Methods:** Tg2576 transgenic mice were exposed to a chronic dosing regimen: JRF/hAb11/1 antibody or PBS was administered intraperitoneally, once a week, starting at the age of 6 months until 20 months. We measured levels of Ab11-40/42 in brain and plasma samples after

treatment. The brains were also analyzed histologically for plaque deposition. Behavior tests, such as holeboard test, novel object recognition and Y-maze, were conducted to monitor cognitive function in these mice. Antibody-amyloid peptide interactions were characterized biophysically by surface plasmon resonance (SPR). **Results:** After treatment with

5 JRF/hAb11/1, we observed increased plasma levels of both full length and truncated forms of Ab. Interestingly, mild improvements in cognitive function were observed during times when Ab levels are known to increase in this mouse model. **Conclusions:** JRF/hAb11/1 is a novel antibody that demonstrates specificity to the beta-amyloid fragment Ab11-40/42. Peripheral administration of this antibody in Tg2576 mice demonstrated a mild improvement in cognitive
10 function during times of active Ab deposition. *In vitro* studies suggest that this antibody may be used to monitor progress or development of beta-amyloid fibril maturation.

Introduction:

The role of b-amyloid in Alzheimer's disease has been extensively studied. This peptide is present in many forms due to differential cleavage of the amyloid precursor protein (APP). b-
15 amyloid is present in normal individuals, mostly as the full-length 1-40. This species is highly soluble and not prone to aggregation. Certain forms of b-amyloid more readily aggregate to form oligomers or fibrils *in vivo*. These are thought to be toxic forms of b-amyloid. BACE-1 cleaves APP at position +1, but overexpression of this enzyme results in an additional cleavage at position +11. This N-terminally truncated peptide has been shown to be elevated in post-
20 mortem brain samples from Alzheimer's and Down Syndrome patients (Liu *et al*).

To better understand the role of this particular truncated form of b-amyloid, a monoclonal antibody specific for b-amyloid 11-40/42 was generated. This antibody, JRF/hAb11/1, recognizes b-amyloid at amino acids 11-16, and preferentially binds to the truncated form.

25 In this study, the Tg2576 (Taconic) mouse model carrying the Swedish mutation in APP, was used to characterize these truncated forms of Ab *in vivo*. Additionally, animals were treated with JRF/hAb11/1 to determine if targeting this peptide has any therapeutic value. Plasma samples were obtained from these animals and examined for levels of Ab11-40/42 compared to PBS-treated transgenic animals or untreated wild-type controls by ELISA.
30 Amyloid burden in the brain was examined by ELISA and histology. Behavior tests such as holeboard test, novel object recognition and Y-maze were conducted to assess improvement in cognitive function.

Methods:

35 **Generation of monoclonal antibodies:** Balb/c mice were primed with peptides in complete Freund's adjuvant. The first two synthetic peptides comprised the first 6 to 8 human amino

acids (AA) at the b-secretase 11 cleavage site: EVHHQ(KI)-C (human Ab11 (6 or 8 AA)). The other two peptides for immunization contained a mouse Ab11 AA sequence; EVRHQ(KL)-C. All the peptides were prepared by coupling the peptides via a COOH-terminal cysteine residue to maleimide activated mc(*Megathura crenulata*) KLH, or to Maleimide Activated Bovine Serum Albumin, using the Inject Maleimide Activated mcKLH/BSA kit of Pierce (#77605),
5 according to the manufacturer's instructions (Pierce, Rockford, IL). Mice were boosted every two weeks with 100 µg KLH-coupled peptide, first in Complete and subsequently in Incomplete Freund's adjuvant.

The spleens of all mice were isolated and frozen in liquid nitrogen except for one spleen of a mouse immunized with human Ab11 (6AA) peptide. The mouse selected showed the highest serum titer and was therefore selected for fusion. On day 4 before fusion or spleen extraction, all mice were boosted intraperitoneally with 100 µg of Ab11 peptides coupled to mcKLH in saline. Mouse spleen cells were fused with SP2/0 cells by a modified procedure of Kohler and Milstein. The hybridoma's were seeded in 30 x 96-well plates and screened after 10 days in a
10 direct ELISA on BSA-coupled hAb11 peptide of 6 AA and confirmed on non-coupled Ab11-40 peptide. Positive cells on free hAb11-40 were immediately subcloned and positive clones were frozen in liquid nitrogen.

All hybridoma's were grown in Dulbecco's modified Eagle's medium (#41965-039) supplemented with 10 % foetal calf serum (#SH30071; Hyclone, Europe), 2.5% ESG Hybridoma supplement (#6010 Elscolab, Kruibeke, Belgium), 2% HT (#H-0137; Sigma, USA),
20 1 mM sodium pyruvate (#11360-039), 2 mM L-glutamine (25030-021) and penicillin (100 U/ml) and Streptomycin (50 mg/ml) (#15140-122). All products were purchased from Life-Technologies (Paisley, U.K.). Cells were incubated in a humidified 8 % CO₂ air incubator.

Animals: Female hemizygous Tg2576 mice, as well as age-matched wild type mice were used in this study. The Tg2576 mouse model (Taconic) carries a transgene coding for the 695-amino acid isoform of human APP derived from a Swedish family with early onset AD. These mice express high concentrations of the mutant Ab, develop significant amyloid plaques, and display memory deficits. Mice were housed 4-5 per cage, and identified with ear tags. The
30 animals were dosed intraperitoneally once weekly beginning at 6 months of age with vehicle (sterile PBS) or test article at 25 mg/kg. Animals were given food and water *ad libitum*.

Sample Collection: Blood collection was done by retro-orbital bleed at 6 months of age, and at each subsequent 2-month testing period. Plasma was frozen at -80°C. At specific time
35 points during the study, as well as at the termination of the study, animals were humanely sacrificed. Brains were removed and fixed in 4% paraformaldehyde for histological

examination. No differences were observed histologically between vehicle (PBS) and JRF/hAb11/1 antibody-treated animals.

Determination of b-amyloid levels: b-amyloid 11-42 was measured by immunoassay.

- 5 NUNC Maxisorp 96-well plates were coated with 2 mg/ml anti-b-amyloid 1-42, and then were blocked. After washing, biological sample was added for 1 hour then washed. Biotinylated anti-b-amyloid was then added for 1 hour. After washing, streptavidin-europium solution was added and incubated for 1 hour before washing. Enhancement solution was then added to each well, and the plates were read using the EnVision plate reader. Ab 11-40 or 11-42 standard
10 curve was used to determine amount of the peptide in samples.

Behavioral Testing

- Holeboard test:** Mildly food-deprived mice were trained to learn the location of the food reward on the holeboard (3 holes baited out of 16). The mice were then retested once every 2
15 months beginning at 6 months of age. The latency to find all three rewards along with the number of errors was recorded.

- Object recognition task:** Mice were habituated to the test box in the absence of any objects. The acquisition trial consisted of presenting 2 identical objects to the mice for a 5-minute period. This was followed by a 5-minute test trial in which one of the original objects was
20 replaced with a novel object. The test trial occurred at 1, 4 or 24 hours after the acquisition trial. The time spent exploring each object was measured. Testing began at 6 months of age and was repeated every other month.

- Y-maze testing:** In the initial training trial, the food-restricted mouse was allowed to chose between either arm of the maze. The choice was reinforced by sequestering the animal in the
25 preferred arm with a food reward for 20 seconds. In subsequent trials, the opposite arm was baited with food pellets and became the “correct” choice. Each animal was tested 5 times per day for a 5-day period. The latency to enter the correct arm and the number of errors were recorded. Testing began at 6 months of age, and continued every other month.

- 30 **Figure 1A-B.** Measurement of b-Amyloid 11-40/42 in plasma samples taken from Tg2576 study animals or wild-type littermates. Mice were dosed weekly i.p., and plasma samples collected at 2-month intervals. Plasma levels of peptide were determined by ELISA using biotinylated JRF/hAb11/1 for detection. No peptide was detected in any group until 16 months of age, after which increasing levels of both Ab11-40 (left) and Ab11-42 (right) were found
35 only in the antibody treated group.

Figure 2. Measurement of b-Amyloid 11-40/42 in brain homogenate samples taken from 20-month old Tg2576 study animals or wild-type littermates. Brains were homogenized in diethylamine to measure soluble Ab levels and formic acid to measure insoluble (plaque) Ab. Levels of Ab11-40/42 peptide were determined by ELISA using biotinylated JRF/hAb11/1 for
5 detection. No differences were observed between vehicle control and antibody treated groups.

Figure 3A-F. Holeboard test – At 6 months of age, Tg2576 animals in the antibody-treatment group demonstrated some improvement in time to complete task (latency). By 18-months of age, a slight trend in improvement of number of correct responses was observed in the
10 JRF/hAb11/1 antibody-treated animals although not statistically significant over vehicle-treated animals.

Figure 4A-B. Novel Object Recognition test – a slight improvement over vehicle control was observed in JRF/hAb11/1-treated Tg2576 animals at 8 months of age, but not at any other time
15 points tested

Figure 5. Y-maze test – a trend in improvement in correct choices is observed in Tg2576 mice treated with JRF/hAb11/1 antibody, as well as in time taken to complete task (latency).

20 **Conclusions:**

- A novel antibody recognizing amino acids 11-16 of the b-amyloid peptide was generated, JRF/hAb11/1
- JRF/hAb11/1 was shown to be specific for peptides truncated at amino acid 11
- Tg2576 mice chronically treated with this antibody demonstrated elevated levels of b-
25 amyloid11-40/42 in the plasma of older mice, but no effect on brain Ab burden by ELISA or histology
- Interestingly, some minor improvements in behavior were observed when Tg2576 animals were treated with JRF/hAb11/1.
- Treatment with a higher dose of antibody or greater affinity antibody to this fragment of Ab
30 may show greater improvements.

References:

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Characterization of Ab11-40/42 Peptide Deposition in Alzheimer's Disease (AD) and Young

5 Down Syndrome Brains: Implication of N-terminally Truncated Ab Species in the Pathogenesis of AD (submitted)

El-Mouedden, M., Vandermeeren, M., Meert, T., and Mercken, M. Development of a specific ELISA for the quantitative study of amino-terminally truncated beta-amyloid peptides. *J*

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15

It will be clear that the invention can be practiced otherwise than as particularly described in the foregoing description and examples.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

20

Table 1.

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4		Vh3b	102	1-30	31	32-45	46	47-78	79	80-102
5		Vh3c	94	1-30	31	32-45	46	47-78	79	80-94
6		Vh4	106	1-30	31	32-45	46	47-78	79	80-106
7		Vh5	97	1-30	31	32-45	46	47-78	79	80-97
8		Vh6	91	1-30	31	32-45	46	47-78	79	80-91
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24		λ 4b	72	1-22	23	24-38	39	40-71	72	
25		λ 5	75	1-22	23	24-39	40	41-74	75	
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    Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Thr Arg Asn Xaa
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 35 40 45

35 Xaa Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
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40 Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
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45   Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Xaa Gln
      35          40          45

50   Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp
      50          55          60

55   Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Xaa
      65          70          75          80

60   Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Ala
      85          90          95

    Pro Ser Val Phe Pro Leu Val Ser Cys Glu Asn Ser Pro Ser Asp Thr

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    Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Xaa Arg Phe
30             35             40             45

    Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser
    50             55             60

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        35           40           45

45   Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
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    Ser Pro Gln Leu Leu Ile Tyr Xaa Gly Val Pro Asp Arg Phe Ser Gly
55  35 40 45
    Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
    50 55 60
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 Glu Arg Ala Thr Leu Ser Cys Xaa Trp Tyr Gln Gln Lys Pro Gly Gln
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5   Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
     50                     55                     60

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15  Ala Ala Ile Phe Ile Ile Gln Xaa Gly Ile Pro Pro Arg Phe Ser Gly
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25 Tyr Xaa Gly Ile Ser Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
      35      40      45

30 Phe Thr Leu Thr Ile Thr Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr
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35 Gly Ile Ser Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
    35 40 45

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 35 40 45
 45 Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln Ser Glu
 50 50 55 60
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    Ala Pro Lys Leu Leu Ile Tyr Xaa Gly Ile Pro Asp Arg Phe Ser Gly
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60 Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr
    50             55             60

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Gly Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Lys Leu
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 Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro
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 35 40 45
 15 Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
 50 55 60
 20 Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Thr Lys Leu
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30 35 40 45

Ser Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Gly Val Gln Ala Glu
50 55 60

35 Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Lys Leu Thr
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Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro
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   20 25 30
45 Pro Val Leu Val Val Tyr Asp Xaa Gly Ile Pro Glu Arg Phe Ser Gly
   35 40 45
50 Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala
   50 55 60
55 Gly Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Lys Leu
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    Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
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50   Thr Ala Ser Ile Thr Cys Xaa Trp Tyr Gln Gln Lys Pro Gly Gln Ser
        20          25          30

55   Pro Val Leu Val Ile Tyr Xaa Gly Ile Pro Glu Arg Phe Ser Gly Ser
        35          40          45

60   Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
        50          55          60

    Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Lys Leu Thr

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

35   Pro Arg Tyr Leu Met Lys Xaa Gly Ile Pro Asp Arg Phe Ser Gly Ser
    35          40          45

40   Ser Ser Gly Ala Glu Arg Tyr Leu Thr Ile Ser Ser Leu Gln Ser Glu
    50          55          60

45   Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Ile Gly Gly Gly Thr
    65          70          75          80

    Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Ser
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    Ser Ala Ser Leu Thr Cys Xaa Trp Tyr Gln Gln Lys Pro Gly Ser Pro
45 20 25 30

    Pro Gln Tyr Leu Leu Arg Tyr Xaa Gly Val Pro Ser Arg Phe Ser Gly
50 35 40 45

    Ser Lys Asp Ala Ser Ala Asn Ala Gly Ile Leu Leu Ile Ser Gly Leu
    50 55 60

55 Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr
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60 Lys Leu Thr Val Leu Ser Gln Pro
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Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
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55
Thr Val Thr Ile Ser Cys Xaa Trp Tyr Gln Gln Arg Pro Gly Ser Ala
          20           25           30

60
Pro Thr Thr Val Ile Tyr Xaa Gly Val Pro Asp Arg Phe Ser Gly Ser
          35           40           45

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      Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly Leu Lys
        50                      55                      60

5      Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Lys
      65                      70                      75                      80

10     Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe
      85                      90                      95

      Pro Pro Ser Ser Ser
15                      100

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 20 25 30
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 35 40 45
 20 Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu
 50 55 60
 25 Asp Glu Ala Glu Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Lys Leu Thr
 65 70 75 80
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20 Thr Val Thr Leu Thr Cys Xaa Trp Tyr Gln Gln Thr Pro Gly Gln Ala
      20      25      30

25 Pro Arg Thr Leu Ile Tyr Xaa Gly Val Pro Asp Arg Phe Ser Gly Ser
      35      40      45

30 Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala Gln Ala Asp
      50      55      60

35 Asp Glu Ser Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Lys Leu Thr
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Val Leu Gly Gln Pro Lys Ala Ala Pro
      85
40

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30 Gln Pro Val Leu Thr Gln Pro Pro Ser Ala Ser Ala Ser Leu Gly Ala
    1 5 10 15

    Ser Val Thr Leu Thr Cys Xaa Trp Tyr Gln Gln Arg Pro Gly Lys Gly
35 20 25 30

    Pro Arg Phe Val Met Arg Xaa Gly Ile Pro Asp Arg Phe Ser Val Leu
40 35 40 45

    Gly Ser Gly Leu Asn Arg Tyr Leu Thr Ile Lys Asn Ile Gln Glu Glu
    50 55 60

45 Asp Glu Ser Asp Tyr His Cys Xaa Phe Gly Gly Gly Thr Lys Leu Thr
    65 70 75 80

50 Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val
    85 90

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45   Thr Ala Thr Leu Thr Cys Xaa Trp Leu Gln Gln His Gln Gly His Pro
    20          25          30

50   Pro Lys Leu Leu Ser Tyr Xaa Gly Ile Ser Glu Arg Phe Ser Ala Ser
    35          40          45

    Arg Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Leu Gln Pro Glu
55   50          55          60

    Asp Glu Ala Asp Tyr Tyr Cys Xaa Phe Gly Gly Gly Thr Lys Leu Thr
60   65          70          75          80

    Val Leu Gly Gln Pro Lys Ala
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40   Gln Pro Asp Gly Asn Val Val Ile Ala Cys Leu Val Gln Gly Phe Phe
      20          25          30

    Pro Gln Glu Pro Leu Ser Val Thr Trp Ser Glu Ser Gly Gln Gly Val
45          35          40          45

    Thr Ala Arg Asn Phe Pro Pro Ser Gln Asp Ala Ser Gly Asp Leu Tyr
50          50          55          60

    Thr Thr Ser Ser Gln Leu Thr Leu Pro Ala Thr Gln Cys Leu Ala Gly
65          70          75          80

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

60   Val Thr Val Pro Cys Pro Val Pro Ser Thr Pro Pro Thr Pro Ser Pro
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40          20          25          30

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

      Thr Ala Arg Asn Phe Pro Pro Ser Gln Asp Ala Ser Gly Asp Leu Tyr
          50          55          60

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

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

60   Val Thr Val Pro Cys Pro Val Pro Pro Pro Pro Cys Cys His Pro
          100          105          110

      Arg Leu Ser Leu His Arg Pro Ala Leu Glu Asp Leu Leu Leu Gly Ser

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15	Pro Pro Glu Arg Asp Leu Cys Gly Cys Tyr Ser Val Ser Ser Val Leu 165 170 175		
20	Pro Gly Cys Ala Gln Pro Trp Asn His Gly Glu Thr Phe Thr Cys Thr 180 185 190		
25	Ala Ala His Pro Glu Leu Lys Thr Pro Leu Thr Ala Asn Ile Thr Lys 195 200 205		
30	Ser Gly Asn Thr Phe Arg Pro Glu Val His Leu Leu Pro Pro Pro Ser 210 215 220		
35	Glu Glu Leu Ala Leu Asn Glu Leu Val Thr Leu Thr Cys Leu Ala Arg 225 230 235 240		
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60	Glu Ala Leu Pro Leu Ala Phe Thr Gln Lys Thr Ile Asp Arg Leu Ala 305 310 315 320		
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     1          5          10          15

    His Pro Lys Asp Asn Ser Pro Val Val Leu Ala Cys Leu Ile Thr Gly
40   20          25          30

    Tyr His Pro Thr Ser Val Thr Val Thr Trp Tyr Met Gly Thr Gln Ser
     35          40          45
45

    Gln Pro Gln Arg Thr Phe Pro Glu Ile Gln Arg Arg Asp Ser Tyr Tyr
     50          55          60

50   Met Thr Ser Ser Gln Leu Ser Thr Pro Leu Gln Gln Trp Arg Gln Gly
     65          70          75          80

55   Glu Tyr Lys Cys Val Val Gln His Thr Ala Ser Lys Ser Lys Lys Glu
     85          90          95

60   Ile Phe Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro
     100         105         110

    Thr Ala Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala

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	115		120		125												
5	Pro	Ala	Thr	Thr	Arg	Asn	Thr	Gly	Arg	Gly	Gly	Glu	Glu	Lys	Lys	Lys	
	130						135					140					
10	Glu	Lys	Glu	Lys	Glu	Glu	Gln	Glu	Glu	Arg	Glu	Thr	Lys	Thr	Pro	Glu	
	145					150					155					160	
15	Cys	Pro	Ser	His	Thr	Gln	Pro	Leu	Gly	Val	Tyr	Leu	Leu	Thr	Pro	Ala	
					165					170					175		
20	Val	Gln	Asp	Leu	Trp	Leu	Arg	Asp	Lys	Ala	Thr	Phe	Thr	Cys	Phe	Val	
				180					185					190			
25	Lys	Val	Pro	Thr	Gly	Gly	Val	Glu	Glu	Gly	Leu	Leu	Glu	Arg	His	Ser	
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	225					230					235					240	
35	Trp	Asn	Ala	Gly	Thr	Ser	Val	Thr	Cys	Thr	Leu	Asn	His	Pro	Ser	Leu	
					245					250					255		
40	Pro	Pro	Gln	Arg	Leu	Met	Ala	Leu	Arg	Glu	Pro	Ala	Ala	Gln	Ala	Pro	
				260					265					270			
45	Val	Lys	Leu	Ser	Leu	Asn	Leu	Leu	Ala	Ser	Ser	Asp	Pro	Pro	Glu	Ala	
			275					280					285				
50	Ala	Ser	Trp	Leu	Leu	Cys	Glu	Val	Ser	Gly	Phe	Ser	Pro	Pro	Asn	Ile	
	290						295					300					
55	Leu	Leu	Met	Trp	Leu	Glu	Asp	Gln	Arg	Glu	Val	Asn	Thr	Ser	Gly	Phe	
	305					310					315					320	
60	Ala	Pro	Ala	Arg	Pro	Pro	Pro	Gln	Pro	Arg	Ser	Thr	Thr	Phe	Trp	Ala	
					325					330					335		
65	Trp	Ser	Val	Leu	Arg	Val	Pro	Ala	Pro	Pro	Ser	Pro	Gln	Pro	Ala	Thr	
				340					345					350			
70	Tyr	Thr	Cys	Val	Val	Ser	His	Glu	Asp	Ser	Arg	Thr	Leu	Leu	Asn	Ala	
			355					360					365				

Ser Arg Ser Leu Glu Val Ser Tyr Val Thr Asp His Gly Pro Met Lys
 370 375 380

5 <210> 34
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 <212> PRT
 <213> Homo sapiens

10 <220>
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 <223> IgE heavy chain constant region

15 <220>
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 <223> CH1

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 <223> CH2

25 <220>
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 <223> CH3

30 <220>
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 <223> CH4

35 <400> 34

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

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

45 Gly Tyr Phe Pro Glu Pro Val Met Val Thr Trp Asp Thr Gly Ser Leu
 35 40 45

50 Asn Gly Thr Thr Met Thr Leu Pro Ala Thr Thr Leu Thr Leu Ser Gly
 50 55 60

55 His Tyr Ala Thr Ile Ser Leu Leu Thr Val Ser Gly Ala Trp Ala Lys
 65 70 75 80

Gln Met Phe Thr Cys Arg Val Ala His Thr Pro Ser Ser Thr Asp Trp
 85 90 95

60 Val Asp Asn Lys Thr Phe Ser Val Cys Ser Arg Asp Phe Thr Pro Pro
 100 105 110

5 Thr Val Lys Ile Leu Gln Ser Ser Cys Asp Gly Gly Gly His Phe Pro
 115 120 125
 10 Pro Thr Ile Gln Leu Leu Cys Leu Val Ser Gly Tyr Thr Pro Gly Thr
 130 135 140
 15 Ile Asn Ile Thr Trp Leu Glu Asp Gly Gln Val Met Asp Val Asp Leu
 145 150 155 160
 20 Glu Leu Thr Leu Ser Gln Lys His Trp Leu Ser Asp Arg Thr Tyr Thr
 180 185 190
 25 Cys Gln Val Thr Tyr Gln Gly His Thr Phe Glu Asp Ser Thr Lys Lys
 195 200 205
 30 Cys Ala Asp Ser Asn Pro Arg Gly Val Ser Ala Tyr Leu Ser Arg Pro
 210 215 220
 35 Val Val Asp Leu Ala Pro Ser Lys Gly Thr Val Asn Leu Thr Trp Ser
 245 250 255
 40 Arg Ala Ser Gly Lys Pro Val Asn His Ser Thr Arg Lys Glu Glu Lys
 260 265 270
 45 Gln Arg Asn Gly Thr Leu Thr Val Thr Ser Thr Leu Pro Val Gly Thr
 275 280 285
 50 Arg Asp Trp Ile Glu Gly Glu Thr Tyr Gln Cys Arg Val Thr His Pro
 290 295 300
 55 His Leu Pro Arg Ala Leu Met Arg Ser Thr Thr Lys Thr Ser Gly Pro
 305 310 315 320
 60 Val Gly Pro Arg Ala Ala Pro Glu Val Tyr Ala Phe Ala Thr Pro Glu
 325 330 335
 Trp Pro Gly Ser Arg Asp Lys Arg Thr Leu Ala Cys Leu Ile Gln Asn
 340 345 350
 Phe Met Pro Glu Asp Ile Ser Val Gln Trp Leu His Asn Glu Val Gln

	355	360	365
5	Leu Pro Asp Ala Arg His Ser Thr Thr Gln Pro Arg Lys Thr Lys Gly 370 375 380		
10	Ser Gly Phe Phe Val Phe Ser Arg Leu Glu Val Thr Arg Ala Glu Trp 385 390 395 400		
15	Glu Gln Lys Asp Glu Phe Ile Cys Arg Ala Val His Glu Ala Ala Ser 405 410 415		
20	Pro Ser Gln Thr Val Gln Arg Ala Val Ser Val Asn Pro Gly Lys Asp 420 425 430		
25	Val Cys Val Glu Glu Ala Glu Gly Glu Ala Pro Trp Thr Trp Thr Gly 435 440 445		
30	Leu Cys Ile Phe Ala Ala Leu Phe Leu Leu Ser Val Ser Tyr Ser Ala 450 455 460		
35	Ala Leu Thr Leu Leu Met Val Gln Arg Phe Leu Ser Ala Thr Arg Gln 465 470 475 480		
40	Gly Arg Pro Gln Thr Ser Leu Asp Tyr Thr Asn Val Leu Gln Pro His 485 490 495		
45	Ala		
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	<220> <221> MISC_FEATURE <222> (99)..(113) <223> hinge		
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10 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

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

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

25 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

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

35 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

40 Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

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

45 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

50 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

60 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

5 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 225 230 235 240

 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

10 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asx Asn Gly Gln Pro Glu
 260 265 270

15 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 275 280 285

20 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 290 295 300

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

25 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Thr His Thr Cys Pro
 325 330 335

30 Pro Cys Pro

35 <210> 36
 <211> 326
 <212> PRT
 <213> Homo sapiens

40 <220>
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 <222> (1)..(326)
 <223> IgG2 heavy chain constant region

45 <220>
 <221> MISC_FEATURE
 <222> (1)..(98)
 <223> CH1

50 <220>
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 <222> (99)..(110)
 <223> hinge

55 <220>
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 <222> (111)..(219)
 <223> CH2

60 <220>
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 <222> (220)..(326)

<223> CH3

<400> 36

5 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1 5 10 15
 10 Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 15 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 20 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 25 Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
 65 70 75 80
 30 Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 35 Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
 100 105 110
 40 Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 115 120 125
 45 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 130 135 140
 50 Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
 145 150 155 160
 55 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
 165 170 175
 60 Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
 180 185 190
 65 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 195 200 205
 70 Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
 210 215 220
 75 Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
 225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 245 250 255
 5 Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 260 265 270
 10 Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 275 280 285
 15 Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 290 295 300
 20 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 305 310 315 320
 Ser Leu Ser Pro Gly Lys
 325
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 <210> 37
 <211> 377
 <212> PRT
 <213> Homo sapiens
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 35 <223> IgG3 heavy chain constant region
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 <222> (1)..(98)
 40 <223> CH1
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 45 <223> hinge 1
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 50 <223> hinge 2
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 55 <223> hinge 3
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 60 <223> hinge 4
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<222> (161) .. (270)
 <223> CH2

 <220>
 5 <221> MISC_FEATURE
 <222> (271) .. (377)
 <223> CH3

 <400> 37
 10 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1 5 10 15

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

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

 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 25

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

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

 35 Arg Val Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro
 100 105 110

 40 Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
 115 120 125

 Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys
 130 135 140
 45

 Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
 145 150 155 160

 50 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 165 170 175

 55 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 180 185 190

 60 Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
 195 200 205

 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

	210	215	220
5	Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His 225 230 235 240		
10	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys 245 250 255		
15	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln 260 265 270		
20	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met 275 280 285		
25	Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro 290 295 300		
30	Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn 305 310 315 320		
35	Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu 325 330 335		
40	Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile 340 345 350		
45	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln 355 360 365		
50	Lys Ser Leu Ser Leu Ser Pro Gly Lys 370 375		
55	<210> 38 <211> 327 <212> PRT <213> Homo sapiens		
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65	<220> <221> MISC_FEATURE <222> (1) ..(98) <223> CH1		
70	<220> <221> MISC_FEATURE <222> (99) ..(110) <223> hinge		

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<222> (111)..(220)
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<220>
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10 <223> CH3

<400> 38

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

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

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

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

30 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
35 85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
40 100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

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

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

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
55 165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

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

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35      <210> 39
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        <223> IgM heavy chain constant region

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        <223> CH1

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        <223> CH2

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        <223> CH3

60      <220>
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        <222> (324)..(476)

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<223> CH4

<400> 39

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 10 Ser Pro Ser Asp Thr Ser Ser Val Ala Val Gly Cys Leu Ala Gln Asp
 20 25 30
 15 Phe Leu Pro Asp Ser Ile Thr Phe Ser Trp Lys Tyr Lys Asn Asn Ser
 35 40 45
 20 Asp Ile Ser Ser Thr Arg Gly Phe Pro Ser Val Leu Arg Gly Gly Lys
 50 55 60
 25 Tyr Ala Ala Thr Ser Gln Val Leu Leu Pro Ser Lys Asp Val Met Gln
 65 70 75 80
 30 Gly Thr Asp Glu His Val Val Cys Lys Val Gln His Pro Asn Gly Asn
 85 90 95
 35 Lys Glu Lys Asn Val Pro Leu Pro Val Ile Ala Glu Leu Pro Pro Lys
 100 105 110
 40 Val Ser Val Phe Val Pro Pro Arg Asp Gly Phe Phe Gly Asn Pro Arg
 115 120 125
 45 Ser Lys Ser Lys Leu Ile Cys Gln Ala Thr Gly Phe Ser Pro Arg Gln
 130 135 140
 50 Ile Gln Val Ser Trp Leu Arg Glu Gly Lys Gln Val Gly Ser Gly Val
 145 150 155 160
 55 Thr Thr Asp Gln Val Gln Ala Glu Ala Lys Glu Ser Gly Pro Thr Thr
 165 170 175
 60 Tyr Lys Val Thr Ser Thr Leu Thr Ile Lys Glu Ser Asp Trp Leu Ser
 180 185 190
 65 Gln Ser Met Phe Thr Cys Arg Val Asp His Arg Gly Leu Thr Phe Gln
 195 200 205
 70 Gln Asn Ala Ser Ser Met Cys Val Pro Asp Gln Asp Thr Ala Ile Arg
 210 215 220
 75 Val Phe Ala Ile Pro Pro Ser Phe Ala Ser Ile Phe Leu Thr Lys Ser
 225 230 235 240

Thr Lys Leu Thr Cys Leu Val Thr Asp Leu Thr Thr Tyr Asp Ser Val
 245 250 255
 5 Thr Ile Ser Trp Thr Arg Gln Asn Gly Glu Ala Val Lys Thr His Thr
 260 265 270
 10 Asn Ile Ser Glu Ser His Pro Asn Ala Thr Phe Ser Ala Val Gly Glu
 275 280 285
 15 Ala Ser Ile Cys Glu Asp Asp Trp Asn Ser Gly Glu Arg Phe Thr Cys
 290 295 300
 20 Thr Val Thr His Thr Asp Leu Pro Ser Pro Leu Lys Gln Thr Ile Ser
 305 310 315 320
 Arg Pro Lys Gly Val Ala Leu His Arg Pro Asp Val Tyr Leu Leu Pro
 325 330 335
 25 Pro Ala Arg Glu Gln Leu Asn Leu Arg Glu Ser Ala Thr Ile Thr Cys
 340 345 350
 30 Leu Val Thr Gly Phe Ser Pro Ala Asp Val Phe Val Gln Trp Gln Met
 355 360 365
 35 Gln Arg Gly Gln Pro Leu Ser Pro Glu Lys Tyr Val Thr Ser Ala Pro
 370 375 380
 40 Met Pro Glu Pro Gln Ala Pro Gly Arg Tyr Phe Ala His Ser Ile Leu
 385 390 395 400
 Thr Val Ser Glu Glu Glu Trp Asn Thr Gly Glu Thr Tyr Thr Cys Val
 405 410 415
 45 Val Ala His Glu Ala Leu Pro Asn Arg Val Thr Glu Arg Thr Val Asp
 420 425 430
 50 Lys Ser Thr Gly Lys Pro Thr Ser Ala Asp Glu Glu Gly Phe Glu Asn
 435 440 445
 55 Leu Trp Ala Thr Ala Ser Thr Phe Ile Val Leu Tyr Asn Val Ser Leu
 450 455 460
 60 Val Met Ser Asp Thr Ala Gly Thr Cys Tyr Val Lys
 465 470 475
 <210> 40
 <211> 107

<212> PRT
 <213> Homo sapiens

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 <223> Light chain kappa constant region (IgKc)

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Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 1 5 10 15

15 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 20 25 30

20 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 35 40 45

25 Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 50 55 60

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

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 85 90 95

35 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 100 105

40 <210> 41
 <211> 107
 <212> PRT
 <213> Homo sapiens

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 <222> (1)..(107)
 <223> Light chain lambda constant region (IgLambda)

50 <400> 41

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
 1 5 10 15

55 Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
 20 25 30

60 Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
 35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
 50 55 60

5 Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
 65 70 75 80

10 Ser His Arg Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr
 85 90 95

15 Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
 100 105

SEQ ID NO:42
 C889A HC CDR1
 20 NYFMH 5

SEQ ID NO:43
 C889A HC CDR2
 ELIPTSGRSNYNEKFKN 17

25 SEQ ID NO:44
 C889A HC CDR3
 GGAYYDPYPFAY 12

30 SEQ ID NO:45
 C889A 1C CDR1
 RSSKSLLYKDGKTYLN 16

SEQ ID NO:46
 35 C889A 1C CDR2
 LMSTRAS 7

SEQ ID NO:47
 C889A 1C CDR2
 40 QQLTDYPFT 9

SEQ ID NO:48
 C889A HC VARIABLE
 MGWSYIILFLVATATDVHSQVQLQQPGAELVKPGASVKLSCKASGYTFTNYFMHWVNQRPGQGLEWIGEI
 45 IPTSGRSNYNEKFKNKAALTVDKSSSTAYMLLSSLTSEDSAVYFCARGGAYYDPYPFAYWGQGLTVTVSA
 140

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

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

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

Thr Asn Tyr Phe Met His Trp Val Asn Gln Arg Pro Gly Gln Gly Leu
 50 55 60
 5 Glu Trp Ile Gly Glu Ile Ile Pro Thr Ser Gly Arg Ser Asn Tyr Asn
 65 70 75 80
 Glu Lys Phe Lys Asn Lys Ala Ala Leu Thr Val Asp Lys Ser Ser Ser
 85 90 95
 10 Thr Ala Tyr Met Leu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
 100 105 110
 15 Tyr Phe Cys Ala Arg Gly Gly Ala Tyr Tyr Asp Pro Tyr Pro Phe Ala
 115 120 125
 Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
 130 135 140
 20 SEQ ID NO:49
 C889A LC VARIABLE
 MRCSLQFLGVLMFWISGVSGDIVLTQDELSNPVISGQSVSISCRSSKSLLYKDGKTYLWNWFLQRPQGSPQ
 LLIYLMSTRASGVSDRFGSGSGTDFTLEISRVTAEADVGVYYCQQLTDYFPFTFGSGTKLEIKR
 25 Met Arg Cys Ser Leu Gln Phe Leu Gly Val Leu Met Phe Trp Ile Ser
 1 5 10 15
 Gly Val Ser Gly Asp Ile Val Leu Thr Gln Asp Glu Leu Ser Asn Pro
 20 25 30
 Val Ile Ser Gly Gln Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser
 35 40 45
 35 Leu Leu Tyr Lys Asp Gly Lys Thr Tyr Leu Asn Trp Phe Leu Gln Arg
 50 55 60
 Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Met Ser Thr Arg Ala
 65 70 75 80
 40 Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
 85 90 95
 45 Thr Leu Glu Ile Ser Arg Val Thr Ala Glu Asp Val Gly Val Tyr Tyr
 100 105 110
 Cys Gln Gln Leu Thr Asp Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys
 115 120 125
 50 Leu Glu Ile Lys Arg
 130
 SEQ ID NO:50
 DAEFRHDSGY EVHHQKLVFF AEDVGSNKGAIIGLMVGGVV IA 42
 55 Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln Lys
 1 5 10 15
 60 Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala Ile Ile
 20 25 30
 Gly Leu Met Val Gly Gly Val Val Ile Ala

35

40

SEQ ID NO:51

C889A HC VARIABLE NUCLEIC ACID

5 atgggatgga gctatatcat cctcttttttg gtagcaacag ctacagatgt ccaactcccag 60
 gtccaattgc agcagcctgg ggctgaactg gtgaagcctg gggcttcagt gaagctgtcc 120
 tgcaaggctt ctggttacac cttcaccaac tacttcatgc actgggtgaa tcagaggcct 180
 ggacaaggcc ttgagtggat tggggagatt attcctacca gcggtcgttc taactacaat 240
 10 gagaagttca agaacaaggc cgcactgact gtagacaaat cctccagcac agcctacatg 300
 ctactcagca gcctgacatc tgaggactct gcggtctatt tctgtgcaag agggggggcc 360
 tactatgata cctaccctt tgcttactgg ggccaaggga ctctgggtcac tgtctctgca 420

SEQ ID NO:52

C889A LC VARIABLE NUCLEIC ACID

15 atgaggtgct ctcttcagtt cctgggggtg cttatgttct ggatctcttg agtcagtggg 60
 gatattgtgc taaccagga tgagctctcc aatcctgtca tttctggaca atcagtttcc 120
 atctcctgca ggtcaagtaa gagtctccta tataaggatg ggaagacata cttgaattgg 180
 tttctgcaga gaccaggaca atctcctcag ctctgatct atttgatgtc caccctgtgc 240
 tcaggagtct cggaccggtt tagtggcagt gggtcaggaa cagatttcac cctggaaatc 300
 20 agtagagtga cggctgagga tgtgggggtg tattactgtc aacaacttac agattatcca 360
 ttcacgttcg gctcggggac aaagttggaa ataaaacgg 399

SEQ ID NO:53

C890A HC CDR1

25 NYFMH 7

SEQ ID NO:54

C890A HC CDR2

30 ELIPTSGRSNYNEKFKN 16

SEQ ID NO:55

C890A HC CDR3

GGAYYDTYPFAY 13

35 SEQ ID NO:56

C890A LC CDR1

RSSKSLLYKDGKTYLN 16

SEQ ID NO:57

40 C890A LC CDR2

LMSTRAS 7

SEQ ID NO:58

C890A LC CDR3

45 QQLTDYPFT 9

SEQ ID NO:59

C890A HC VARIABLE

50 MGWSYIILFLVATATDVHSQVQLQQPGAELVKPGASVKLSCKASGYTFINYMHWVKQRPQGLEWIGE
 IPTSGRSNYNEKFKNRAALTVDKSSSTAYMQLSSLTSEDSAVYYCARGGAYYDTYPFAYWGQGLTVTVSA

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

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SEQ ID NO:60

C890A LC VARIABLE

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30 MRCSLQLFLGVLMFWISGVSGDIVLTQDELSNPVISGQSVSISCRSSKSLLYKDGKTYLWFLQRPQGSPQ
LLIYLMSTRASGVSDRFSGSGSGTDFLTLEISRVTAEVDGVVYQCQLTDYPTTFGSGTKLEIKR

```

```

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

```

60 SEQ ID NO:61

C890A HC VARIABLE NUCLEIC ACID

```

atgggatgga gctatatcat cctctttttg gtagcaacag ctacagatgt ccactcccag 60
gtccaattgc agcagcctgg ggctgaactg gtgaagcctg gggcttcagt gaagctgtcc 120

```

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      tgcaaggctt ctggctacac cttcatcaac tacttcatgc actgggtgaa gcagaggcct 180
      ggacaaggcc ttgagtggat tggggagatt attcctacca ggggtcggtc taactacaat 240
      gagaagttca agaacagggc cgcactgact gtagacaaat cctccagcac agcctacatg 300
5    caactcagca gcctgacatc tgaggactct ggggtctatt actgtgcaag agggggggcc 360
      tactatgata cctaccctt tgcttactgg ggccaaggga ctctggtcac tgtctctgca 420

```

SEQ ID NO:62

C890A LC VARIABLE NUCLEIC ACID

```

10
      atgaggtgct ctcttcagtt cctggggggtg cttatgttct ggatctctgg agtcagtggt 60
      gatattgtgc taaccaggga tgaactctcc aatcctgtca tttctggaca atcagtttcc 120
      atctcctgca ggtcaagtaa gagtctccta tataaggatg ggaagacata cttgaattgg 180
      tttctgcaga gaccaggaca atctcctcag ctctgatct atttgatgtc caccctgca 240
15    tcaggagtct cggaccggtt tagtggcagt gggtcaggaa cagatttcac cctggaaatc 300
      agtagagtga cggctgagga tgtgggtgtg tattactgtc aacaacttac agattatcca 360
      ttcacgttcg gctcggggac aaagttggaa ataaaacgg 399

```

20 AEFRHDSGYEVH (SEQ ID NO:83);

EFRHDSGYEVHH (SEQ ID NO:84);

25 IGLMVGGVVIA (SEQ ID NO:85);

IGLMVGGVVIA (SEQ ID NO:86);

IGLMVGGVVI (SEQ ID NO:87);

30 IGLMVGGVV (SEQ ID NO:88);

IGLMVGGV (SEQ ID NO:89);

35 IGLMVGG (SEQ ID NO:90);

LMVGGV (SEQ ID NO:91).

DAEFRHDSGYEVHHQ (SEQ ID NO:92);

40 AEFRHDSGYEVHHQ (SEQ ID NO:93);

DAEFRHDSGYEVH (SEQ ID NO:94);

45 EFRHDSGYEVHH (SEQ ID NO:95);

EFRHDSGYEVH (SEQ ID NO:96);

DAEFRHDSGY (SEQ ID NO:97);

50 DAEFRHDSG (SEQ ID NO:98);

AEFRHDSG (SEQ ID NO:99);

EFRHDSG (SEQ ID NO:100);

EFRHDS (SEQ ID NO:101)

5 DAEFRHDSGYEVHHQ (SEQ ID NO:102);

AEFRHDSGYEVHHQ (SEQ ID NO:103);

10 AEFRHDSGYEVHH (SEQ ID NO:104);

AEFRHDSGYEVH (SEQ ID NO:105);

DAEFRHDSGYE (SEQ ID NO:106);

15 AEFRHDSGYE (SEQ ID NO:107);

DAEFRHDSG (SEQ ID NO:108);

20 AEFRHDSG (SEQ ID NO:109);

DAEFRHDSG (SEQ ID NO:110);

AEFRHD (SEQ ID NO:111)

25 EFRHDSGYEVHHQKL (SEQ ID NO:112);

FRHDSGYEVHHQKL (SEQ ID NO:113);

30 EVHHQKLVFFAEDV (SEQ ID NO:114);

YEVHHQKLVFFA (SEQ ID NO:115);

VFFAEDVGSNKG (SEQ ID NO:116);

35 KLVFFAEDVGSN (SEQ ID NO:117);

EDVGSNKGAIIG (SEQ ID NO:118);

40 FFAEDVGSNKG (SEQ ID NO:119);

SNKGAIIGLMV (SEQ ID NO:120);

FAEDVGSNKG (SEQ ID NO:121);

45 KGAIIGLMVG (SEQ ID NO:122);

LVFFAEDVG (SEQ ID NO:123);

50 EDVGSNKG (SEQ ID NO:124);

KLVFFAED (SEQ ID NO:125);

DVGSNKGA (SEQ ID NO:126);

EVHHQKL (SEQ ID NO:127);

5

QKLVFFA (SEQ ID NO:128);

RHDSGY (SEQ ID NO:129);

10

SGYEVH (SEQ ID NO:130);

GVVIAT (SEQ ID NO:131).

WHAT IS CLAIMED IS:

- 1 . At least one isolated mammalian amyloid antibody,
comprising at least one variable region comprising at least one heavy chain and at least one
light chain of SEQ ID NOS:48-49.
- 5 2 . At least one isolated mammalian amyloid antibody,
comprising either (i) at least two of the heavy chain complementarity determining regions
(CDR) amino acid sequences of at least one of SEQ ID NOS:42-44; or (ii) at least two of the
light chain CDR amino acids sequences of at least one of SEQ ID NOS:45-47.
- 10 3 . At least one isolated mammalian amyloid antibody,
comprising at least one heavy chain or light chain CDR having the amino acid sequence of at
least one of SEQ ID NOS:48-49.
- 15 4 . At least one isolated mammalian amyloid antibody that binds
to the same region of an amyloid polypeptide as an antibody comprising at least one heavy
chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:42-
47.
- 5 . At least one isolated mammalian amyloid antibody,
comprising at least one variable region comprising at least one heavy chain and at least one
light chain of SEQ ID NOS:59-60.
- 20 6 . At least one isolated mammalian amyloid antibody,
comprising either (i) at least two of the heavy chain complementarity determining regions
(CDR) amino acid sequences of at least one of SEQ ID NOS:53-55; or (ii) at least two of the
light chain CDR amino acids sequences of at least one of SEQ ID NOS:56-58.
- 7 . At least one isolated mammalian amyloid antibody,
comprising at least one heavy chain or light chain CDR having the amino acid sequence of at
25 least one of SEQ ID NOS:59-60.
- 8 . At least one isolated mammalian amyloid antibody that binds
to the same region of an amyloid polypeptide as an antibody comprising at least one heavy
chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:53-
58.
- 30 9 . At least one isolated mammalian amyloid antibody,
comprising at least one human CDR, wherein said antibody specifically binds at least one
epitope selected from amino acids 2-7, 3-8, 33-42, or 34-40 of SEQ ID NO:50.
- 10 . At least one isolated mammalian amyloid antibody,
comprising at least one human CDR, wherein said antibody specifically binds at least one
35 epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:50.
- 11 . An amyloid antibody according to any of claims 1-10, wherein

said antibody binds amyloid with an affinity of at least one selected from at least 10^{-9} M, at least 10^{-10} M, at least 10^{-11} M, or at least 10^{-12} M.

12. An amyloid antibody according to any of claims 1-10, wherein said antibody substantially modulates at least one activity of at least one amyloid polypeptide.

5 13. An isolated nucleic acid encoding at least one isolated mammalian amyloid antibody according to any of claims 1-10 and having at least one human CDR of SEQ ID NOS:51, 52, 61, and 62.

14. An isolated nucleic acid vector comprising an isolated nucleic acid according to claim 13.

10 15. A prokaryotic or eukaryotic host cell comprising an isolated nucleic acid according to claim 13.

16. A host cell according to claim 15, wherein said host cell is at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell
15 thereof.

17. A method for producing at least one amyloid antibody, comprising translating a nucleic acid according to claim 13 under conditions in vitro, in vivo or in situ, such that the amyloid antibody is expressed in detectable or recoverable amounts.

18. A composition comprising at least one isolated mammalian
20 amyloid antibody according to any of claims 1-10 having at least one human CDR, wherein said antibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:50, and at least one pharmaceutically acceptable carrier or diluent.

19. A composition according to claim 18, further comprising at
25 least one at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic
30 or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

20. An anti-idiotypic antibody or fragment that specifically binds at least one amyloid antibody according to any of claims 1-10.

21. A method for diagnosing or treating an amyloid related condition in a cell, tissue, organ or animal, comprising

35 (a) contacting or administering a composition comprising an effective amount of at least one antibody according to any of claims 1-10, with, or to, said cell, tissue, organ or

animal.

22 . A method according to claim 21, wherein said effective amount is 0.001-50 mg/kilogram of said cells, tissue, organ or animal.

23 . A method according to claim 21, wherein said contacting or
5 said administering is by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal,
10 intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

24 . A method according to claim 21, further comprising administering, prior, concurrently or after said (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected
15 from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine
20 antagonist.

25 . A medical device, comprising at least one amyloid antibody according to any of claims 1-10, wherein said device is suitable to contacting or administering said at least one amyloid antibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular,
25 intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

30 26 . An article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one amyloid antibody according to any of claims 1-10.

27 . The article of manufacture of claim 26, wherein said container is a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular,
35 intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic,

intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

5 28 . A method for producing at least one isolated mammalian amyloid antibody according to any of claims 1-10, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts said antibody.

10 29 . At least one amyloid antibody produced by a method according to claim 35.

30 . Any invention described herein.

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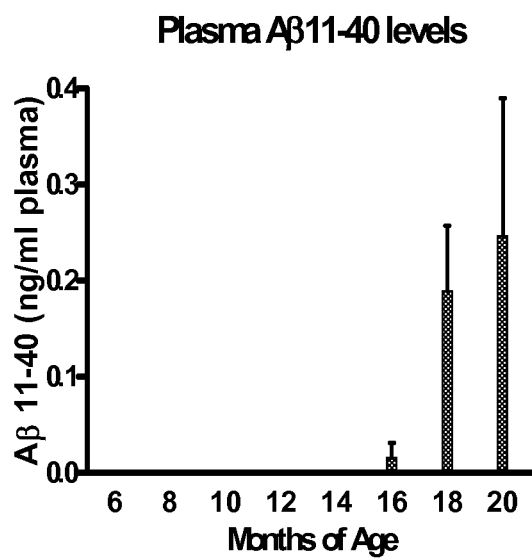


FIGURE 1A

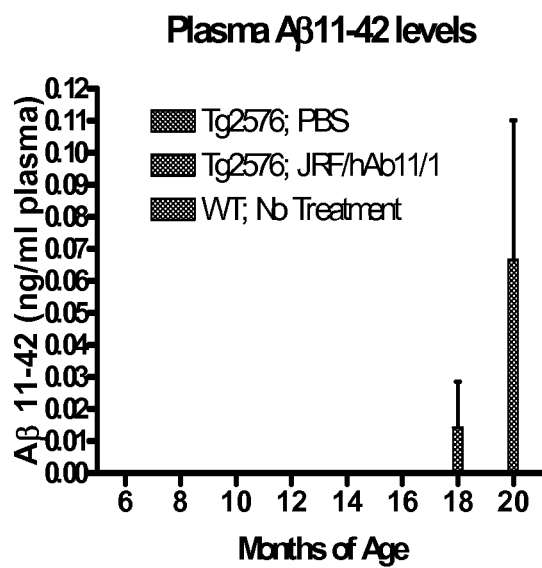


FIGURE 1B

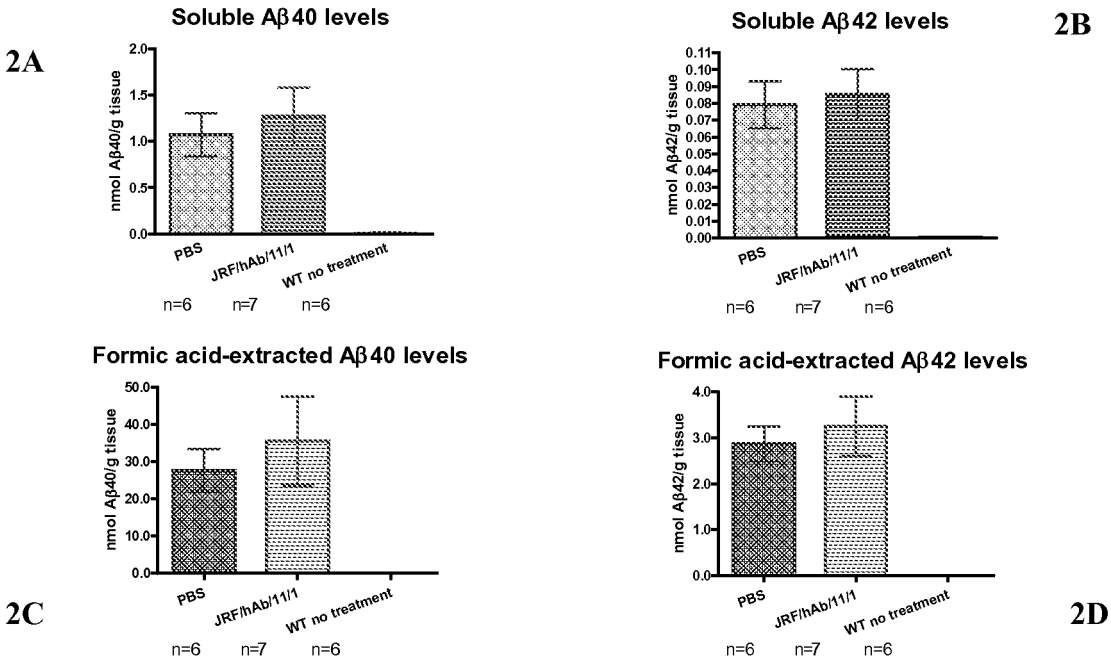


FIGURE 2A-D

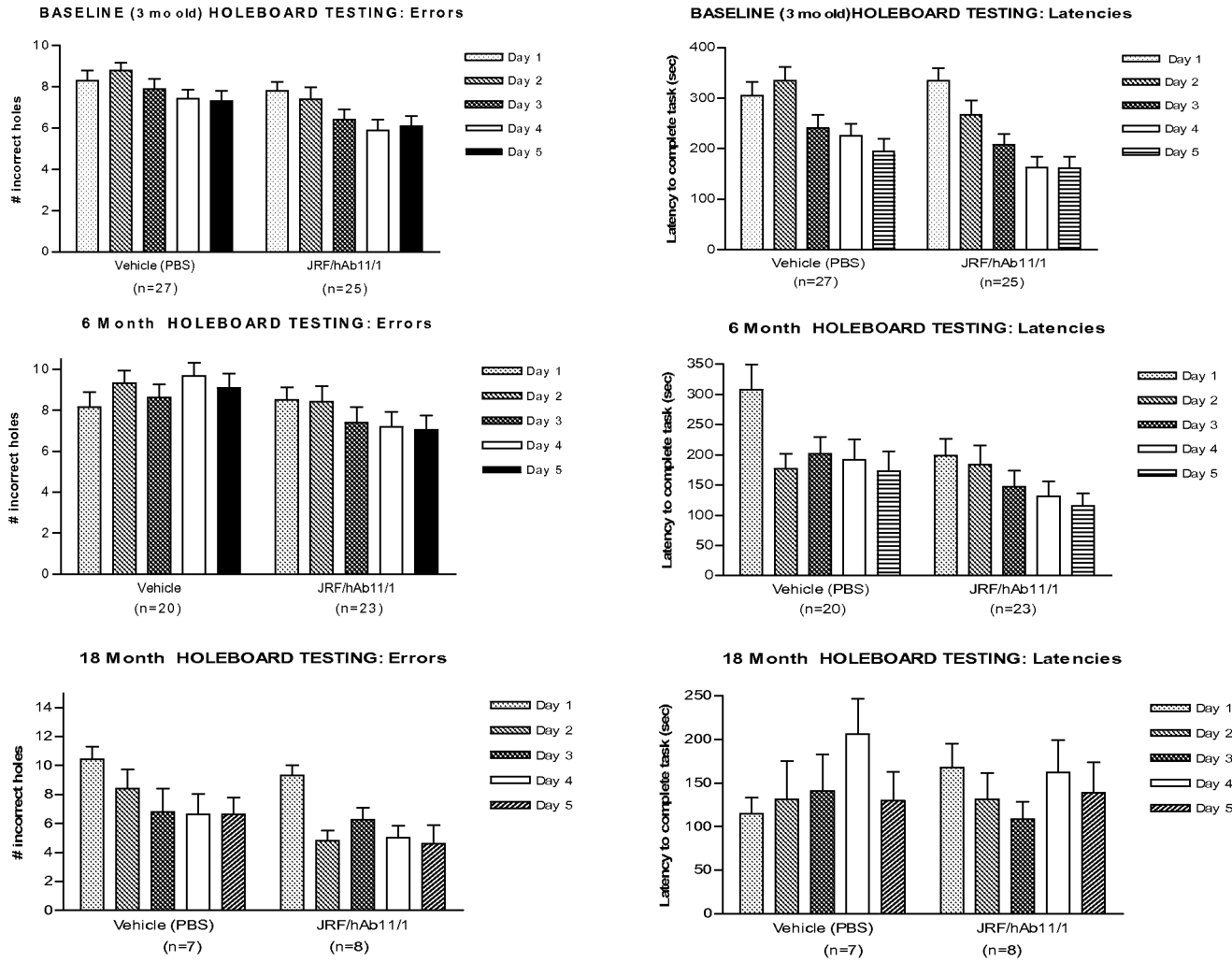


FIGURE 3A-F

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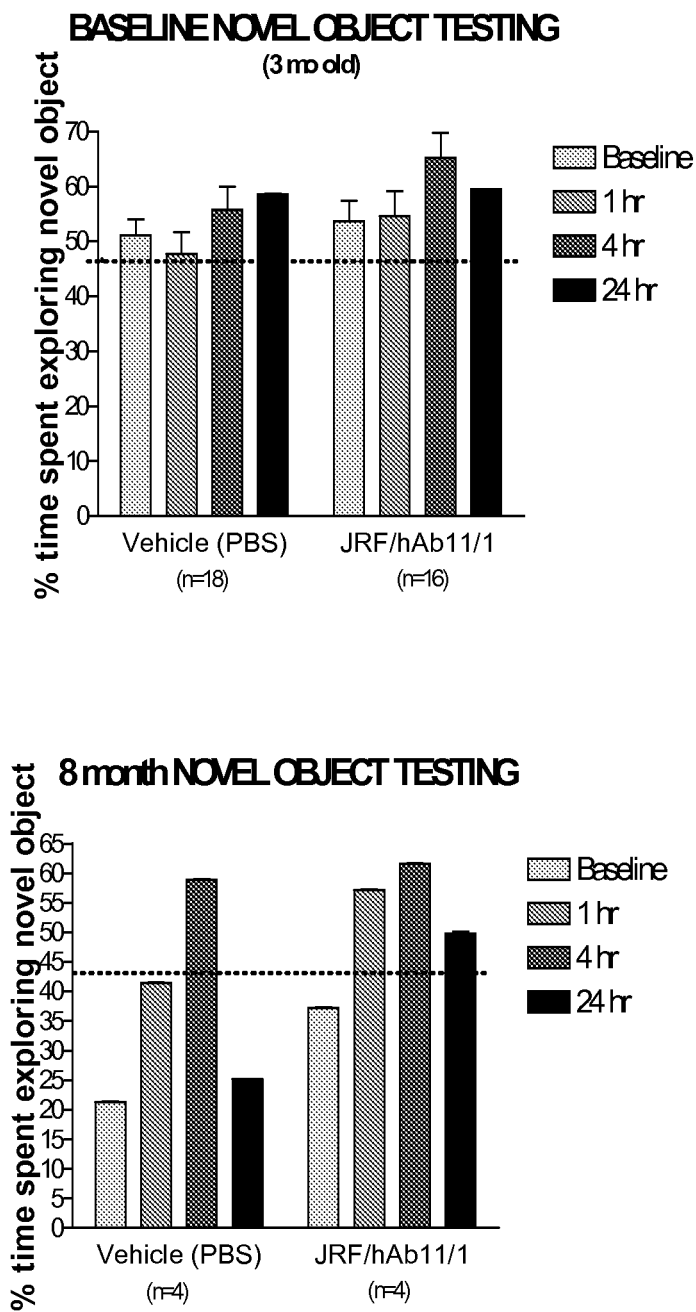


FIGURE 4A-B

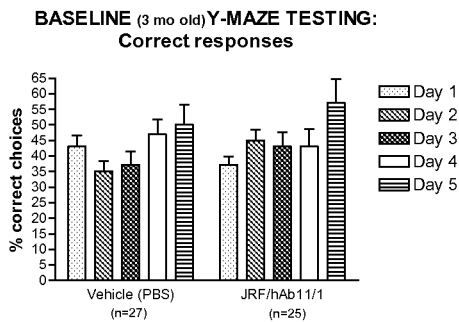


FIGURE 5A

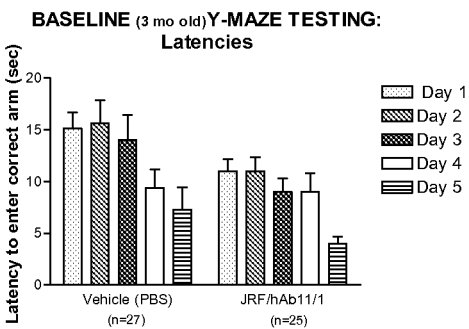


FIGURE 5B

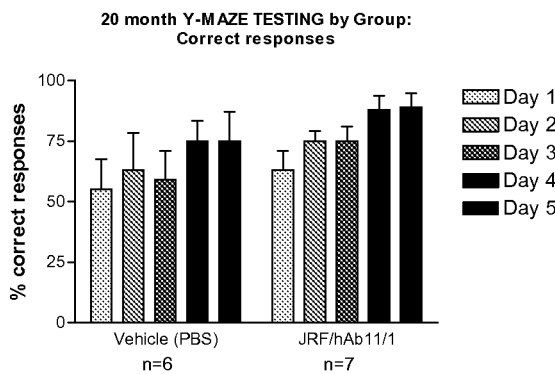


FIGURE 5C

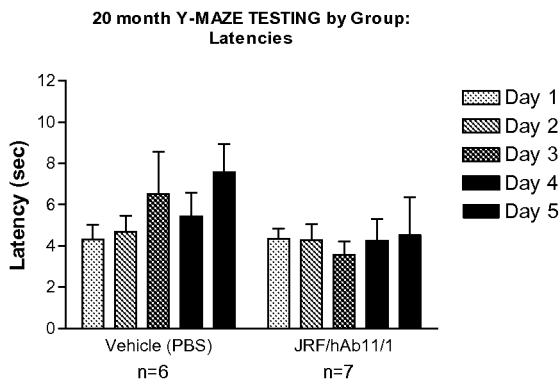


FIGURE 5D

FIGURE 5A-D