COMPOSITIONS AND METHODS FOR TREATING AMYLOID PLAQUE ASSOCIATED SYMPTOMS

GOVERNMENT SUPPORT

[0001] This invention was made with government support under AG013956 awarded by the NIH. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0002] The invention relates to compositions and methods for delaying or preventing Aβ plaque associated symptoms, such as those associated with Alzheimer's Disease (AD) in a subject. In particular, the invention relates to modulating the concentration of amyloid-β (Aβ) in the brain of a subject.

BACKGROUND OF THE INVENTION

[0003] Alzheimer's Disease (AD) is the most common cause of dementia and is an increasing public health problem. It is currently estimated to afflict 5 million people in the United States, with an expected increase to 13 million by the year 2050. Alzheimer's Disease leads to loss of memory, cognitive function, and ultimately loss of independence. It takes a heavy personal and financial toll on the subject and the family. Because of the severity and increasing prevalence of the disease in the population, it is urgent that better treatments be developed.

[0004] Biochemical, genetic, and animal model evidence implicates amyloid-β (Aβ) as a pathogenic peptide in AD. The neuropathologic and neurochemical hallmarks of AD include synaptic loss and selective neuronal death, a decrease in certain neurotransmitters, and the presence of abnormal proteinaceous deposits within neurons (neurofibrillary tangles) and in the extracellular space (cerebrovascular, diffuse, and neuritic plaques). The main constituent of these plaques is Aβ, a 38–43 amino acid sequence peptide cleaved from the amyloid precursor protein (APP).

[0005] Throughout life, soluble Aβ is secreted primarily by neurons, but also other cell types. Excessive Aβ deposition may result from increased Aβ synthesis, as occurs

in familial early-onset AD, or decreased Aβ clearance in brain. The lack of compelling evidence that Aβ production occurs in the more common late-onset forms of AD suggests that insufficient Aβ clearance may drive Aβ deposition and amyloid plaque formation as well.

[0006] The apolipoprotein E (ApoE) gene remains the most widely replicated genetic risk factor for late-onset AD, with carriers of the E4 allelle having a 3-15-fold greater risk as well as an earlier age of disease onset. In brain, ApoE is mainly synthesized and secreted by astrocytes and microglia which are found to surround amyloid plaques. The present invention provides ApoE antibodies effective at reducing amyloid plaque load in AD mouse models.

SUMMARY

[0006a] In one aspect, there is provided the use of at least one anti-ApoE antibody in the manufacture of a medicament for reversing at least one symptom or sign of Aβ plaque associated symptoms in a subject having Alzheimer's disease, Lewy body dementia, or cerebral amyloid angiopathy.

[0006b] In one aspect, there is provided the use of at least one anti-ApoE antibody in the manufacture of a medicament for decreasing the amyloid plaque load in the brain of a subject having Alzheimer's disease, Lewy body dementia, or cerebral amyloid angiopathy.

[0007] Disclosed is a method of effectively treating at least one clinically detectable Aβ plaque associated symptom which comprises administering an effective amount of an anti-ApoE antibody to a living human subject. Also disclosed is an antibody useful in such treatment. For instance, an antibody that therapeutically attenuates the toxic effects of the Aβ peptide in a living mammal.

[0008] Disclosed is a composition comprising at least one anti-ApoE antibody. In one embodiment, the disclosure encompasses a composition comprising at least one anti-ApoE antibody produced from hybridoma HJ6.1, HJ6.2, HJ6.3, HJ6.4 or a combination thereof. In one embodiment, the disclosure encompasses a medicinal composition comprising at least one anti-ApoE antibody. In one embodiment, the disclosure encompasses a medicinal composition comprising at least one anti-ApoE antibody produced from hybridoma HJ6.1, HJ6.2, HJ6.3, HJ6.4 or a combination thereof.

[0009] Yet another embodiment of the disclosure encompasses a medicinal composition useful to treat at least one clinically detectable Aβ plaque associated symptom. The composition comprises a medicinally effective amount of an anti-ApoE antibody adapted for administration to a living human subject. In one embodiment, an antibody useful in such

treatment includes an antibody that therapeutically attenuates the toxic effects of the Aβ peptide in a living mammal. In one embodiment, the medicinal composition is effectively administered to a living subject.

[0010] Still another embodiment the disclosure encompasses a medicinal kit comprising a container containing a functional therapeutic medicinal composition of a medicinally effective amount of an anti-ApoE antibody adapted for administration to a living human subject and any medical devices to be used for said administration. In one embodiment, an antibody useful in such treatment includes an antibody that therapeutically attenuates the toxic effects of the Aβ peptide in a living mammal.

[0011] Other aspects and iterations of the disclosure are detailed below.

BRIEF DESCRIPTION OF THE FIGURES

[0012] **FIG. 1** graphically depicts a strong effect of anti-ApoE antibodies in decreased amyloid plaque load in samples of hippocampus from PS/APP mice treated intraperitoneally once weekly with 10 mg/kg beginning at 3 months of age until 7 months of age with either an anti-Aβ antibody (HJ3.4) or one of two anti-ApoE antibodies (HJ6.2 or HJ6.3). The control group was treated with phosphate buffered saline (PBS). Animal numbers assessed are N=7 (PBS), N=16 (HJ3.4), N=16 (HJ6.2), N=16).

[0013] **FIG. 2** graphically depicts a strong effect of anti-ApoE antibodies in decreased amyloid plaque load in samples of brain cortex from PS/APP mice treated intraperitoneally once weekly with 10 mg/kg with either an anti-Aβ antibody (HJ3.4) or one of two anti-ApoE antibodies (HJ6.2 or HJ6.3). The control group was treated with PBS. Animal numbers assessed are N=7 (PBS), N=16 (HJ3.4), N=16 (HJ6.2), N=16).

[0014] **FIG. 3** graphically depicts binding of anti-apoE antibodies HJ6.1, HJ6.2, HJ6.3 and HJ6.4 to human apoE using an ELISA assay.

[0015] **FIG. 4** graphically depicts (**A**) binding of anti-apoE antibodies HJ6.1, HJ6.2, HJ6.3 and HJ6.4 to human apoE in plasma, and (**B**) levels of cholesterol in the same mice that received the HJ6.1, HJ6.2, HJ6.3 and HJ6.4 antibodies.

[0016] **FIG. 5** graphically depicts the presence of anti-apoE antibodies HJ6.1, HJ6.2, HJ6.3 and HJ6.4 in the central nervous system after peripheral administration.

[0017] FIG. 6 graphically depicts microglial activation after short term administration of HJ6.2 and HJ6.3 (anti-apoE antibodies), and HJ3.4 (an anti-Aβ antibody) to mice over 10 days.

[0018] FIG. 7 depicts the amino acid sequences of (A) HJ6.1 heavy chain variable region and first constant region (SEQ ID NO:4); (B) HJ6.1 light chain variable region and constant region (SEQ ID NO:2); (C) HJ6.2 heavy chain variable region and first constant region (SEQ ID NO:8); (D) HJ6.2 light chain variable region and constant region (SEQ ID NO:6); (E) HJ6.3 heavy chain variable region and first constant region (SEQ ID NO:12); (F) HJ6.3 light chain variable region and constant region (SEQ ID NO:10); (G) HJ6.4 heavy chain variable region and first constant region (SEQ ID NO:16); (H) HJ6.4 light chain variable region and constant region (SEQ ID NO:14). Regions comprising CDRs are highlighted.

DETAILED DESCRIPTION

[0019] Applicants have discovered antibodies and methods of use thereof for effectively treating Aβ plaque associated symptoms. The method comprises effectively administering a pharmacologically effective amount of anti-ApoE antibody to a living subject. The present invention encompasses the discovery that anti-ApoE antibodies provide a treatment for subjects suffering from Aβ plaque associated symptoms. Thus, the invention provides evidence that signs and symptoms of Aβ plaque associated symptoms may be due, at least in part, to the deleterious effects of ApoE. In an aspect, at least one preclinical or clinical symptom or sign is presented by that subject. In an aspect, an antibody useful in such treating includes an antibody that therapeutically attenuates the toxic effects of the Aβ peptide in a living mammal. In an aspect, antibodies useful in such treating include those which bind an epitope within ApoE.

[0020] In an aspect, an anti-ApoE antibody is admixed with at least one suitable compatible adjuvant or excipient resulting in a therapeutic medicinal composition which is capably and effectively administered (given) to a living subject, such as to a human afflicted with Aβ plaque associated symptoms. Typically this is an aqueous composition of high purity.

[0021] As used herein, the terms "treating" or "treatment" include prevention, attenuation, reversal, or improvement in at least one symptom or sign of Aβ plaque associated symptoms.

[0022] As used herein the term "therapeutically attenuate" includes inducing a change or having a beneficial positive effect resulting therefrom.

[0023] One definition of Aβ plaque associated symptoms refers to any symptom caused by the formation of amyloid plaques being composed of regularly ordered fibrillar aggregates called amyloid fibrils. Exemplary disorders that have Aβ plaque associated symptoms include, but are not limited to, Alzheimer's Disease, Lewy body dementia, and cerebral amyloid angiopathy.

[0024] Exemplary Aβ plaque associated symptoms may include impaired cognitive function, altered behavior, emotional dysregulation, seizures, impaired nervous system structure or function, and an increased risk of development of Alzheimer's disease. Impaired cognitive function may include but is not limited to difficulties with memory, attention, concentration, language, abstract thought, creativity, executive function, planning, and organization. Altered behavior may include but is not limited to physical or verbal aggression, impulsivity, decreased inhibition, apathy, decreased initiation, changes in personality, abuse of alcohol, tobacco or drugs, and other addiction-related behaviors. Emotional dysregulation may include but is not limited to depression, anxiety, mania, irritability, and emotional incontinence. Seizures may include but are not limited to generalized tonic-clonic seizures, complex partial seizures, and non-epileptic, psychogenic seizures. Impaired nervous system structure or function may include but is not limited to hydrocephalus, Parkinsonism, sleep disorders, psychosis, impairment of balance and coordination. This may include motor impairments such as monoparesis, hemiparesis, tetraparesis, ataxia, ballismus and tremor. This also may include sensory loss or dysfunction including olfactory, tactile, gustatory, visual and auditory sensation. Furthermore, this may include autonomic nervous system impairments such as bowel and bladder dysfunction, sexual dysfunction, blood pressure and temperature dysregulation. Finally, this may include hormonal impairments attributable to dysfunction of the hypothalamus and pituitary

gland such as deficiencies and dysregulation of growth hormone, thyroid stimulating hormone, lutenizing hormone, follicle stimulating hormone, gonadotropin releasing hormone, prolactin, and numerous other hormones and modulators. Increased risk of development of Alzheimer's disease includes that risk that is elevated over the expected risk given the subjects age, family history, genetic status and other known risk factors.

[0025] Aβ peptides are those derived from a region in the carboxy terminus of a larger protein called amyloid precursor protein (APP). The gene encoding APP is located on chromosome 21. There are many forms of Aβ that may have toxic effects: Aβ peptides are typically 38-43 amino acid sequences long, though they can have truncations and modifications changing their overall size. They can be found in soluble and insoluble compartments, in monomeric, oligomeric and aggregated forms, intracellularly or extracellularly, and may be complexed with other proteins or molecules. The adverse or toxic effects of Aβ may be attributable to any or all of the above noted forms, as well as to others not described specifically.

[0026] In one embodiment, the invention provides a method for decreasing the amyloid plaque load in the brain of a subject. The method comprises administering a therapeutically effective amount of an antibody that specifically binds to ApoE to the subject. Suitable antibodies include those disclosed herein. In an exemplary embodiment, a suitable Ab comprises an antibody delineated in Table A below. A method of the invention may decrease the amyloid plaque load in the hippocampus of a subject. A method of the invention may also decrease the amyloid plaque load in the brain cortex of a subject. In each of the above embodiments, the amyloid plaque load may be decreased by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% compared to untreated or negative control treated subjects. In some embodiments, the amyloid plaque load may be decreased by at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95% compared to untreated or negative control treated subjects. In other embodiments, the amyloid plaque load may be decreased by at least 100, 125, 150, 200, 250, 300, 350, 400, or 450% compared to untreated or negative control treated subjects. Methods of measuring amyloid plaque load are known in the art.

[0027] Anti-ApoE antibodies useful herein include all antibodies that therapeutically attenuate the adverse or toxic effects of Aβ. Useful antibodies include but are not limited to those that specifically bind to an epitope within the ApoE coding sequence. Anti-ApoE antibodies useful herein include also antibodies that attenuate the adverse or toxic effects of Aβ and bind to specific regions of ApoE and to other forms of ApoE. Specific regions of ApoE include, but are not limited to, the C-terminal, the N-terminal, and other central domains. Other forms of ApoE include but are not limited to truncated, modified, soluble, insoluble, intracellular, extracellular, monomeric ApoE, oligomeric ApoE, fibrillar, aggregated ApoE or ApoE complexed with other proteins or molecules.

[0028] In an aspect, antibodies useful herein include those antibodies which have been isolated, characterized, purified, are functional and have been recovered (obtained) for use in a functional therapeutic composition which is administered to a living subject having Aβ plaque associated symptoms.

[0029] "Monoclonal antibody" refers to an antibody that is derived from a single copy or clone, including e.g., any eukaryotic, prokaryotic, or phage clone. "Monoclonal antibody" is not limited to antibodies produced through hybridoma technology. Monoclonal antibodies can be produced using e.g., hybridoma techniques well known in the art, as well as recombinant technologies, phage display technologies, synthetic technologies or combinations of such technologies and other technologies readily known in the art. Furthermore, the monoclonal antibody may be labeled with a detectable label, immobilized on a solid phase and/or conjugated with a heterologous compound (e.g., an enzyme or toxin) according to methods known in the art.

[0030] Further by "antibody" is meant a functional monoclonal antibody, or an immunologically effective fragment thereof, such as an Fab, Fab', or F(ab')2 fragment thereof. In some contexts herein, fragments will be mentioned specifically for emphasis; nevertheless, it will be understood that regardless of whether fragments are specified, the term "antibody" includes such fragments as well as single-chain forms. As long as the protein retains the ability specifically to bind its intended target, it is included within the term "antibody." Also included within the definition "antibody" for example are single

chain forms, generally designated Fv, regions, of antibodies with this specificity. Preferably, but not necessarily, the antibodies useful in the discovery are produced recombinantly, as manipulation of the typically murine or other non-human antibodies with the appropriate specificity is required in order to convert them to humanized form. Antibodies may or may not be glycosylated, though glycosylated antibodies are preferred. Antibodies are properly cross-linked via disulfide bonds, as is known.

[0031] The basic antibody structural unit of an antibody useful herein comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acid sequences primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function.

[0032] Anti-ApoE antibodies useful herein include those which are isolated, characterized, purified, functional and have been recovered (obtained) from a process for their preparation and thus available for use herein in a useful form in a therapeutically and medicinally sufficient amount.

[0033] Light chains are classified as gamma, mu, alpha, and lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, and define the antibody's isotype as IgO, IgM, IgA, IgD and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acid sequences, with the heavy chain also including a "D" region of about 10 more amino acid sequences.

[0034] The variable regions of each light/heavy chain pair form the antibody binding site. Thus, an intact antibody has two binding sites. The chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarily determining regions (hereinafter referred to as "CDRs.") The CDRs from the two chains are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4

respectively. The assignment of amino acid sequences to each domain is in accordance with known conventions (See, Kabat "Sequences of Proteins of Immunological Interest" National Institutes of Health, Bethesda, Md., 1987 and 1991; Chothia, et al, J. Mol. Bio. (1987) 196:901-917; Chothia, et al., Nature (1989) 342:878-883).

[0035] In an aspect, monoclonal anti-apoE antibodies are generated with appropriate specificity by standard techniques of immunization of mammals, forming hybridomas from the antibody-producing cells of said mammals or otherwise immortalizing them, and culturing the hybridomas or immortalized cells to assess them for the appropriate specificity. In the present case, such antibodies could be generated by immunizing a human, rabbit, rat or mouse, for example, with a peptide representing an epitope encompassing a region of the ApoE protein coding sequence or an appropriate subregion thereof. Materials for recombinant manipulation can be obtained by retrieving the nucleotide sequences encoding the desired antibody from the hybridoma or other cell that produces it. These nucleotide sequences can then be manipulated and isolated, characterized, purified and, recovered to provide them in humanized form, for use herein if desired.

[0036] As used herein "humanized antibody" includes an anti-ApoE antibody that is composed partially or fully of amino acid sequence sequences derived from a human antibody germline by altering the sequence of an 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 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. CDRs may also be randomly mutated such that binding activity and affinity for ApoE is maintained or enhanced in the context of fully human germline

framework regions or framework regions that are substantially human. Substantially human frameworks have at least 90%, 95%, or 99% sequence identity with a known human framework sequence. Fully useful human antibodies are produced in genetically modified mice whose immune systems have been altered to correspond to human immune systems. As mentioned above, it is sufficient for use in the methods of this discovery, to employ an immunologically specific fragment of the antibody, including fragments representing single chain forms.

[0037] Further, as used herein the term "humanized antibody" refers to an anti-ApoE antibody comprising a human framework, at least one CDR from a nonhuman antibody, and in which any constant region present is substantially identical to a human immunoglobulin constant region, i.e., at least about 85-90%, preferably at least 95% identical. Hence, all parts of a humanized antibody, except possibly the CDRs, are substantially identical to corresponding pairs of one or more native human immunoglobulin sequences.

[0038] If desired, the design of humanized immunoglobulins may be carried out as follows. When an amino acid sequence falls under the following category, the framework amino acid sequence of a human immunoglobulin to be used (acceptor immunoglobulin) is replaced by a framework amino acid sequence from a CDR-providing nonhuman immunoglobulin (donor immunoglobulin): (a) the amino acid sequence in the human framework region of the acceptor immunoglobulin is unusual for human immunoglobulin at that position, whereas the corresponding amino acid sequence in the donor immunoglobulin is typical for human immunoglobulin at that position; (b) the position of the amino acid sequence is immediately adjacent to one of the CDRs; or (c) any side chain atom of a framework amino acid sequence is within about 5-6 angstroms (center-to-center) of any atom of a CDR amino acid sequence in a three dimensional immunoglobulin model (Queen, et al., op. cit., and Co, et al, Proc. Natl. Acad. Sci. USA (1991) 88:2869). When each of the amino acid sequences in the human framework region of the acceptor immunoglobulin and a corresponding amino acid sequence in the donor immunoglobulin is unusual for human immunoglobulin at

that position, such an amino acid sequence is replaced by an amino acid sequence typical for human immunoglobulin at that position.

[0039] In all instances, an antibody of the invention specifically binds ApoE. In exemplary embodiments, an antibody of the invention specifically binds human ApoE. The phrase "specifically binds" herein means antibodies bind to the protein with a binding constant in the range of at least 10^{-4}- 10^{-6} M^{-1}, with a preferred range being 10^{-7} - 10^{-9} M^{-1}.The sequence of ApoE from a variety of species is known in the art, and methods of determining whether an antibody binds to ApoE are known in the art. For instance, see the Examples. An antibody of the invention may recognize ApoE2, ApoE3, ApoE4, or an allelic variant thereof. In one embodiment, an antibody of the invention may recognize human ApoE4.

[0040] A preferred antibody is a humanized form of mouse antibody derived from a hybridoma designated HJ6.1 (ATCC Patent Deposit Designation PT-11805), HJ6.2 (ATCC Patent Deposit Designation PT-11806), HJ6.3 (ATCC Patent Deposit Designation PT-11807), or HJ6.4 (ATCC Patent Deposit Designation PT-11808). As used herein, the term "derived from" means that the "derived" antibody comprises at least one CDR region from the antibody produced by HJ6.1, HJ6.2, HJ6.3, or HJ6.4. Stated another way, the "derived antibody" comprises at least one CDR region comprised of the amino acid sequence selected from the group consisting of SEQ ID NO: 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, and 39.

[0041] In one embodiment, an antibody of the invention may be derived from the hybridoma HJ6.1, and may be encoded by a nucleic acid sequence comprising 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the light chain variable region of SEQ ID NO:1, or may be encoded by a nucleic acid sequence comprising 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the heavy chain variable region of SEQ ID NO:2. In another embodiment, an antibody of the invention may be derived from the hybridoma HJ6.1, and may comprise an amino acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the light chain variable region of SEQ ID NO:3, or may comprise an amino acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the

heavy chain variable region of SEQ ID NO:4. In each of the above embodiments, the antibody may be humanized.

[0042] In yet another embodiment, an antibody of the invention may be derived from the hybridoma HJ6.2, and may be encoded by a nucleic acid sequence comprising 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the light chain variable region of SEQ ID NO:5, or may be encoded by a nucleic acid sequence comprising 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the heavy chain variable region of SEQ ID NO:6. In another embodiment, an antibody of the invention may be derived from the hybridoma HJ6.2, and may comprise an amino acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the light chain variable region of SEQ ID NO:7, or may comprise an amino acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the heavy chain variable region of SEQ ID NO:8. In each of the above embodiments, the antibody may be humanized.

[0043] In an additional embodiment, an antibody of the invention may be derived from the hybridoma HJ6.3, and may be encoded by a nucleic acid sequence comprising 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the light chain variable region of SEQ ID NO:9, or may be encoded by a nucleic acid sequence comprising 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the heavy chain variable region of SEQ ID NO:10. In another embodiment, an antibody of the invention may be derived from the hybridoma HJ6.3, and may comprise an amino acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the light chain variable region of SEQ ID NO:11, or comprise an amino acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the heavy chain variable region of SEQ ID NO:12. In each of the above embodiments, the antibody may be humanized.

[0044] In still another embodiment, an antibody of the invention may be derived from the hybridoma HJ6.4, and may have a nucleic acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the light chain variable region of SEQ ID NO:13, and a nucleic acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the heavy chain variable region of SEQ ID NO:14. In another embodiment, an antibody of the invention may be derived from the hybridoma HJ6.4, and may have an amino

acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the light chain variable region of SEQ ID NO:15, or an amino acid sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the heavy chain variable region of SEQ ID NO:16. In each of the above embodiments, the antibody may be humanized.

[0045] In an exemplary embodiment of an antibody of the invention that binds to anti-apoE, the antibody comprises the light chain nucleic acid sequence of SEQ ID NO:1 and the heavy chain nucleic acid sequence of SEQ ID NO:2 [i.e. the monoclonal antibody referred to herein as HJ6.1]. In another exemplary embodiment of an antibody of the invention that binds to anti-apoE, the antibody comprises the light chain amino acid sequence of SEQ ID NO:3 and the heavy chain amino acid sequence of SEQ ID NO:4 [i.e. the monoclonal antibody referred to herein as HJ6.1]. In yet another exemplary embodiment of an antibody of the invention that binds to anti-apoE, the antibody comprises the light chain nucleic acid sequence of SEQ ID NO:5 and the heavy chain nucleic acid sequence of SEQ ID NO:6 [i.e. the monoclonal antibody referred to herein as HJ6.2]. In still another exemplary embodiment of an antibody of the invention that binds to anti-apoE, the antibody comprises the light chain amino acid sequence of SEQ ID NO:7 and the heavy chain amino acid sequence of SEQ ID NO:8 [i.e. the monoclonal antibody referred to herein as HJ6.2].

[0046] In certain embodiments, an antibody of the invention is encoded by the light chain nucleic acid sequence of SEQ ID NO:9 and the heavy chain nucleic acid sequence of SEQ ID NO:10 [i.e. the monoclonal antibody referred to herein as HJ6.3]. In other embodiments, an antibody of the invention is encoded by the light chain amino acid sequence of SEQ ID NO:11 and the heavy chain amino acid sequence of SEQ ID NO:12 [i.e. the monoclonal antibody referred to herein as HJ6.3]. In another embodiment, an antibody of the invention is encoded by the light chain nucleic acid sequence of SEQ ID NO:13 and the heavy chain nucleic acid sequence of SEQ ID NO:14 [i.e. the monoclonal antibody referred to herein as HJ6.4]. In yet another embodiment, an antibody of the invention is encoded by the light chain amino acid sequence of SEQ ID NO:15 and the heavy chain amino acid sequence of SEQ ID NO:16 [i.e. the monoclonal antibody referred to herein as HJ6.4].

[0047] In one embodiment, an antibody of the invention may comprise a light chain CDR1, such as the antibodies 1, 49, 97, and 145 of Table A. In another embodiment, an antibody of the invention may comprise a light chain CDR2, such as the antibodies 4, 52, 100, and 148 of Table A. In yet another embodiment, an antibody of the invention may comprise a light chain CDR3, such as the antibodies 6, 54, 102, and 150 of Table A. In an alternative embodiment, an antibody of the invention may comprise a combination of two or three light chain CDRs, such as the antibodies 2, 3, 5, 50, 51, 53, 98, 99, 101, 146, 147, and 149 of Table A.

[0048] Similarly, in one embodiment, an antibody of the invention may comprise a heavy chain CDR1, such as the antibodies 7, 55, 103, and 151 of Table A. In another embodiment, an antibody of the invention may comprise a heavy chain CDR2, such as the antibodies 10, 58, 106, and 154 of Table A. In yet another embodiment, an antibody of the invention may comprise a heavy chain CDR3, such as the antibodies 12, 60, 108, and 156 of Table A. In an alternative embodiment, an antibody of the invention may comprise a combination of two or three heavy chain CDRs, such as the antibodies 8, 9, 11, 56, 57, 59, 104, 105, 107, 152, 153, and 155 of Table A.

[0049] Alternatively, an antibody of the invention may comprise one or more light chain CDRs and one or more heavy chain CDRs, such as the antibodies 13-48, 61-96, 109-144, and 157-192 of Table A.

TABLE A

Anti-body	Light Chain			Heavy Chain		
	CDR1	CDR2	CDR3	CDR1	CDR2	CDR3
1	SEQ ID NO:17					
2	SEQ ID NO:17	SEQ ID NO:18				
3	SEQ ID NO:17	SEQ ID NO:18	LSP			
4		SEQ ID NO:18				
5		SEQ ID NO:18	LSP			
6			LSP			
7				SEQ ID NO:19		
8				SEQ ID NO:19	SEQ ID NO:20	
9				SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:21

10					SEQ ID NO:20	
11					SEQ ID NO:20	SEQ ID NO:21
12						SEQ ID NO:21
13	SEQ ID NO:17			SEQ ID NO:19		
14	SEQ ID NO:17			SEQ ID NO:19	SEQ ID NO:20	
15	SEQ ID NO:17			SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:21
16	SEQ ID NO:17				SEQ ID NO:20	
17	SEQ ID NO:17				SEQ ID NO:20	SEQ ID NO:21
18	SEQ ID NO:17					SEQ ID NO:21
19	SEQ ID NO:17	SEQ ID NO:18		SEQ ID NO:19		
20	SEQ ID NO:17	SEQ ID NO:18		SEQ ID NO:19	SEQ ID NO:20	
21	SEQ ID NO:17	SEQ ID NO:18		SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:21
22	SEQ ID NO:17	SEQ ID NO:18			SEQ ID NO:20	
23	SEQ ID NO:17	SEQ ID NO:18			SEQ ID NO:20	SEQ ID NO:21
24	SEQ ID NO:17	SEQ ID NO:18				SEQ ID NO:21
25	SEQ ID NO:17	SEQ ID NO:18	LSP	SEQ ID NO:19		
26	SEQ ID NO:17	SEQ ID NO:18	LSP	SEQ ID NO:19	SEQ ID NO:20	
27	SEQ ID NO:17	SEQ ID NO:18	LSP	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:21
28	SEQ ID NO:17	SEQ ID NO:18	LSP		SEQ ID NO:20	
29	SEQ ID NO:17	SEQ ID NO:18	LSP		SEQ ID NO:20	SEQ ID NO:21
30	SEQ ID NO:17	SEQ ID NO:18	LSP			SEQ ID NO:21
31		SEQ ID NO:18		SEQ ID NO:19		
32		SEQ ID NO:18		SEQ ID NO:19	SEQ ID NO:20	
33		SEQ ID NO:18		SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:21
34		SEQ ID NO:18			SEQ ID NO:20	
35		SEQ ID NO:18			SEQ ID NO:20	SEQ ID NO:21
36		SEQ ID NO:18				SEQ ID NO:21
37		SEQ ID NO:18	LSP	SEQ ID NO:19		
38		SEQ ID NO:18	LSP	SEQ ID NO:19	SEQ ID NO:20	
39		SEQ ID NO:18	LSP	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:21
40		SEQ ID NO:18	LSP		SEQ ID NO:20	
41		SEQ ID NO:18	LSP		SEQ ID NO:20	SEQ ID NO:21
42		SEQ ID NO:18	LSP			SEQ ID NO:21
43			LSP	SEQ ID NO:19		
44			LSP	SEQ ID NO:19	SEQ ID NO:20	
45			LSP	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:21
46			LSP		SEQ ID NO:20	

47			LSP		SEQ ID NO:20	SEQ ID NO:21
48			LSP			SEQ ID NO:21
49	SEQ ID NO:22					
50	SEQ ID NO:22	SEQ ID NO:23				
51	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24			
52		SEQ ID NO:23				
53		SEQ ID NO:23	SEQ ID NO:24			
54			SEQ ID NO:24			
55				SEQ ID NO:25		
56				SEQ ID NO:25	SEQ ID NO:26	
57				SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27
58					SEQ ID NO:26	
59					SEQ ID NO:26	SEQ ID NO:27
60						SEQ ID NO:27
61	SEQ ID NO:22			SEQ ID NO:25		
62	SEQ ID NO:22			SEQ ID NO:25	SEQ ID NO:26	
63	SEQ ID NO:22			SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27
64	SEQ ID NO:22				SEQ ID NO:26	
65	SEQ ID NO:22				SEQ ID NO:26	SEQ ID NO:27
66	SEQ ID NO:22					SEQ ID NO:27
67	SEQ ID NO:22	SEQ ID NO:23		SEQ ID NO:25		
68	SEQ ID NO:22	SEQ ID NO:23		SEQ ID NO:25	SEQ ID NO:26	
69	SEQ ID NO:22	SEQ ID NO:23		SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27
70	SEQ ID NO:22	SEQ ID NO:23			SEQ ID NO:26	
71	SEQ ID NO:22	SEQ ID NO:23			SEQ ID NO:26	SEQ ID NO:27
72	SEQ ID NO:22	SEQ ID NO:23				SEQ ID NO:27
73	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:25		
74	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:25	SEQ ID NO:26	
75	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27
76	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24		SEQ ID NO:26	
77	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24		SEQ ID NO:26	SEQ ID NO:27
78	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24			SEQ ID NO:27
79		SEQ ID NO:23		SEQ ID NO:25		
80		SEQ ID NO:23		SEQ ID NO:25	SEQ ID NO:26	
81		SEQ ID NO:23		SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27
82		SEQ ID NO:23			SEQ ID NO:26	
83		SEQ ID NO:23			SEQ ID NO:26	SEQ ID NO:27

84		SEQ ID NO:23				SEQ ID NO:27
85		SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:25		
86		SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:25	SEQ ID NO:26	
87		SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27
88		SEQ ID NO:23	SEQ ID NO:24		SEQ ID NO:26	
89		SEQ ID NO:23	SEQ ID NO:24		SEQ ID NO:26	SEQ ID NO:27
90		SEQ ID NO:23	SEQ ID NO:24			SEQ ID NO:27
91			SEQ ID NO:24	SEQ ID NO:25		
92			SEQ ID NO:24	SEQ ID NO:25	SEQ ID NO:26	
93			SEQ ID NO:24	SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27
94			SEQ ID NO:24		SEQ ID NO:26	
95			SEQ ID NO:24		SEQ ID NO:26	SEQ ID NO:27
96			SEQ ID NO:24			SEQ ID NO:27
97	SEQ ID NO:28					
98	SEQ ID NO:28	SEQ ID NO:29				
99	SEQ ID NO:28	SEQ ID NO:29	SEQ ID NO:30			
100		SEQ ID NO:29				
101		SEQ ID NO:29	SEQ ID NO:30			
102			SEQ ID NO:30			
103				SEQ ID NO:31		
104				SEQ ID NO:31	SEQ ID NO:32	
105				SEQ ID NO:31	SEQ ID NO:32	SEQ ID NO:33
106					SEQ ID NO:32	
107					SEQ ID NO:32	SEQ ID NO:33
108						SEQ ID NO:33
109	SEQ ID NO:28			SEQ ID NO:31		
110	SEQ ID NO:28			SEQ ID NO:31	SEQ ID NO:32	
111	SEQ ID NO:28			SEQ ID NO:31	SEQ ID NO:32	SEQ ID NO:33
112	SEQ ID NO:28				SEQ ID NO:32	
113	SEQ ID NO:28				SEQ ID NO:32	SEQ ID NO:33
114	SEQ ID NO:28					SEQ ID NO:33
115	SEQ ID NO:28	SEQ ID NO:29		SEQ ID NO:31		
116	SEQ ID NO:28	SEQ ID NO:29		SEQ ID NO:31	SEQ ID NO:32	
117	SEQ ID NO:28	SEQ ID NO:29		SEQ ID NO:31	SEQ ID NO:32	SEQ ID NO:33
118	SEQ ID NO:28	SEQ ID NO:29			SEQ ID NO:32	
119	SEQ ID NO:28	SEQ ID NO:29			SEQ ID NO:32	SEQ ID NO:33
120	SEQ ID NO:28	SEQ ID NO:29				SEQ ID NO:33

121	SEQ ID NO:28	SEQ ID NO:29	SEQ ID NO:30	SEQ ID NO:31		
122	SEQ ID NO:28	SEQ ID NO:29	SEQ ID NO:30	SEQ ID NO:31	SEQ ID NO:32	
123	SEQ ID NO:28	SEQ ID NO:29	SEQ ID NO:30	SEQ ID NO:31	SEQ ID NO:32	SEQ ID NO:33
124	SEQ ID NO:28	SEQ ID NO:29	SEQ ID NO:30		SEQ ID NO:32	
125	SEQ ID NO:28	SEQ ID NO:29	SEQ ID NO:30		SEQ ID NO:32	SEQ ID NO:33
126	SEQ ID NO:28	SEQ ID NO:29	SEQ ID NO:30			SEQ ID NO:33
127		SEQ ID NO:29		SEQ ID NO:31		
128		SEQ ID NO:29		SEQ ID NO:31	SEQ ID NO:32	
129		SEQ ID NO:29		SEQ ID NO:31	SEQ ID NO:32	SEQ ID NO:33
130		SEQ ID NO:29			SEQ ID NO:32	
131		SEQ ID NO:29			SEQ ID NO:32	SEQ ID NO:33
132		SEQ ID NO:29				SEQ ID NO:33
133		SEQ ID NO:29	SEQ ID NO:30	SEQ ID NO:31		
134		SEQ ID NO:29	SEQ ID NO:30	SEQ ID NO:31	SEQ ID NO:32	
135		SEQ ID NO:29	SEQ ID NO:30	SEQ ID NO:31	SEQ ID NO:32	SEQ ID NO:33
136		SEQ ID NO:29	SEQ ID NO:30		SEQ ID NO:32	
137		SEQ ID NO:29	SEQ ID NO:30		SEQ ID NO:32	SEQ ID NO:33
138		SEQ ID NO:29	SEQ ID NO:30			SEQ ID NO:33
139			SEQ ID NO:30	SEQ ID NO:31		
140			SEQ ID NO:30	SEQ ID NO:31	SEQ ID NO:32	
141			SEQ ID NO:30	SEQ ID NO:31	SEQ ID NO:32	SEQ ID NO:33
142			SEQ ID NO:30		SEQ ID NO:32	
143			SEQ ID NO:30		SEQ ID NO:32	SEQ ID NO:33
144			SEQ ID NO:30			SEQ ID NO:33
145	SEQ ID NO:34					
146	SEQ ID NO:34	SEQ ID NO:35				
147	SEQ ID NO:34	SEQ ID NO:35	SEQ ID NO:36			
148		SEQ ID NO:35				
149		SEQ ID NO:35	SEQ ID NO:36			
150			SEQ ID NO:36			
151				SEQ ID NO:37		
152				SEQ ID NO:37	SEQ ID NO:38	
153				SEQ ID NO:37	SEQ ID NO:38	SEQ ID NO:39
154					SEQ ID NO:38	
155					SEQ ID NO:38	SEQ ID NO:39
156						SEQ ID NO:39
157	SEQ ID NO:34			SEQ ID NO:37		

158	SEQ ID NO:34			SEQ ID NO:37	SEQ ID NO:38	
159	SEQ ID NO:34			SEQ ID NO:37	SEQ ID NO:38	SEQ ID NO:39
160	SEQ ID NO:34				SEQ ID NO:38	
161	SEQ ID NO:34				SEQ ID NO:38	SEQ ID NO:39
162	SEQ ID NO:34					SEQ ID NO:39
163	SEQ ID NO:34	SEQ ID NO:35		SEQ ID NO:37		
164	SEQ ID NO:34	SEQ ID NO:35		SEQ ID NO:37	SEQ ID NO:38	
165	SEQ ID NO:34	SEQ ID NO:35		SEQ ID NO:37	SEQ ID NO:38	SEQ ID NO:39
166	SEQ ID NO:34	SEQ ID NO:35			SEQ ID NO:38	
167	SEQ ID NO:34	SEQ ID NO:35			SEQ ID NO:38	SEQ ID NO:39
168	SEQ ID NO:34	SEQ ID NO:35				SEQ ID NO:39
169	SEQ ID NO:34	SEQ ID NO:35	SEQ ID NO:36	SEQ ID NO:37		
170	SEQ ID NO:34	SEQ ID NO:35	SEQ ID NO:36	SEQ ID NO:37	SEQ ID NO:38	
171	SEQ ID NO:34	SEQ ID NO:35	SEQ ID NO:36	SEQ ID NO:37	SEQ ID NO:38	SEQ ID NO:39
172	SEQ ID NO:34	SEQ ID NO:35	SEQ ID NO:36		SEQ ID NO:38	
173	SEQ ID NO:34	SEQ ID NO:35	SEQ ID NO:36		SEQ ID NO:38	SEQ ID NO:39
174	SEQ ID NO:34	SEQ ID NO:35	SEQ ID NO:36			SEQ ID NO:39
175		SEQ ID NO:35		SEQ ID NO:37		
176		SEQ ID NO:35		SEQ ID NO:37	SEQ ID NO:38	
177		SEQ ID NO:35		SEQ ID NO:37	SEQ ID NO:38	SEQ ID NO:39
178		SEQ ID NO:35			SEQ ID NO:38	
179		SEQ ID NO:35			SEQ ID NO:38	SEQ ID NO:39
180		SEQ ID NO:35				SEQ ID NO:39
181		SEQ ID NO:35	SEQ ID NO:36	SEQ ID NO:37		
182		SEQ ID NO:35	SEQ ID NO:36	SEQ ID NO:37	SEQ ID NO:38	
183		SEQ ID NO:35	SEQ ID NO:36	SEQ ID NO:37	SEQ ID NO:38	SEQ ID NO:39
184		SEQ ID NO:35	SEQ ID NO:36		SEQ ID NO:38	
185		SEQ ID NO:35	SEQ ID NO:36		SEQ ID NO:38	SEQ ID NO:39
186		SEQ ID NO:35	SEQ ID NO:36			SEQ ID NO:39
187			SEQ ID NO:36	SEQ ID NO:37		
188			SEQ ID NO:36	SEQ ID NO:37	SEQ ID NO:38	
189			SEQ ID NO:36	SEQ ID NO:37	SEQ ID NO:38	SEQ ID NO:39
190			SEQ ID NO:36		SEQ ID NO:38	
191			SEQ ID NO:36		SEQ ID NO:38	SEQ ID NO:39
192			SEQ ID NO:36			SEQ ID NO:39

[0050] In various embodiments, an antibody of the invention is humanized. For instance, in one embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 17 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 18 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence LSP, or may comprise a heavy chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 19 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 20 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence SEQ ID NO: 21 with zero to two amino acid substitutions. In a preferred embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 17 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 18 with zero to two amino acid substitutions, a CDR3 of amino acid sequence LSP, a heavy chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 19 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 20 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence SEQ ID NO: 21 with zero to two amino acid substitutions. In an exemplary embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 17, a CDR2 of amino acid sequence SEQ ID NO: 18, a CDR3 of amino acid sequence LSP, a heavy chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 19, a CDR2 of amino acid sequence SEQ ID NO: 20, and a CDR3 of amino acid sequence SEQ ID NO: 21. The invention also encompasses the corresponding nucleic acid sequences of SEQ ID NO:17, 18, 19, 20, and 21, which can readily be determined by one of skill in the art, and may be incorporated into a vector or other large DNA molecule, such as a chromosome, in order to express an antibody of the invention.

[0051] In another embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 22 with zero to two amino acid substitutions, a CDR2 of amino acid sequence

SEQ ID NO: 23 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence SEQ ID NO: 24 with zero to two amino acid substitutions, or may comprise a heavy chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 25 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 26 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence SEQ ID NO: 27 with zero to two amino acid substitutions. In a preferred embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 22 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 23 with zero to two amino acid substitutions, a CDR3 of amino acid sequence SEQ ID NO: 24 with zero to two amino acid substitutions, and a heavy chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 25 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 26 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence SEQ ID NO: 27 with zero to two amino acid substitutions. In an exemplary embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 22, a CDR2 of amino acid sequence SEQ ID NO: 23, a CDR3 of amino acid sequence SEQ ID NO: 24, a heavy chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 25, a CDR2 of amino acid sequence SEQ ID NO: 26, and a CDR3 of amino acid sequence SEQ ID NO: 27. The invention also encompasses the corresponding nucleic acid sequences of SEQ ID NO:22, 23, 24, 25, 26 and 27, which can readily be determined by one of skill in the art, and may be incorporated into a vector or other large DNA molecule, such as a chromosome, in order to express an antibody of the invention.

[0052] In still another embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence of SEQ ID NO: 28 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 29 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence SEQ ID NO: 30 with zero to two amino acid substitutions, or may comprise a heavy chain variable region comprising a CDR1 of amino acid sequence

SEQ ID NO: 31 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 32 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence SEQ ID NO: 33 with zero to two amino acid substitutions. In a preferred embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence of SEQ ID NO: 28 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 29 with zero to two amino acid substitutions, a CDR3 of amino acid sequence SEQ ID NO: 30 with zero to two amino acid substitutions, and a heavy chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 31 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 32 with zero to two amino acid substitutions, and a CDR3 of amino acid sequence SEQ ID NO: 33 with zero to two amino acid substitutions. In an exemplary embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence of SEQ ID NO: 28, a CDR2 of amino acid sequence SEQ ID NO: 29, a CDR3 of amino acid sequence SEQ ID NO: 30, a heavy chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 31, a CDR2 of amino acid sequence SEQ ID NO: 32, and a CDR3 of amino acid sequence SEQ ID NO: 33. The invention also encompasses the corresponding nucleic acid sequences of SEQ ID NO:28, 29, 30, 31, 32 and 33, which can readily be determined by one of skill in the art, and may be incorporated into a vector or other large DNA molecule, such as a chromosome, in order to express an antibody of the invention.

[0053] In yet another embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 of amino acid sequence SEQ ID NO: 34 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 35 with zero to two amino acid substitutions, a CDR3 comprising amino acid sequence SEQ ID NO: 36 with zero to two amino acid substitutions, or may comprise a heavy chain variable region comprising a CDR1 comprising amino acid sequence SEQ ID NO: 37 with zero to two amino acid substitutions, a CDR2 comprising amino acid sequence SEQ ID NO: 38 with zero to two amino acid substitutions, and a CDR3 comprising amino acid sequence SEQ ID NO: 39 with zero to two amino acid

substitutions. In a preferred embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 comprising amino acid sequence SEQ ID NO: 34 with zero to two amino acid substitutions, a CDR2 of amino acid sequence SEQ ID NO: 35 with zero to two amino acid substitutions, a CDR3 comprising amino acid sequence SEQ ID NO: 36 with zero to two amino acid substitutions, a heavy chain variable region comprising a CDR1 comprising amino acid sequence SEQ ID NO: 37 with zero to two amino acid substitutions, a CDR2 comprising amino acid sequence SEQ ID NO: 38 with zero to two amino acid substitutions, and a CDR3 comprising amino acid sequence SEQ ID NO: 39 with zero to two amino acid substitutions. In an exemplary embodiment, a humanized antibody of the invention may comprise a light chain variable region comprising a CDR1 comprising amino acid sequence SEQ ID NO: 34, a CDR2 comprising amino acid sequence SEQ ID NO: 35, a CDR3 comprising amino acid sequence SEQ ID NO: 36, a heavy chain variable region comprising a CDR1 comprising amino acid sequence SEQ ID NO: 37, a CDR2 comprising amino acid sequence SEQ ID NO: 38, and a CDR3 comprising amino acid sequence SEQ ID NO: 39. The invention also encompasses the corresponding nucleic acid sequences of SEQ ID NO:34, 35, 36, 37, 38 and 39, which can readily be determined by one of skill in the art, and may be incorporated into a vector or other large DNA molecule, such as a chromosome, in order to express an antibody of the invention.

[0054] In an aspect, the antibodies in a pharmacologically effective amount preferred in pharmaceutical grade, including immunologically reactive fragments, are administered to a subject such as to a living subject to be treated for Aβ plaque associated symptoms. Administration is performed using standard effective techniques, include peripherally (i.e. not by administration into the central nervous system) or locally to the central nervous system. Peripheral administration includes but is not limited to intravenous, intraperitoneal, subcutaneous, pulmonary, transdermal, intramuscular, intranasal, buccal, sublingual, or suppository administration. Local administration, including directly into the central nervous system (CNS) includes but is not limited to via

a lumbar, intraventricular or intraparenchymal catheter or using a surgically implanted controlled release formulation.

[0055] Pharmaceutical compositions for effective administration are deliberately designed to be appropriate for the selected mode of administration, and pharmaceutically acceptable excipients such as compatible dispersing agents, buffers, surfactants, preservatives, solubilizing agents, isotonicity agents, stabilizing agents and the like are used as appropriate. Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton Pa., 16Ed ISBN: 0-912734-04-3, latest edition, incorporated herein by reference in its entirety, provides a compendium of formulation techniques as are generally known to practitioners. It may be particularly useful to alter the solubility characteristics of the antibodies useful in this discovery, making them more lipophilic, for example, by encapsulating them in liposomes or by blocking polar groups.

[0056] Effective peripheral systemic delivery by intravenous or intraperitoneal or subcutaneous injection is a preferred method of administration to a living subject. Suitable vehicles for such injections are straightforward. In addition, however, administration may also be effected through the mucosal membranes by means of nasal aerosols or suppositories. Suitable formulations for such modes of administration are well known and typically include surfactants that facilitate cross-membrane transfer. Such surfactants are often derived from steroids or are cationic lipids, such as N-[1-(2,3-dioleoyl)propyl]-N,N,N-trimethyl ammonium chloride (DOTMA) or various compounds such as cholesterol hemisuccinate, phosphatidyl glycerols and the like.

[0057] The concentration of humanized antibody in formulations to be administered is an effective amount and ranges from as low as about 0.1% by weight to as much as about 15 or about 20% by weight and will be selected primarily based on fluid volumes, viscosities, and so forth, in accordance with the particular mode of administration selected if desired. A typical composition for injection to a living subject could be made up to contain 1 mL sterile buffered water of phosphate buffered saline and about 1-1000 mg of any one of or a combination of the humanized antibody of the present discovery. The formulation could be sterile filtered after making the formulation, or otherwise made microbiologically acceptable. A typical composition for intravenous

infusion could have volumes between 1-250 mL of fluid, such as sterile Ringer's solution, and 1-100 mg per ml, or more in anti-ApoE antibody concentration. Therapeutic agents of the discovery can be frozen or lyophilized for storage and reconstituted in a suitable sterile carrier prior to use. Lyophilization and reconstitution may lead to varying degrees of antibody activity loss (e.g. with conventional immune globulins, IgM antibodies tend to have greater activity loss than IgG antibodies). Dosages administered are effective dosages and may have to be adjusted to compensate. The pH of the formulations generally pharmaceutical grade quality, will be selected to balance antibody stability (chemical and physical) and comfort to the subject when administered. Generally, a pH between 4 and 8 is tolerated. Doses will vary from individual to individual based on size, weight, and other physiobiological characteristics of the individual receiving the successful administration.

[0058] As used herein, the term "effective amount" means an amount of a substance such as a compound that leads to measurable and beneficial effects for the subject administered the substance, i.e., significant efficacy. The effective amount or dose of compound administered according to this discovery will be determined by the circumstances surrounding the case, including the compound administered, the route of administration, the status of the symptoms being treated and similar subject and administration situation considerations among other considerations. In an aspect, a typical dose contains from about 0.01 mg/kg to about 100 mg/kg of an anti-ApoE antibody described herein. Doses can range from about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg. The frequency of dosing may be daily or once, twice, three times or more per week or per month, as needed as to effectively treat the symptoms.

[0059] The timing of administration of the treatment relative to the disease itself and duration of treatment will be determined by the circumstances surrounding the case. Treatment could begin immediately, such as at the site of the injury as administered by emergency medical personnel. Treatment could begin in a hospital or clinic itself, or at a later time after discharge from the hospital or after being seen in an

outsubject clinic. Duration of treatment could range from a single dose administered on a one-time basis to a life-long course of therapeutic treatments.

[0060] Although the foregoing methods appear the most convenient and most appropriate and effective for administration of proteins such as humanized antibodies, by suitable adaptation, other effective techniques for administration, such as intraventricular administration, transdermal administration and oral administration may be employed provided proper formulation is utilized herein.

[0061] In addition, it may be desirable to employ controlled release formulations using biodegradable films and matrices, or osmotic mini-pumps, or delivery systems based on dextran beads, alginate, or collagen.

[0062] Typical dosage levels can be determined and optimized using standard clinical techniques and will be dependent on the mode of administration.

[0063] The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent techniques discovered by the inventors to function well in the practice of the invention. Those of skill in the art should, however, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth or shown in the accompanying examples and drawings is to be interpreted as illustrative and not in a limiting sense.

EXAMPLES:

[0064] The following examples illustrate various iterations of the invention.

[0065] Antibodies specific for the ApoE protein were generated using hybridoma techniques, as described below in Examples 1 and 2. Specifically, four hybridomas were generated and ApoE antibodies were obtained from the hybridomas. The hybridomas HJ6.1, HJ6.2, HJ6.3, and HJ6.4 have been assigned ATCC Patent Deposit Designations PTA-11805, PTA-11806, PTA-11807, and PTA-11808 respectively.

Example 1: Preparation of Hybridomas

[0066] At first, 100 µl of the antigen peptide (ApoE, 1 mg/ml) in saline was mixed with an equal volume of Freund's complete adjuvant, emulsified and inoculated to the back of a mouse (Balb/c, 6 weeks of age). After 2 weeks, the mouse was re-immunized with a mixture of the 50 µl of the saline solution of antigen peptide (ApoE, 1 mg/ml) and Freund's incomplete adjuvant, emulsified by ultrasonic treatment, and after that, additional immunizations were carried out every week. On 40 days after immunization, the spleen was removed, the lymphocytes were harvested in PRM1640 medium (supplemented with penicillin and streptomycin) and treated with 0.17 M ammonium chloride to remove red blood cells. Isolated lymphocytes were fused with myeloma cells P3U1 strain derived from a mouse bone marrow tumor by the polyethylene glycol method (PEG4000) to obtain hybridoma cells. The hybridoma cells thus obtained were suspended in HAT medium with feeder cells and then distributed to 96-well plates and cultured for 15 days.

Example 2: Screening for the Monoclonal Antibody

[0067] The culture medium supernatants were recovered from wells in which the hybridoma cells obtained in Example 1 were cultured, and monoclonal antibodies which react with the antigen peptide by the enzyme-linked immunosorbent assay (ELISA) method were selected.

[0068] At first, 100 µl of 10 µg/ml antigen peptide was added to each well of 96-well plates, immobilized to the solid phase after keeping at 4° C. overnight and blocked with 200 µl of 10% calf serum at 37° C. overnight. Then, 100 µl of the culture medium supernatant of hybridoma cells was added to each well, reacted at 37° C. for 2 hours, and then horseradish peroxidase (HRP)-conjugated anti-mouse antibody, which was diluted 1000 folds, was added and reacted at 37° C. for 1 hour. The color was developed using Tetra Methyl Benzidine Microwell Peroxidase Substrate (TMB) as a substrate.

[0069] After terminating the reaction by adding 100 µl of 4N sulfuric acid, absorbance at 450 to 540 nm was measured, and the monoclonal antibodies, which

showed the absorbance of about 3, were selected and cloned by the limited dilution method.

[0070] Mouse (Balb/c), injected with 0.5 ml pristine intraperitoneally 7 days and 3 days before, were inoculated intraperitoneally with selected monoclonal antibody-producing hybridoma cells, and ascites was collected about 10 days later. The collected ascites was kept at room temperature for 30 minutes, at 4° C. overnight and centrifuged at 15,000×rpm for 10 minutes, and then the supernatant was recovered.

[0071] The titers of selected monoclonal antibodies were measured by the ELISA method. ApoE was immobilized on a microwell plate, monoclonal antibodies were added, and after the reaction, color was developed using horse radish peroxidase (HRP)-conjugated anti-mouse antibody and TMB. The results indicate that selected monoclonal antibodies reacted in a concentration-dependent manner.

Example 3: Anti-ApoE antibodies cause reduction in plaque load

[0072] PS/APP mice, which exhibit age related amyloid plaque formation similar to that observed in Alzheimer's Disease subjects, are used as a mouse model for Alzheimer's Disease. PS/APP mice were treated intraperitoneally once weekly with 10 mg/kg with either an anti-Aß antibody (HJ3.4) or one of two anti-ApoE antibodies (HJ6.2 or HJ6.3). Another group was treated with PBS as a control. Treatment was from 3-7 months of age. There was a strong effect of the anti-ApoE antibodies associated with a decrease in Aß plaque load as demonstrated in both the hippocampus (FIG. 1) and cortex (FIG. 2).

Example 4: Binding of Anti-ApoE antibodies to human apoE.

[0073] An ELISA sandwich assay was used to measure binding of anti-apoE HJ6.1, HJ6.2, HJ6.3, and HJ6.4 antibodies to human apoE. Monoclonal antibody WUE4 which binds to human apoE was first coated on an ELISA plate. Then differing concentrations of human apoE4 were applied. Biotinylated anti-apoE antibodies HJ6.1, HJ6.2, HJ6.3, and HJ6.4 were applied last and the optical density (OD) was read from a plate reader (FIG. 3).

[0074] These results show that anti-apoE antibodies HJ6.1, HJ6.2 and HJ6.3 bind to human apoE in an ELISA format with decreasing potency. However, anti-apoE antibody HJ6.4 does not bind to human apoE in this assay.

Example 5: Anti-apoE antibodies bind to human apoE in plasma but do not affect plasma cholesterol.

[0075] For these experiments, human ApoE4 knockin mice were used to measure plasma apoE/antibody complexes. ApoE4 knockin mice received 500 micrograms of biotinylated HJ6 mAbs intraperitoneally. Twenty fours later, the plasma was diluted (1:1000) and loaded to an ELISA plate coated with 5 µg/ml WUE4, which binds to human apoE. The ApoE/antibody complex was detected by a 1:5000 dilution HRP40. The optical density (OD) was read on a plate reader (FIG. 4A). These results show that HJ6.1, HJ6.2 and HJ6.3 antibodies bind to human apoE in plasma, whereas HJ6.4 did not bind to human apoE in plasma. No signal was obtained when this experiment was performed in apoE-/- mice.

[0076] Total plasma cholesterol was also measured in the same apoE4+/+ mice that received intraperitoneal injections of 500 micrograms of HJ6 series monoclonal antibodies HJ6.1, HJ6.2, HJ6.3, and HJ6.4. Plasma cholesterol did not change relative to animals that received phosphate buffered saline (FIG. 4B).

Example 6: HJ6 series antibodies to human apoE found in the central nervous system (CNS) after peripheral administration.

[0077] The cerebrospinal fluid (CSF) of ApoE4+/+ or ApoE4-/- mice that received HJ6 series mAbs or PBS in (see FIG. 4) was diluted (1:23) and the apoE4/biotinylated antibody complex in the CSF was captured by WUE4 and then detected by HRP40. The results demonstrate that in CSF there are complexes of apoE4 with the anti-apoE antibodies HJ6.1B, HJ6.2B or HJ6.3B (FIG. 5), suggesting that a fraction of the apoE mAbs were able to enter the CNS compartment and bind to apoE. The OD_{650} followed the order HJ6.1B>HJ6.2B=HJ6.3B>>>HJ6.4B, which is consistent with the pattern seen

for the ability of these antibodies to bind apoE on an ELISA plate (FIG. 3) and in plasma (FIG 4).

Example 7: Microglial activation in mice administered HJ6 series antibodies.

[0078] 10 mg/kg of HJ6.2, HJ6.3 and HJ3.4 antibodies diluted in PBS, or the same volume of PBS was injected into PSAPP mice intraperitoneally at timepoint 0, day 3, day 6, and day 9. On day 10, brains were removed, fixed, and stained with antibody CD45 which marks activated microglia. There was an increase in the amount of cortex covered by activated microglia in the HJ6.3 and HJ3.4 injected mice. The PSAPP mice in this experiment express mouse apoE. These results show that short term administration of HJ6.3 (an anti-apoE antibody) and HJ3.4 (an anti-Aβ antibody) to 6 month old PSAPP mice that already have amyloid plaques over 10 days, results in microglial activation whereas one anti-apoE antibody (HJ6.2) does not appear to have this effect (FIG. 6).

CLAIMS

What is claimed is:

1. Use of at least one anti-ApoE antibody in the manufacture of a medicament for reversing at least one symptom or sign of Aβ plaque associated symptoms in a subject having Alzheimer's disease, Lewy body dementia, or cerebral amyloid angiopathy.

2. The use according to claim 1, wherein a symptom or sign of Aβ plaque associated symptoms includes impaired cognitive function, altered behavior, abnormal language function, emotional dysregulation, seizures, impaired nervous system structure or function, and an increased risk of development of Alzheimer's disease or cerebral amyloid angiopathy.

3. The use according to claim 1, wherein the anti-ApoE antibody binds an epitope within the ApoE coding sequence.

4. Use of at least one anti-ApoE antibody in the manufacture of a medicament for decreasing the amyloid plaque load in the brain of a subject having Alzheimer's disease, Lewy body dementia, or cerebral amyloid angiopathy.

5. The use according to claim 4, wherein the anti-ApoE antibody binds an epitope within the ApoE coding sequence.

6. The use according to claim 4, wherein the amyloid plaque loads are decreased in the hippocampus.

7. The use according to claim 4, wherein the amyloid plaque loads are decreased in the cortex.

SEQUENCE LISTING

<110> THE WASHINGTON UNIVERSITY
HOLTZMAN, David
KIM, Jungsu
JIANG, Hong
ELTORAI, Adam

<120> COMPOSITIONS AND METHODS FOR TREATING AMYLOID PLAQUE ASSOCIATED SYMPTOMS

<130> 047563-434951

<150> US 61/419,060
<151> 2010-12-02

<150> US 61/548,542
<151> 2011-10-18

<160> 39

<170> PatentIn version 3.5

<210> 1
<211> 687
<212> DNA
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 1
atggagtcag acacactcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60

gacattgtgc tcacccaatc tccagcttct ttggctgtgt ctctagggca gagagccacc 120

atctcctgca gagccagtga aagtgttgaa tattatggca caagtttaat gcagtggtac 180

caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa cgtagaatct 240

ggggtccctg ccaggtttag tggcagtggg tctgggacag acttcagcct caacatccat 300

cctgtggagg aggatgatat tgcaatgtat ttctgtcagc aaagtaggaa ggttccgtgg 360

acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc 420

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 480

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 540

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 600

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 660

actcacaaga catcaacttc acccatt 687

<210> 2
<211> 700
<212> DNA
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 2
atgtcctctc ctcagacact gaacacactg actctaacca tgggatggag ctggatcttt 60

ctctttctcc tgtcagaaac tgcaggtgtc ctctctgagg tccagctgca acagtctgga 120

cctgagctgg tgaagcctgg ggcttcagtg aagatgtcct gcaaggcttc tggatacaca 180

ttcactgact acaacatgca ctgggtgaag cagagccatg gaaagagcct tgagtggatt 240

ggatatatta accctaacaa tggtggtact agctacaacc agaagttcaa gggcaaggcc 300

acattgactg taaacaagtc ctccagcaca gcctacatgg agctccgcag cctgacatcg 360

gaagattctg cagtctatta ctgtacactt ctatccccgt ggggccaagg caccactctc 420

acagtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct 480

gcccaaacta actccatggt gaccctggga tgcctggtca agggctattt ccctgagcca 540

gtgacagtga cctggaactc tggatccctg tccagcggtg tgcacacctt cccagctgtc 600

ctgcagtctg acctctacac tctgagcagc tcagtgactg tccctccag cacctggccc 660

agccagaccg tcacctgcaa cgttgcccac ccggccagca 700

<210> 3
<211> 229
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 3

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

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
20 25 30

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

Val Glu Tyr Tyr Gly Thr Ser Leu Met Gln Trp Tyr Gln Gln Lys Pro
50 55 60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser
65 70 75 80

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

Leu Asn Ile His Pro Val Glu Glu Asp Asp Ile Ala Met Tyr Phe Cys
100 105 110

Gln Gln Ser Arg Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

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

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

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

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

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

Ser Thr Ser Pro Ile
225
```

<210> 4
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 4

```
Met Ser Ser Pro Gln Thr Leu Asn Thr Leu Thr Leu Thr Met Gly Trp
1               5                   10                  15

Ser Trp Ile Phe Leu Phe Leu Leu Ser Glu Thr Ala Gly Val Leu Ser
            20                  25                  30

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
    50                  55                  60

Asn Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
65                  70                  75                  80

Gly Tyr Ile Asn Pro Asn Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
                85                  90                  95

Lys Gly Lys Ala Thr Leu Thr Val Asn Lys Ser Ser Ser Thr Ala Tyr
            100                 105                 110

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
        115                 120                 125

Thr Leu Leu Ser Pro Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
```

130 135 140

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

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
165 170 175

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

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

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

Thr Cys Asn Val Ala His Pro Ala Ser
225 230

<210> 5
<211> 690
<212> DNA
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 5
atggaatcac agactcaggt cttcctctcc ctgctgctct gggtatctgg tacctgtggg 60

aacattatga tgacacagtc gccatcatct ctggctgtgt ctgcaggaga aaaggtcact 120

atgagctgta agtccagtca aagtgtttta tacagttcaa atcagaagaa ctacttggcc 180

tggtaccagc agaaaccagg gcagtctcct aaactgctga tctactgggc atccgctagg 240

aaatctggtg tccctgatcg cttcacaggc agtggatctg ggacagattt tactcttacc 300

atcagcagtg tacaagctga agacctggca gtttattact gtcatcaata cctctcctcg 360

tacacgttcg gaggggggac caagctggaa ataaaacggg ctgatgctgc accaactgta 420

tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480

ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 540

caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600

agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660

gccactcaca agacatcaac ttcacccatt 690

<210> 6
<211> 670
<212> DNA
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 6
atggattggg tgtggacctt gctattcctg atagcagctg cccaaagtgc ccaagcacag 60

atccagttgg tgcagtctgg acctgagctg aagaagcctg gagagacagt caagatctcc 120

tgcaaggctt ctgggtatac cttcacagaa tatccaatgc actgggtgaa gcaggctcca 180

ggaaaggatt tcaagtggat gggcatgata tacaccgaca ctggagagcc aacatatgct 240

gaagagttca agggacggtt tgccttctct ttggagacct ctgccaacac tgcctatttg 300

cagatcaaca acctcaaaaa tgaggacacg gctacatatt tctgtgtggg tggttacttg 360

ttttcttact ggggccaagg gactctggtc actgtctctg cagccaaaac gacaccccca 420

tctgtctatc cactggcccc tggatctgct gcccaaacta actccatggt gaccctggga 480

tgcctggtca agggctattt ccctgagcca gtgacagtga cctggaactc tggatccctg 540

tccagcggtg tgcacacctt cccagctgtc ctgcagtctg acctctacac tctgagcagc 600

tcagtgactg tcccctccag cacctggccc agccagaccg tcacctgcaa cgttgcccac 660

ccggccagca 670

<210> 7
<211> 230
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 7

Met Glu Ser Gln Thr Gln Val Phe Leu Ser Leu Leu Leu Trp Val Ser
1 5 10 15

Gly Thr Cys Gly Asn Ile Met Met Thr Gln Ser Pro Ser Ser Leu Ala
20 25 30

Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
35 40 45

Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg
65 70 75 80

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

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

Tyr Cys His Gln Tyr Leu Ser Ser Tyr Thr Phe Gly Gly Gly Thr Lys
115 120 125

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

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

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

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

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

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

Thr Ser Thr Ser Pro Ile
225 230

<210> 8
<211> 223
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 8

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

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

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

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

Lys Trp Met Gly Met Ile Tyr Thr Asp Thr Gly Glu Pro Thr Tyr Ala
65 70 75 80

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

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr
100 105 110

Tyr Phe Cys Val Gly Gly Tyr Leu Phe Ser Tyr Trp Gly Gln Gly Thr

115 120 125

Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro
130 135 140

Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly
145 150 155 160

Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn
165 170 175

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

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

Trp Pro Ser Gln Thr Val Thr Cys Asn Val Ala His Pro Ala Ser
210 215 220

<210> 9
<211> 681
<212> DNA
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 9
atggacatga ggacccctgc tcagtttctt ggaatcttgt tgctctggtt tccaggtatc 60

aaatgtgaca tcaaactgac ccagtctcca tcttccatgt atgcatctct aggagagaga 120

gtcactatca cttgcaaggc gagtgaggac attaatagct atttaagctg gttccagcag 180

aaaccaggga aatctcctaa gaccctgatc tatcgtgcaa acagattggt agatggggtc 240

ccatcaaggt tcagtggcag tggatctggg caagattatt ctctcaccat cagcagcctg 300

gagtatgaag atatgggaat ttattattgt ctacagtatg atgagtttcc tctcacgttc 360

ggtgctggga ccaagctgga gctgacacgg gctgatgctg caccaactgt atccatcttc 420

ccaccatcca gtgagcagtt aacatctgga ggtgcctcag tcgtgtgctt cttgaacaac 480

ttctacccca aagacatcaa tgtcaagtgg aagattgatg gcagtgaacg acaaaatggc 540

gtcctgaaca gttggactga tcaggacagc aaagacagca cctacagcat gagcagcacc 600

ctcacgttga ccaaggacga gtatgaacga cataacagct atacctgtga ggccactcac 660

aagacatcaa cttcacccat t 681

<210> 10
<211> 398
<212> DNA
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 10
atggcagcag ctcaaagtat ccaagcacag atccagttgg tgcagtctgg acctgagctg 60

aagaagcctg gagagacagt caagatctcc tgcaaggctt ctgggtatac cttcacaact 120

gctggaatgc agtgggtgca aaagatgcca ggaaagggtt ttaagtggat tggctggata 180

aacacccact ctggagagcc aaaatatgca gaagatttca agggacggtt tgccttctct 240

ttggaaacct ctgccagcac tgcctattta cagataagca acctcaaaaa tgaggacacg 300

gctacgtatt tctgtgcgag aatgggaggc tatgctatgg actactgggg tcaaggaacc 360

tcagtcaccg tctcctctgc caaaacaaca cccccatc 398

<210> 11
<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 11

Met Asp Met Arg Thr Pro Ala Gln Phe Leu Gly Ile Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ile Lys Cys Asp Ile Lys Leu Thr Gln Ser Pro Ser Ser
20 25 30

Met Tyr Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Glu Asp Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys
50 55 60

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

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr
85 90 95

Ile Ser Ser Leu Glu Tyr Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln
100 105 110

Tyr Asp Glu Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
115 120 125

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

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

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

165 170 175

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

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

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

Ser Pro Ile
225

<210> 12
<211> 133
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 12

Met Ala Ala Ala Gln Ser Ile Gln Ala Gln Ile Gln Leu Val Gln Ser
1 5 10 15

Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys
20 25 30

Ala Ser Gly Tyr Thr Phe Thr Thr Ala Gly Met Gln Trp Val Gln Lys
35 40 45

Met Pro Gly Lys Gly Phe Lys Trp Ile Gly Trp Ile Asn Thr His Ser
50 55 60

Gly Glu Pro Lys Tyr Ala Glu Asp Phe Lys Gly Arg Phe Ala Phe Ser
65 70 75 80

Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Gln Ile Ser Asn Leu Lys
85 90 95

Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Met Gly Gly Tyr Ala
100 105 110

Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys
115 120 125

Thr Thr Pro Pro Ser
130

<210> 13
<211> 690
<212> DNA

<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 13
atggaatcac agactcaggt cttcctctcc ctgctgctct gggtatctgg tacctgtggg 60

aacattatga tgacacagtc gccatcatct ctggctgtgt ctgcaggaga aaaggtcact 120

atgagctgta agtccagtca aagtgtttta tacagttcaa atcagaagaa ctacttggcc 180

tggtaccagc agaaaccagg gcagtctcct aaactgctga tctactgggc atccactagg 240

gaatctggtg tccctgatcg cttcacaggc agtggatctg ggacagattt tactcttacc 300

atcaccaatg tacaagctga agacctggca gtttattact gtcatcaata cctctcctcg 360

tacacgttcg gaggggggac caagttggaa ataaaacggg ctgatgctgc accaactgta 420

tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480

ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 540

caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600

agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660

gccactcaca agacatcaac ttcacccatt 690

<210> 14
<211> 670
<212> DNA
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 14
atggattggg tgtggacctt gctattcctg atagcagctg cccaaagtgc ccaagcacag 60

atccagttgg tgcagtctgg acctgagctg aagaagcctg gagagacagt caagatctcc 120

tgcaaggctt ctgggtatac cttcacagaa tatccaatgc actgggtgaa gcaggctcca 180

ggaaagggtt tcaagtggat gggcatgata tacaccgaca ctggagagcc aacatatgtt 240

gaagagttca agggacggtt tgccttctct ttggagacct ctgccagcac tgcctatttg 300

cagatcaaca acctcaaaaa tgaggacacg gctacatatt tctgtgtagg tggttacttg 360

ttttcttact ggggccaagg gactctggtc actgtctctg cagccaaaac gacaccccca 420

tctgtctatc cactggcccc tggatctgct gcccaaacta actccatggt gaccctggga 480

tgcctggtca agggctattt ccctgagcca gtgacagtga cctggaactc tggatccctg 540

tccagcggtg tgcacacctt cccagctgtc ctgcagtctg acctctacac tctgagcagc 600

tcagtgactg tcccctccag cacctggccc agccagaccg tcacctgcaa cgttgcccac 660

ccggccagca 670

<210> 15
<211> 230
<212> PRT

<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 15

```
Met Glu Ser Gln Thr Gln Val Phe Leu Ser Leu Leu Leu Trp Val Ser
1               5                  10                  15

Gly Thr Cys Gly Asn Ile Met Met Thr Gln Ser Pro Ser Ser Leu Ala
            20                  25                  30

Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
        35                  40                  45

Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
    50                  55                  60

Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
65                  70                  75                  80

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

Phe Thr Leu Thr Ile Thr Asn Val Gln Ala Glu Asp Leu Ala Val Tyr
            100                 105                 110

Tyr Cys His Gln Tyr Leu Ser Ser Tyr Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

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

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

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

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

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

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

Thr Ser Thr Ser Pro Ile
225                 230
```

<210> 16

<211> 223
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 16

```
Met Asp Trp Val Trp Thr Leu Leu Phe Leu Ile Ala Ala Ala Gln Ser
1               5                  10                  15

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

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

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

Lys Trp Met Gly Met Ile Tyr Thr Asp Thr Gly Glu Pro Thr Tyr Val
65                  70                  75                  80

Glu Glu Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser
                85                  90                  95

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr
            100                 105                 110

Tyr Phe Cys Val Gly Gly Tyr Leu Phe Ser Tyr Trp Gly Gln Gly Thr
        115                 120                 125

Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro
    130                 135                 140

Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly
145                 150                 155                 160

Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn
                165                 170                 175

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

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

Trp Pro Ser Gln Thr Val Thr Cys Asn Val Ala His Pro Ala Ser
    210                 215                 220
```

<210> 17
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 17

Gly Tyr Thr Phe Thr Asp Tyr Asn Met His
1 5 10

<210> 18
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 18

Tyr Ile Asn Pro Asn Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 19
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 19

Arg Ala Ser Glu Ser Val Glu Tyr Tyr Gly Thr Ser Leu Met Gln
1 5 10 15

<210> 20
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 20

Ala Ala Ser Asn Val Glu Ser
1 5

<210> 21
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 21

Gln Gln Ser Arg Lys Val Pro Trp Thr

1 5

<210> 22
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 22

Gly Tyr Thr Phe Thr Glu Tyr Pro Met His
1 5 10

<210> 23
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 23

Met Ile Tyr Thr Asp Thr Gly Glu Pro Thr Tyr Ala Glu Glu Phe Lys
1 5 10 15

Gly

<210> 24
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 24

Gly Tyr Leu Phe Ser Tyr
1 5

<210> 25
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 25

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 26

<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 26

Trp Ala Ser Ala Arg Lys Ser
1 5

<210> 27
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 27

His Gln Tyr Leu Ser Ser Tyr Thr
1 5

<210> 28
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 28

Gly Tyr Thr Phe Thr Thr Ala Gly Met Gln
1 5 10

<210> 29
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 29

Trp Ile Asn Thr His Ser Gly Glu Pro Lys Tyr Ala Glu Asp Phe Lys
1 5 10 15

Gly

<210> 30
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 30

Met Gly Gly Tyr Ala Met Asp Tyr
1 5

<210> 31
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 31

Lys Ala Ser Glu Asp Ile Asn Ser Tyr Leu Ser
1 5 10

<210> 32
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 32

Arg Ala Asn Arg Leu Val Asp
1 5

<210> 33
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 33

Leu Gln Tyr Asp Glu Phe Pro Leu Thr
1 5

<210> 34
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 34

Gly Tyr Thr Phe Thr Glu Tyr Pro Met His
1 5 10

<210> 35
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 35

Met Ile Tyr Thr Asp Thr Gly Glu Pro Thr Tyr Val Glu Glu Phe Lys
1 5 10 15

Gly

<210> 36
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 36

Gly Tyr Leu Phe Ser Tyr
1 5

<210> 37
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 37

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 38
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 38

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 39
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> based on mus musculus

<400> 39

His Gln Tyr Leu Ser Ser Tyr Thr

1 5

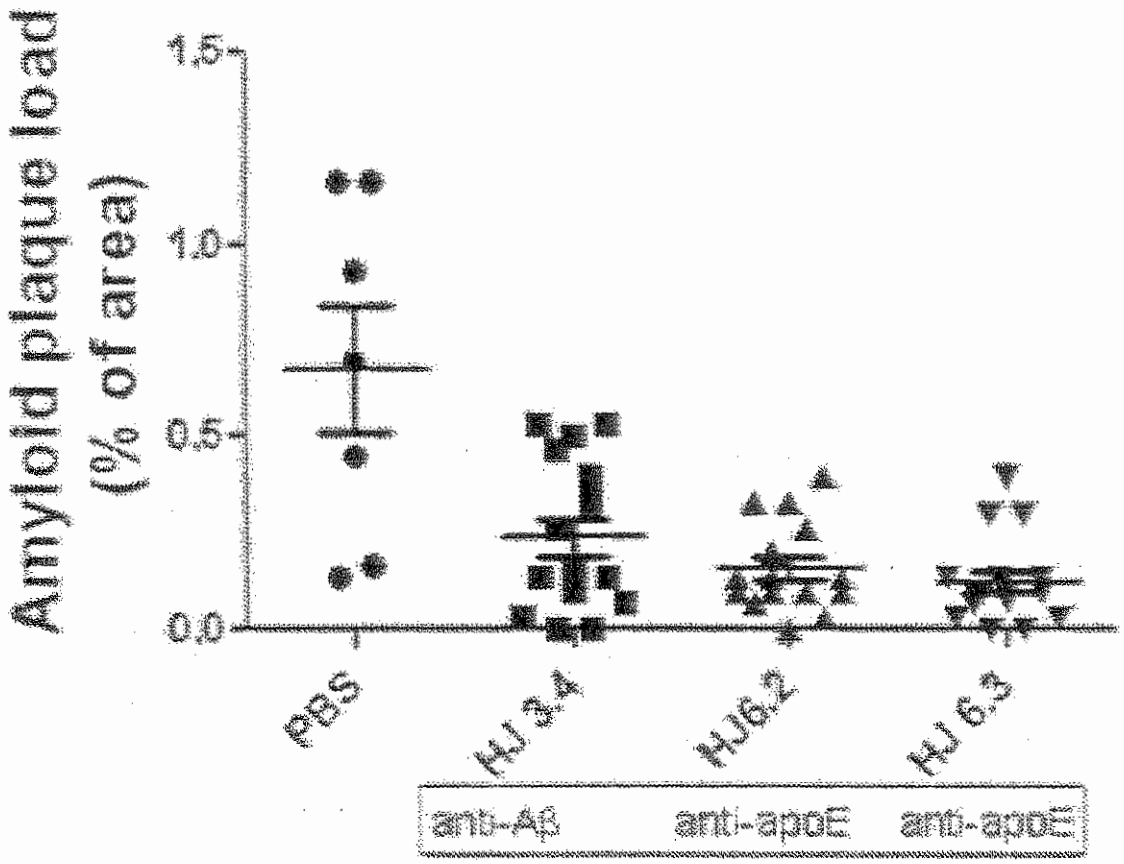

Amyloid plaque load
(% of area)
1.5
1.0
0.5
0.0
PBS
HJ 3.4
HJ6.2
HJ 6.3
anti-Aβ
anti-apoE
anti-apoE

FIG. 1

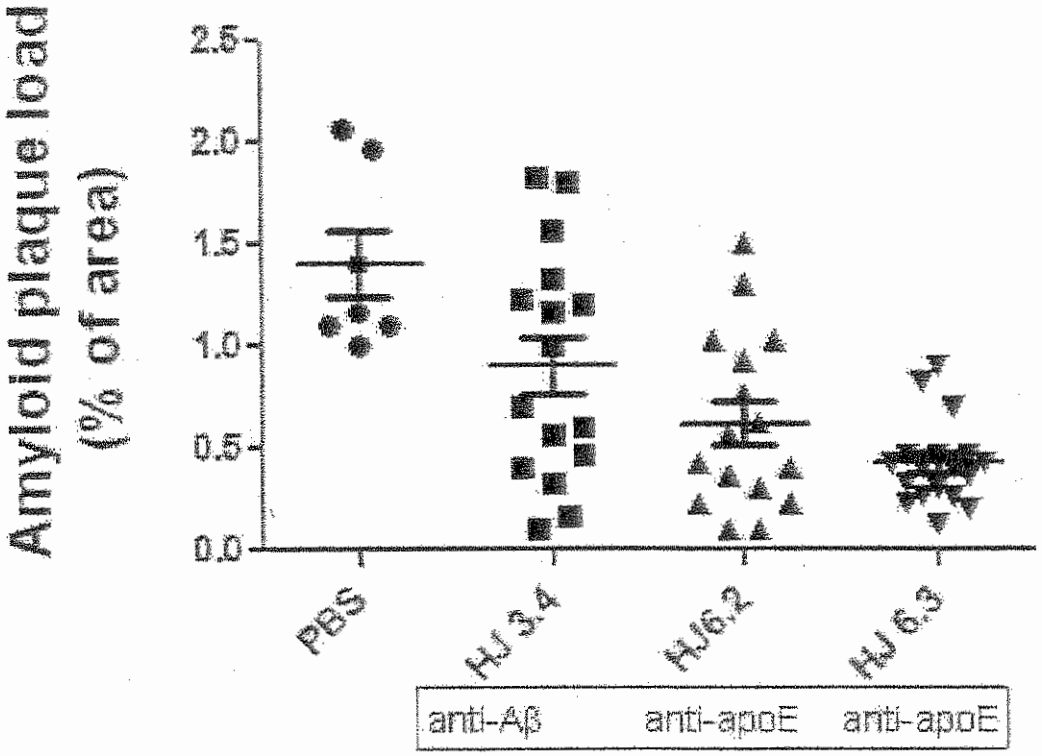

Amyloid plaque load
(% of area)
2.5
2.0
1.5
1.0
0.5
0.0
PBS
HJ 3.4
HJ6.2
HJ 6.3
anti-Aβ
anti-apoE
anti-apoE

FIG. 2

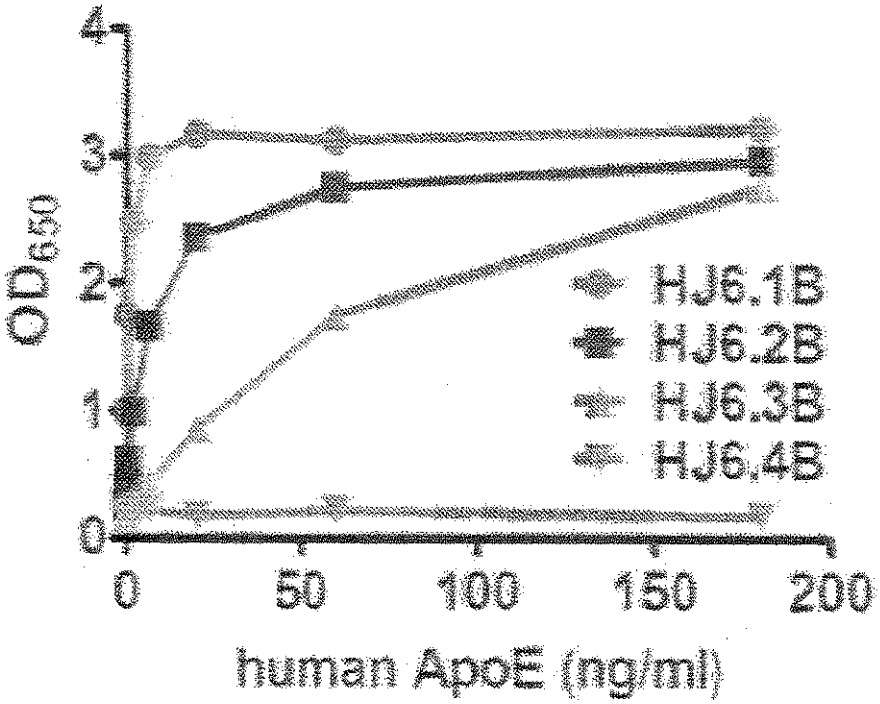

4
3
2
1
0
OD_{650}
HJ6.1B
HJ6.2B
HJ6.3B
HJ6.4B
0
50
100
150
200
human ApoE (ng/ml)

FIG. 3

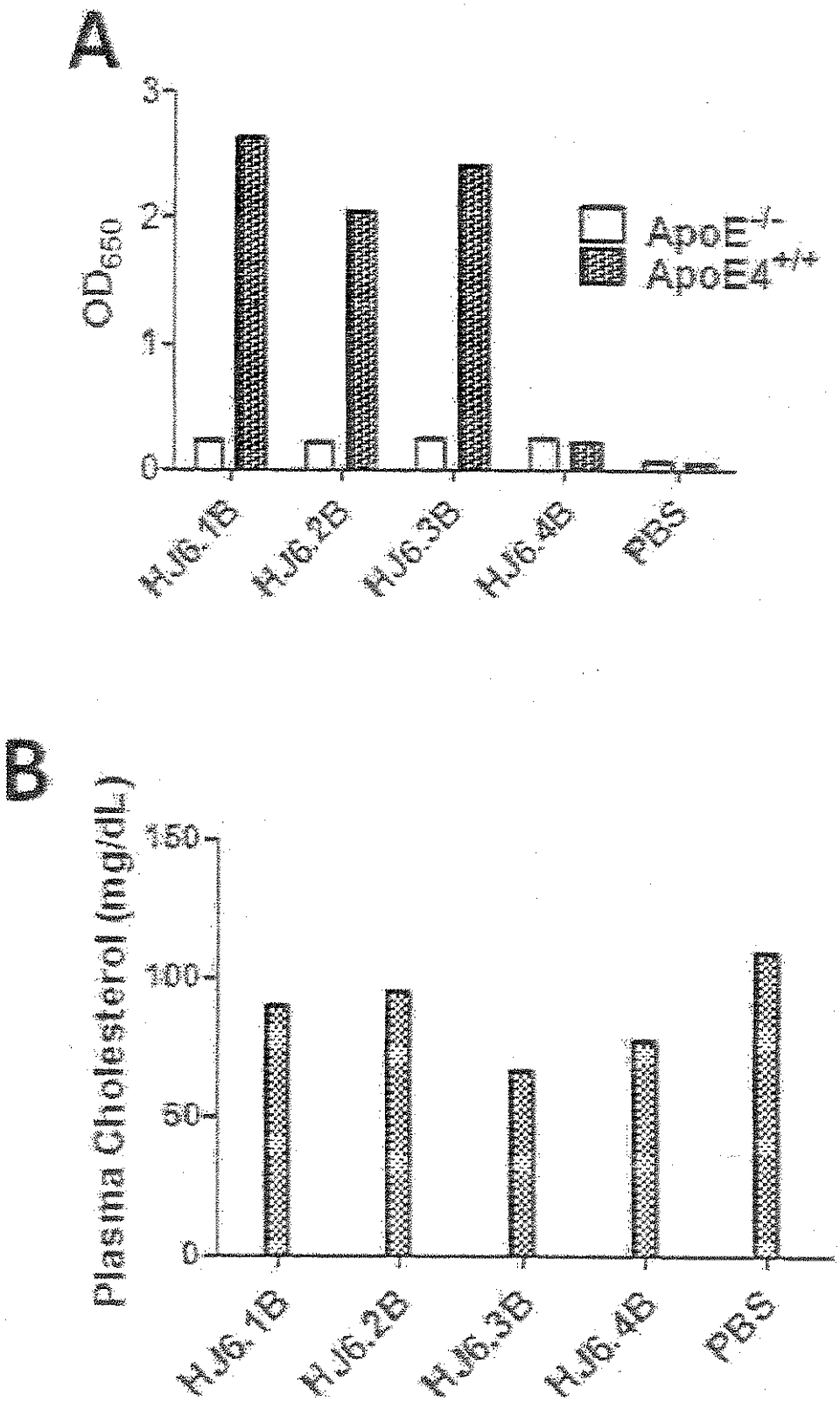

A
3
2
1
0
OD_{650}
ApoE$^{-/-}$
ApoE4$^{+/+}$
HJ6.1B
HJ6.2B
HJ6.3B
HJ6.4B
PBS
B
Plasma Cholesterol (mg/dL)
150
100
50
0
HJ6.1B
HJ6.2B
HJ6.3B
HJ6.4B
PBS

FIG. 4

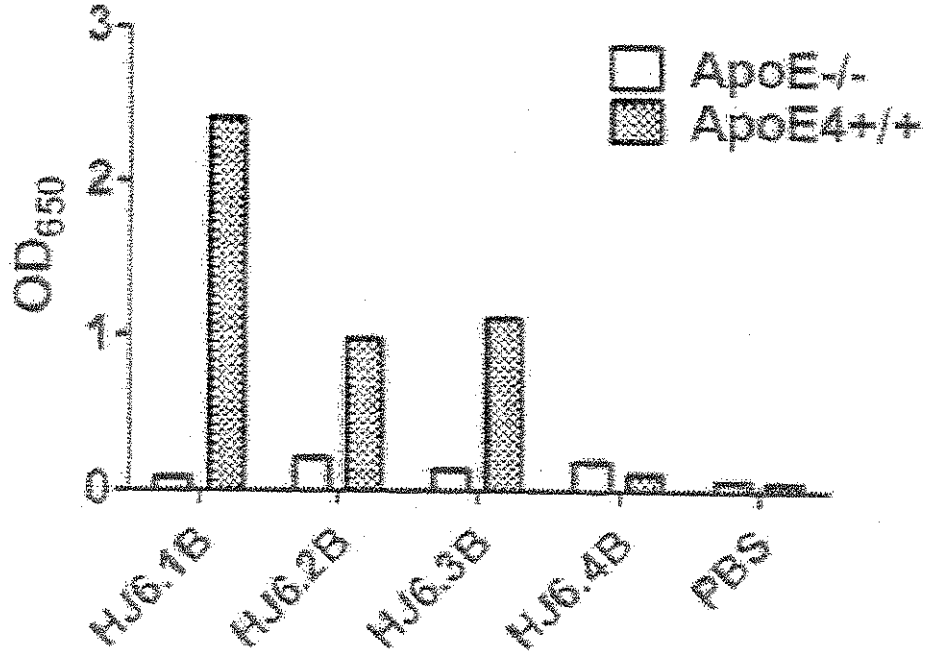

ApoE-/-
ApoE4+/+
OD_{650}
0
1
2
3
HJ6.1B
HJ6.2B
HJ6.3B
HJ6.4B
PBS

FIG. 5

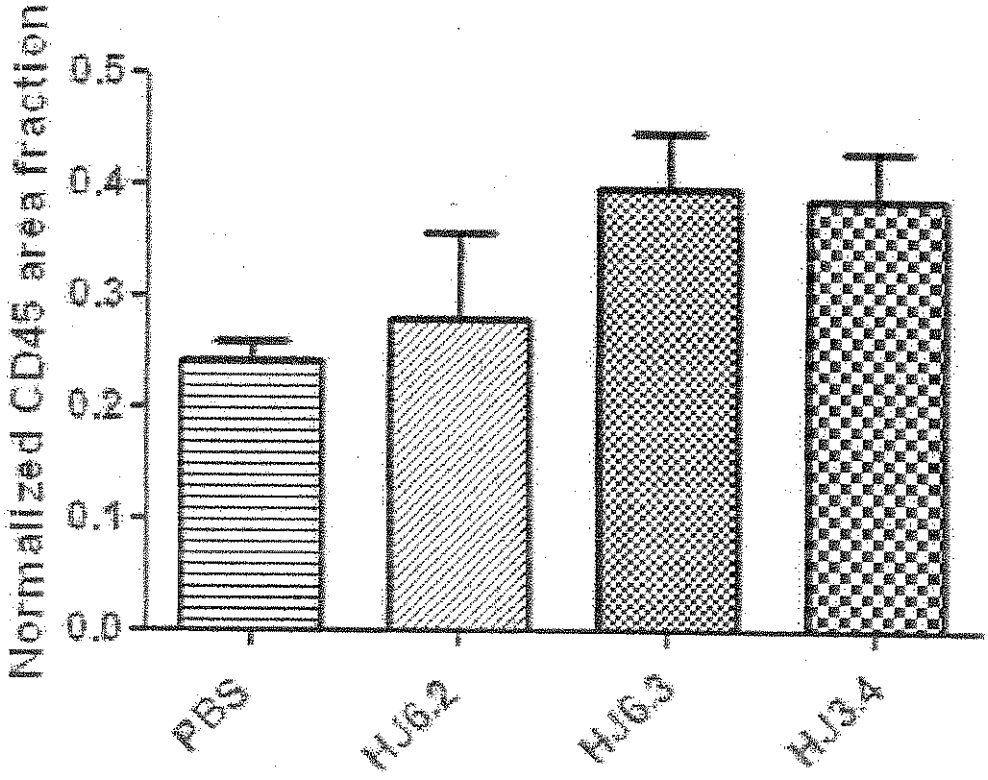

Normalized CD45 area fraction
0.0
0.1
0.2
0.3
0.4
0.5
PBS
HJ6.2
HJ6.3
HJ3.4

FIG. 6

A

M S S P Q T L N T L T L T M G W S W I F L F L L S E T A G V L S E V
Q L Q Q S G P E L V K P G A S V K M S C K A S G Y T F T D Y N M H W
V K Q S H G K S L E W I G Y I N P N N G G T S Y N Q K F K G K A T L
T V N K S S S T A Y M E L R S L T S E D S A V Y Y C T L L S P W G Q
G T T L T V S S A K T T P P S V Y P L A P G S A A Q T N S M V T L G
C L V K G Y F P E P V T V T W N S G S L S S G V H T F P A V L Q S D
L Y T L S S S V T V P S S T W P S Q T V T C N V A H P A S

B

M E S D T L L L W V L L L W V P G S T G D I V L T Q S P A S L A V S
L G Q R A T I S C R A S E S V E Y Y G T S L M Q W Y Q Q K P G Q P P
K L L I Y A A S N V E S G V P A R F S G S G S G T D F S L N I H P V
E E D D I A M Y F C Q Q S R K V P W T F G G G T K L E I K R A D A A
P T V S I F P P S S E Q L T S G G A S V V C F L N N F Y P K D I N V
K W K I D G S E R Q N G V L N S W T D Q D S K D S T Y S M S S T L T
L T K D E Y E R H N S Y T C E A T H K T S T S P I

C

M D W V W T L L F L I A A A Q S A Q A Q I Q L V Q S G P E L K K P G
E T V K I S C K A S G Y T F T E Y P M H W V K Q A P G K D F K W M G
M I N T D T G E P T Y A E E F K G R F A F S L E T S A N T A Y L Q I
N N L K N E D T A T Y F C V G G Y L P S W W G Q G T L V T V S A A K
T T P P S V Y P L A P G S A A Q T N S M V T L G C L V K G Y F P E P
V T V T W N S G S L S S G V H T F P A V L Q S D L Y T L S S S V T V
P S S T W P S Q T V T C N V A H P A S

D

M E S Q T Q V F L S L L L W V S G T C G N I M M T Q S P S S L A V S
A G E K V T M S C K S S Q S V L Y S S N Q K N Y L A W Y Q Q K P G Q
S P K L L I Y W A S A R K S G V P D R F T G S G S G T D F T L T I S
S V Q A E D L A V Y Y C H Q Y L S S R T F G G G T K L E I K R A D A
A P T V S I F P P S S E Q L T S G G A S V V C F L N N F Y P K D I N
V K W K I D G S E R Q N G V L N S W T D Q D S K D S T Y S M S S T L
T L T K D E Y E R H N S Y T C E A T H K T S T S P I

FIG. 7


E
M A A A Q S I Q A Q I Q L V Q S G P E L K K P G E T V K I S C K A S
G Y T F T T A G M Q W V Q K M P G K G F K W I G W I N T H S G E P K
Y A E D F K G R F A F S L E T S A S T A Y L Q I S N L K N E D T A T
Y F C A R M G G Y A M D Y W G Q G T S V T V S S A K T T P P S
F
M D M R T P A Q F L G I L L L W F P G I K C D I K L T Q S P S S M Y
A S L G E R V T I T C K A S E D I N S Y L S W F Q Q K P G K S P K T
L I Y R A N R L V D G V P S R F S G S G S G Q D Y S L T I S S L E Y
E D M G I Y Y C L Q Y D E F P L T F G A G T K L E L T R A D A A P T
V S I F P P S S E Q L T S G G A S V V C F L N N F Y P K D I N V K W
K I D G S E R Q N G V L N S W T D Q D S K D S T Y S M S S T L T L T
K D E Y E R H N S Y T C E A T H K T S T S P I
G
M D W V W T L L F L I A A A Q S A Q A Q I Q L V Q S G P E L K K P G
E T V K I S C K A S G Y T F T E Y P M H W V K Q A P G K G F K W M G
M I V T D T G E P T Y V E E F K G R F A F S L E T S A S T A Y L Q I
N N L K N E D T A T Y F C V G G Y L F S Y W G Q G T L V T V S A A K
T T P P S V Y P L A P G S A A Q T N S M V T L G C L V K G Y F P E P
V T V T W N S G S L S S G V H T F P A V L Q S D L Y T L S S S V T V
P S S T W P S Q T V T C N V A H P A S
H
M E S Q T Q V F L S L L L W V S G T C G N I M M T Q S P S S L A V S
A G E K V T M S C K S S Q S V L Y S S N Q K N Y L A W Y Q Q K P G Q
S P K L L I Y W A S T R E S G V P D R F I G S G S G T D F T L T I T
N V Q A E D L A V Y Y C H Q Y L S S Y T F G G G T K L E I K R A D A
A P T V S I F P P S S E Q L T S G G A S V V C F L N N F Y P K D I N
V K W K I D G S E R Q N G V L N S W T D Q D S K D S T Y S M S S T L
T L T K D E Y E R H N S Y T C E A T H K T S T S P I

FIG. 7