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(54) **ANTI-ApoE ANTIBODIES AND POLYNUCLEOTIDES THEREOF**

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(57) **ABSTRACT**

Methods and compositions for preventing or treating cognitive decline associated with dementia and/or mild cognitive impairment and/or neurodegeneration using antibodies, peptides, fusion proteins, or genome editing systems that modulate HSPG/heparin binding affinities of ApoE.

**22 Claims, 58 Drawing Sheets**

**Specification includes a Sequence Listing.**

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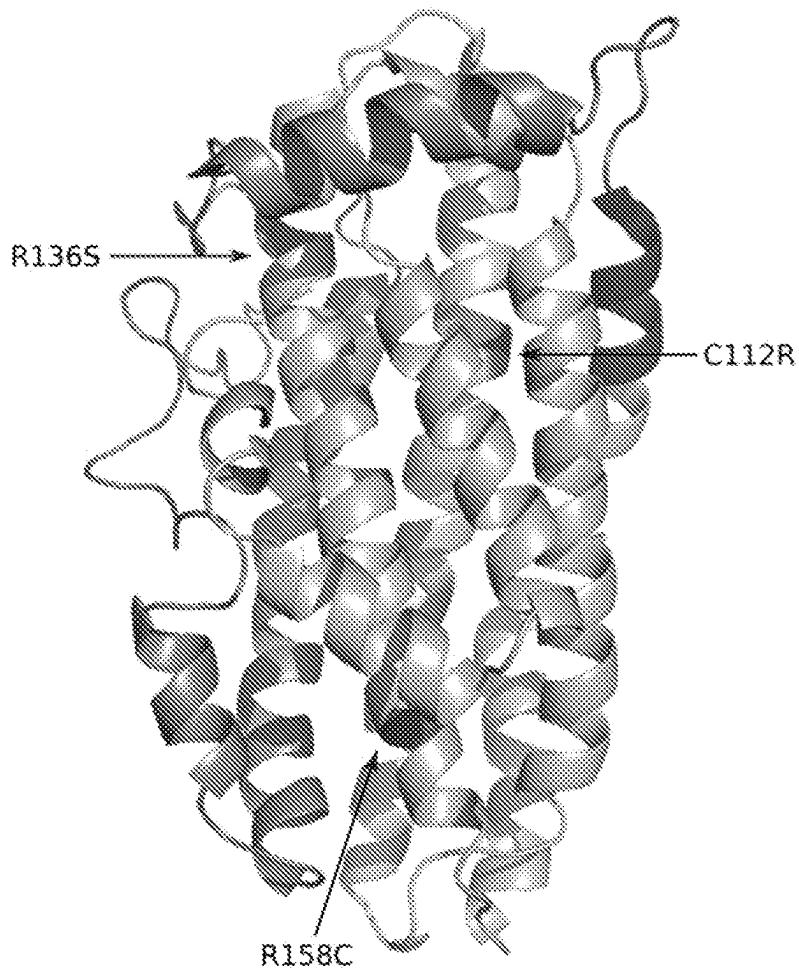
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\* cited by examiner



**FIG. 1**

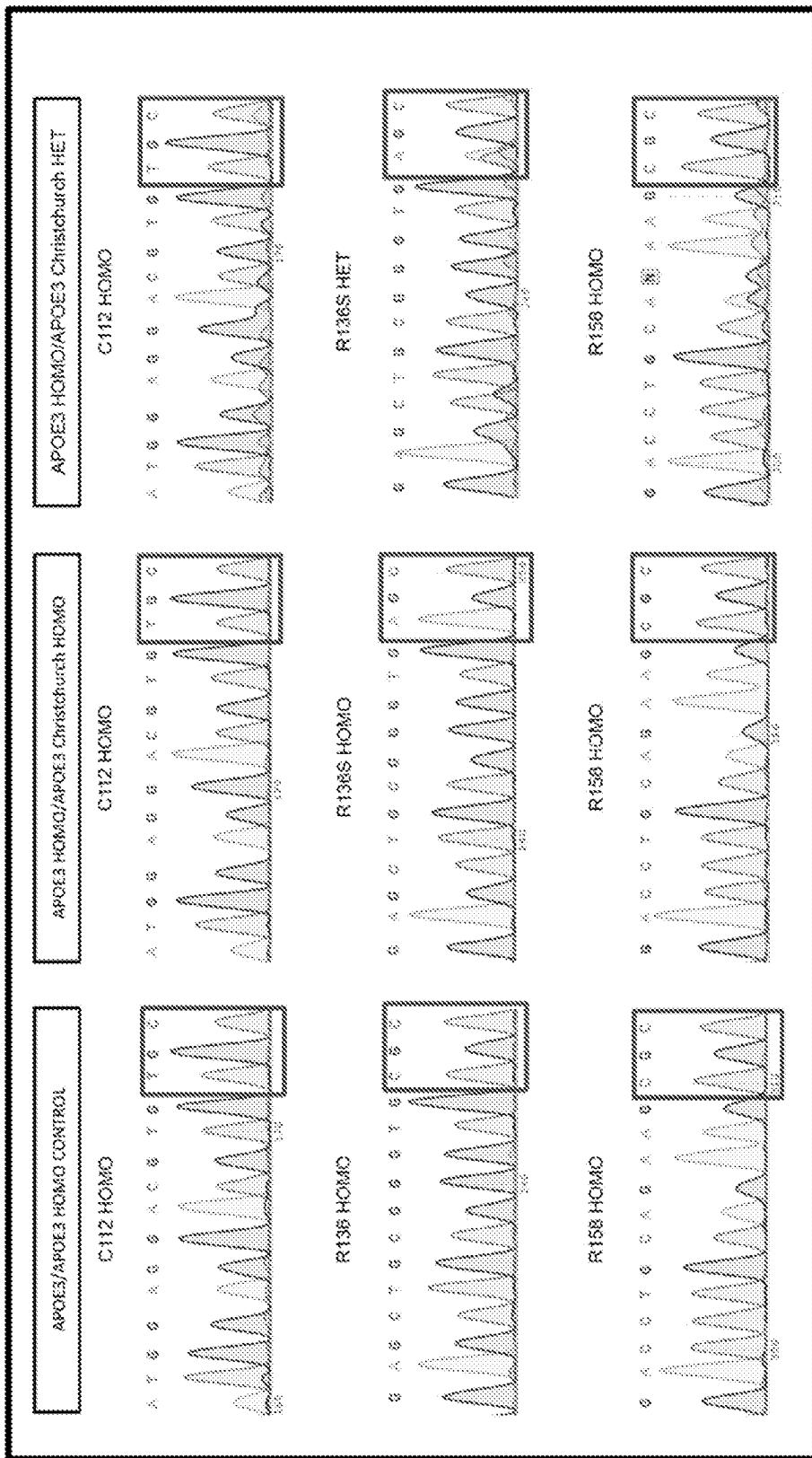


FIG. 2

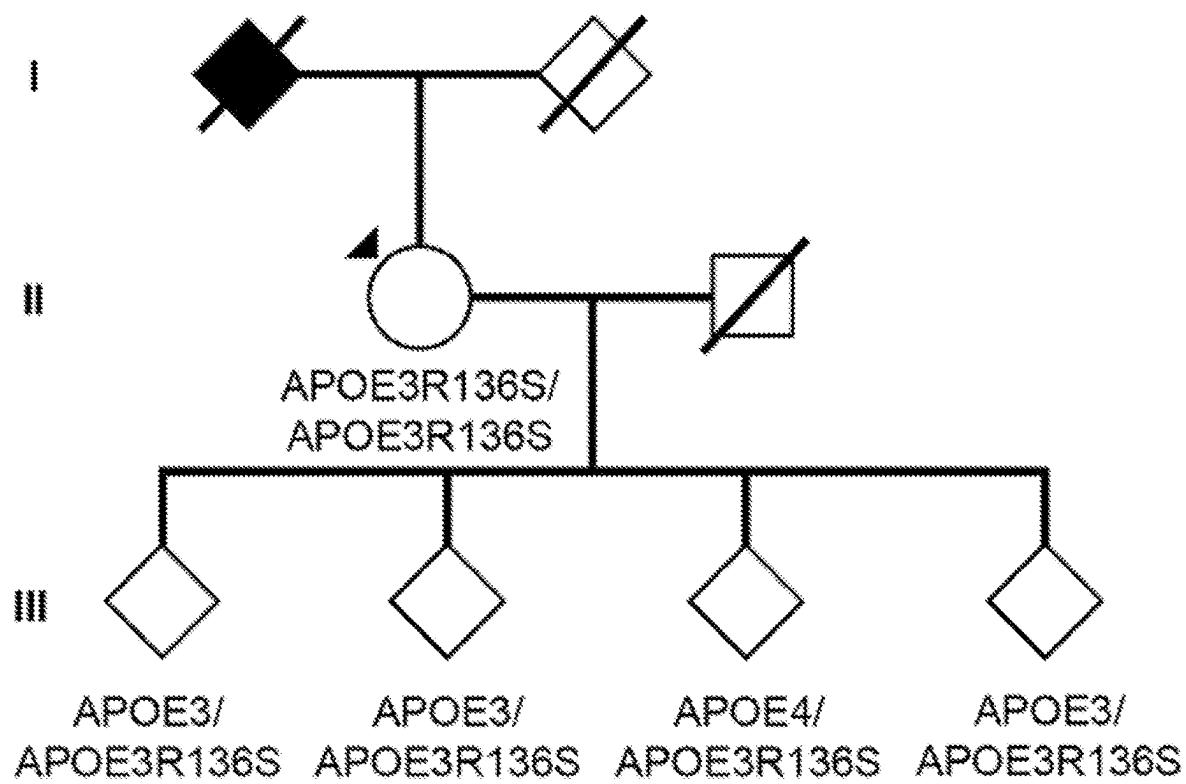
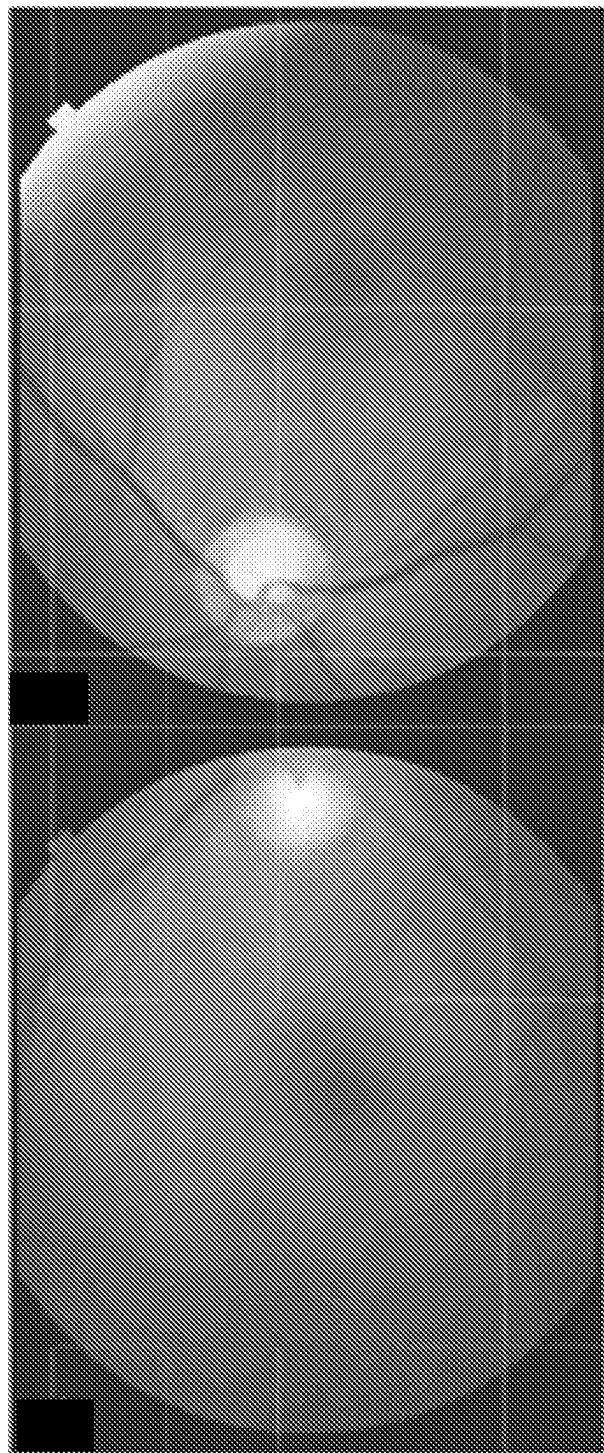
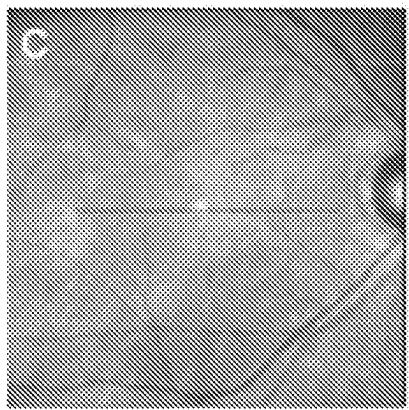
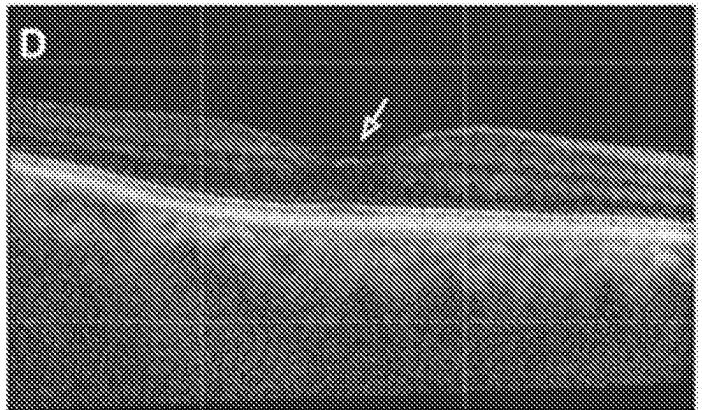
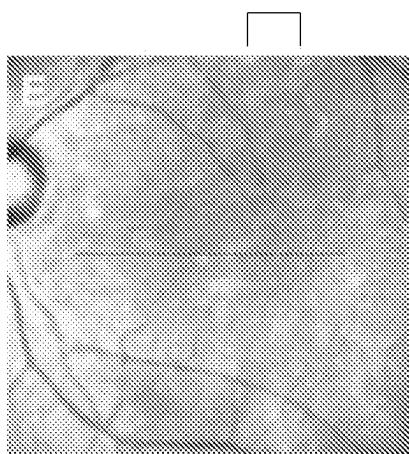
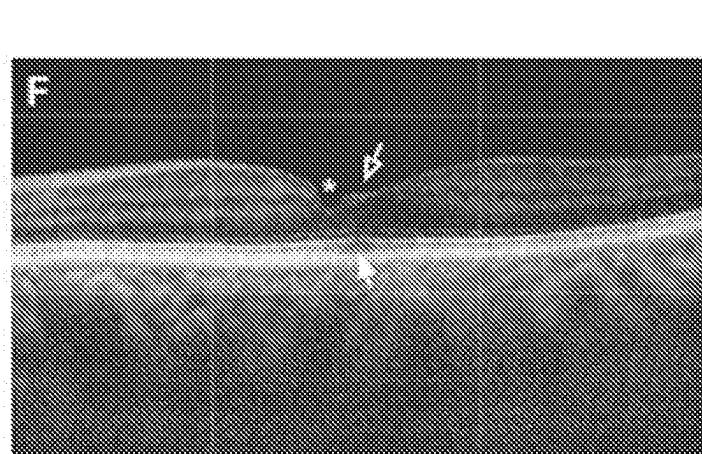


FIG. 3



**FIG. 4A**  
**FIG. 4B**

**FIG. 4C****FIG. 4D****FIG. 4E****FIG. 4F**

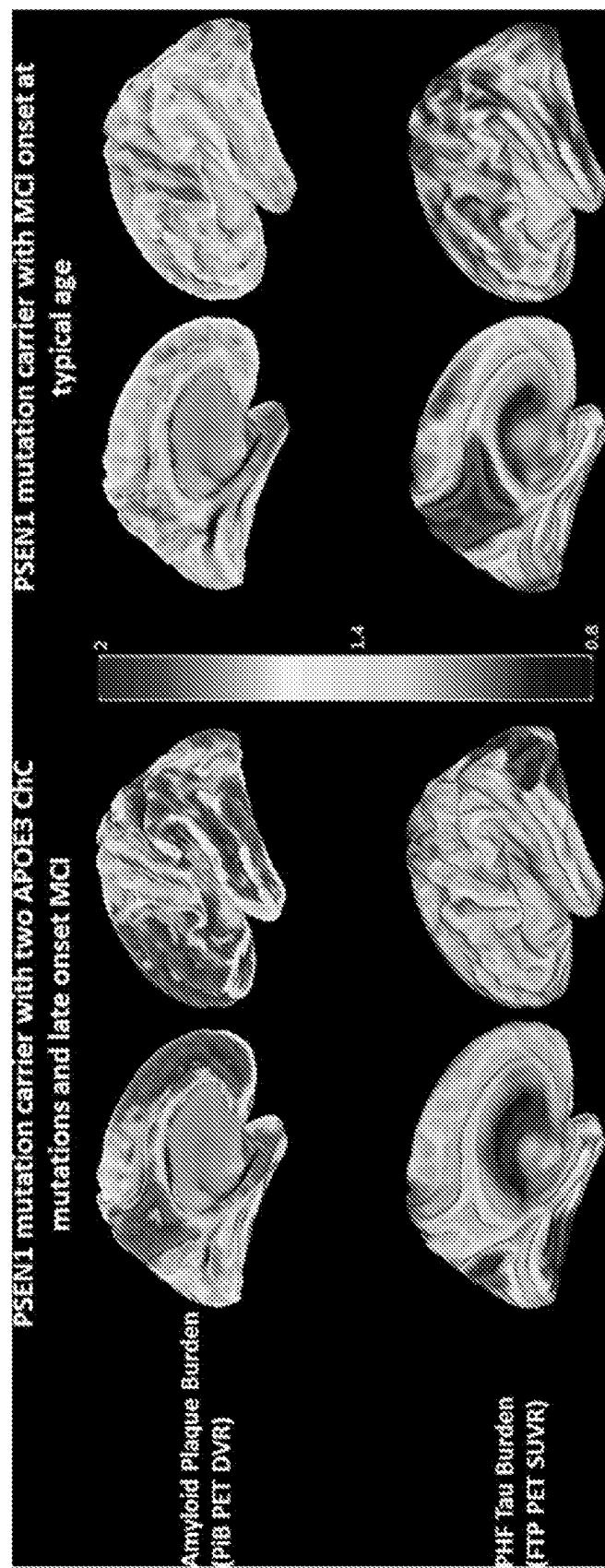


FIG. 5

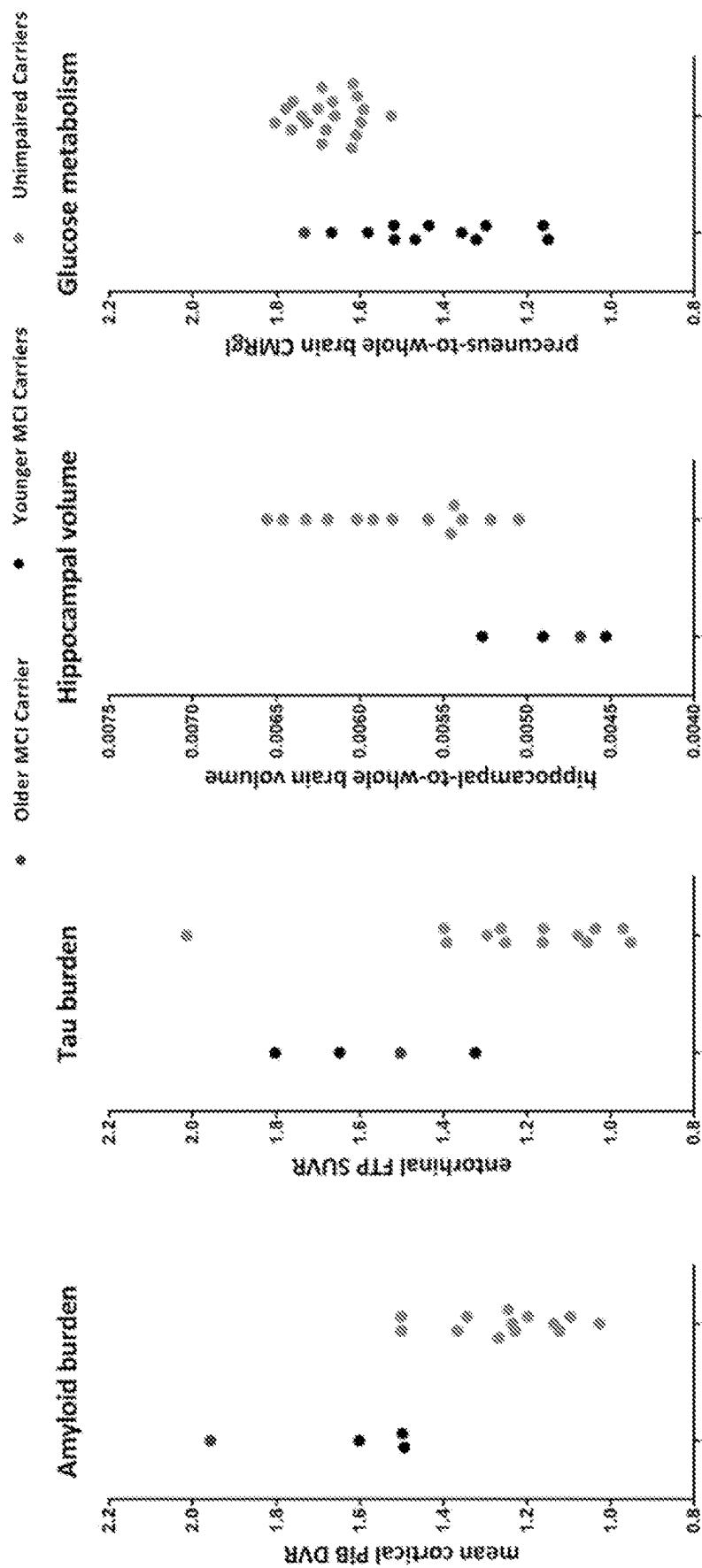


FIG. 6

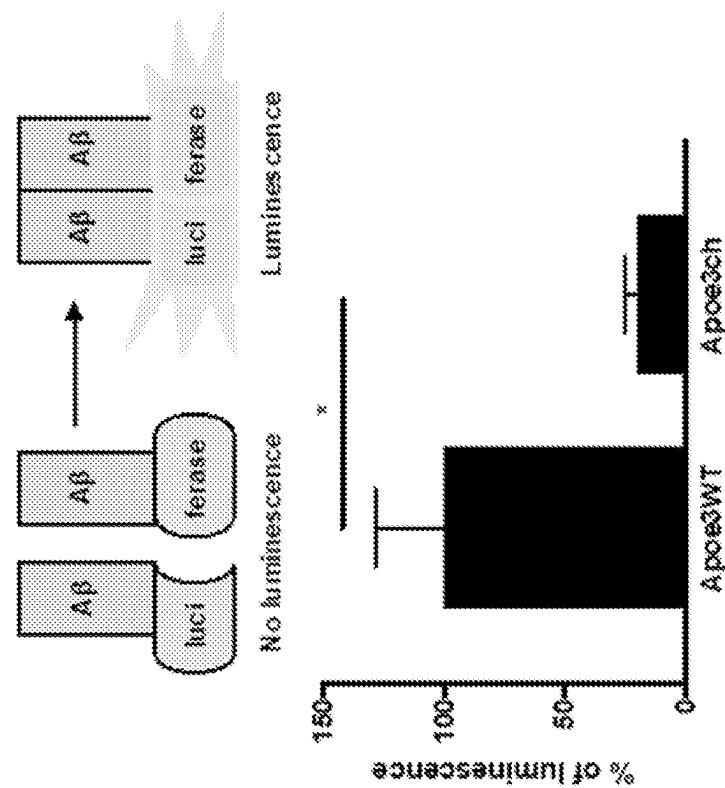


FIG. 8

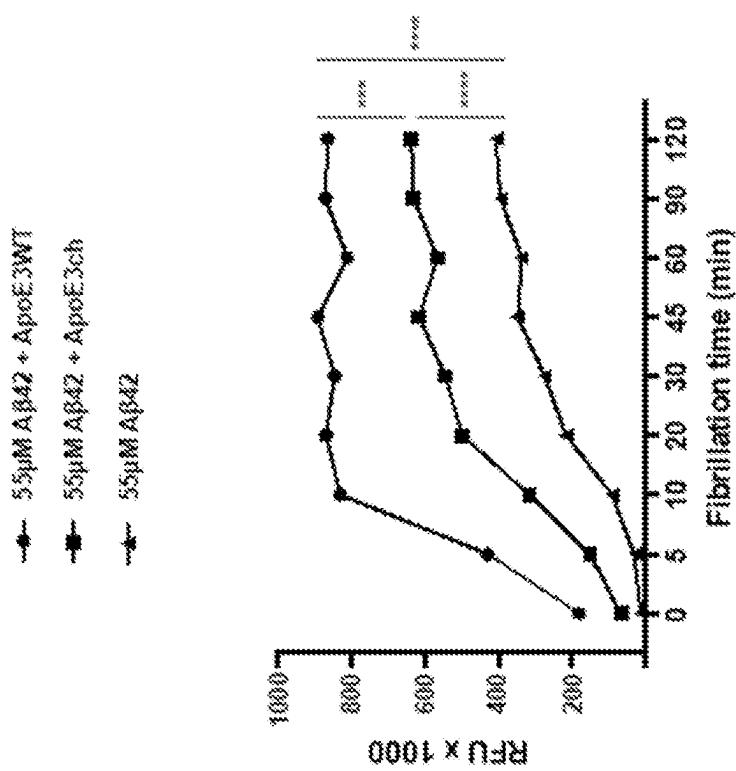


FIG. 7

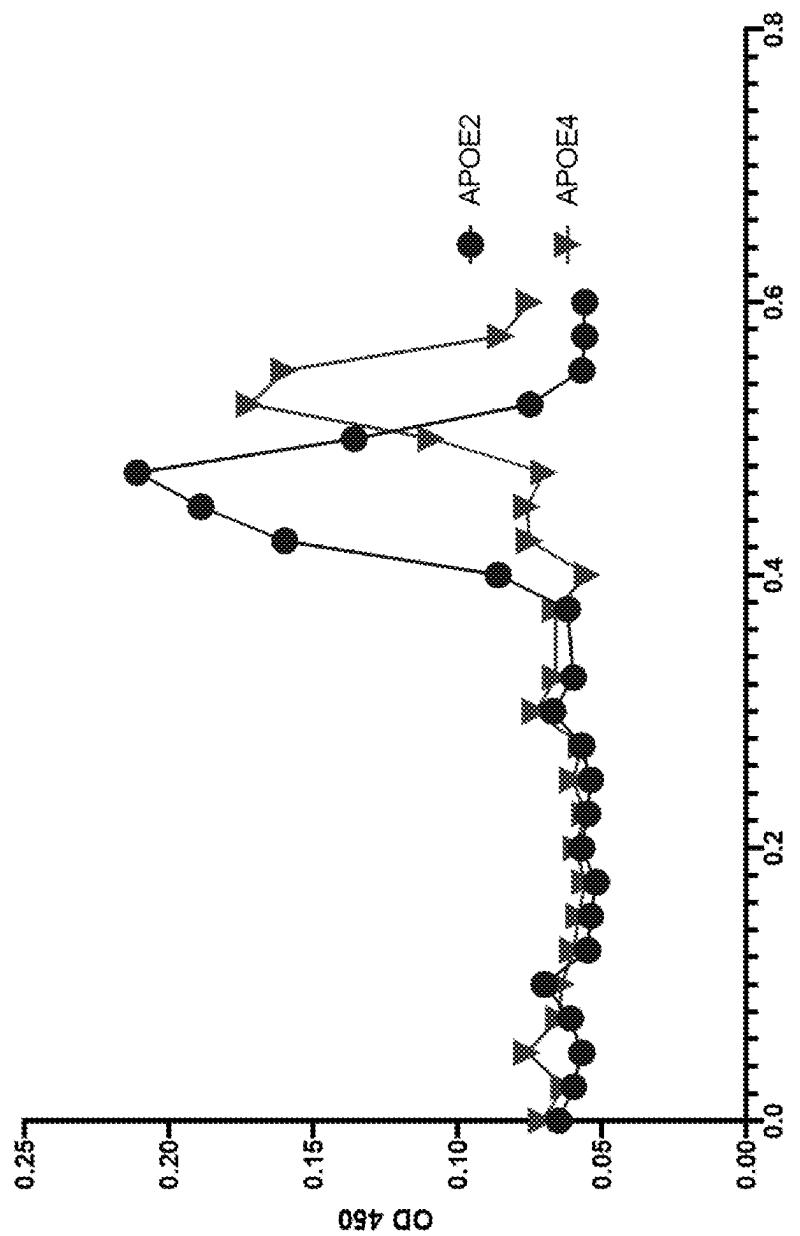


FIG. 9

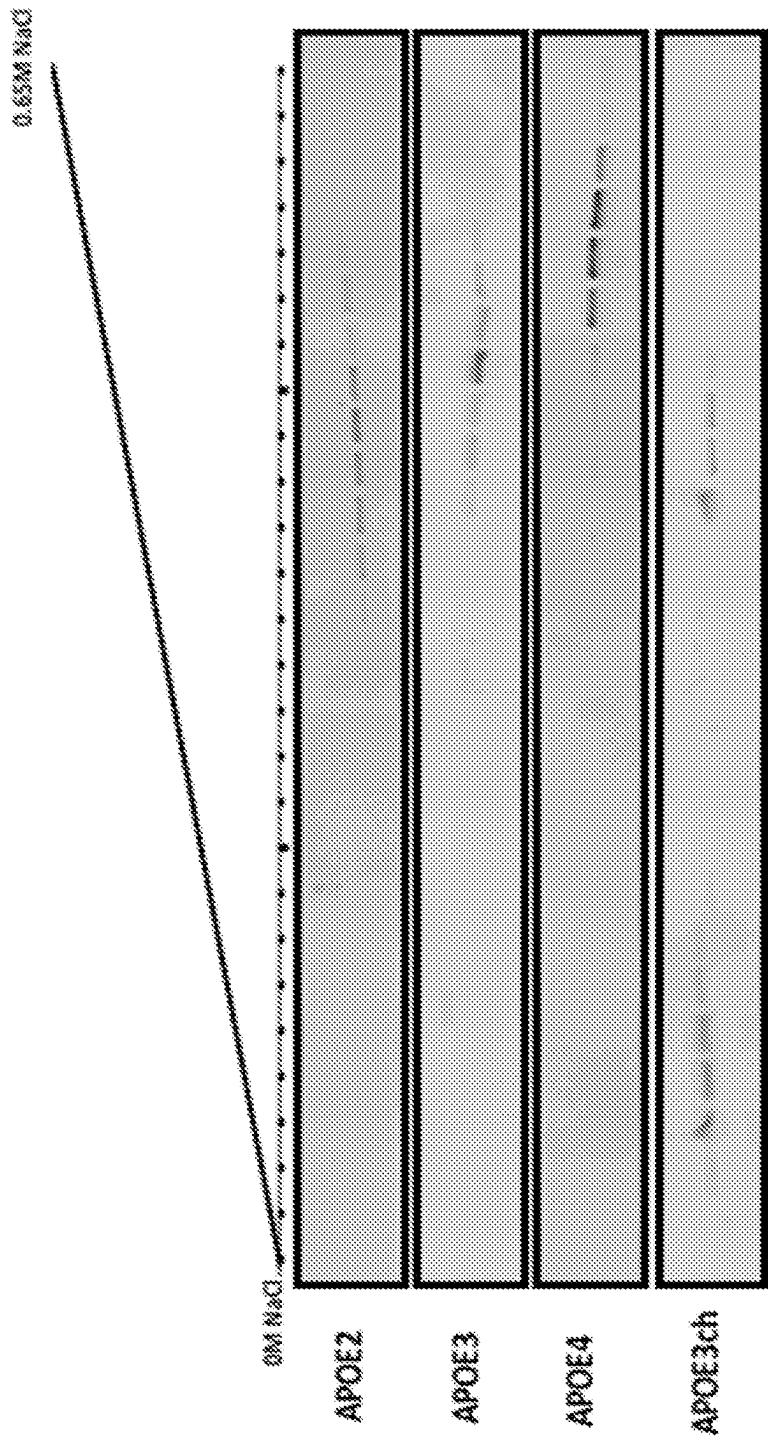


FIG. 10

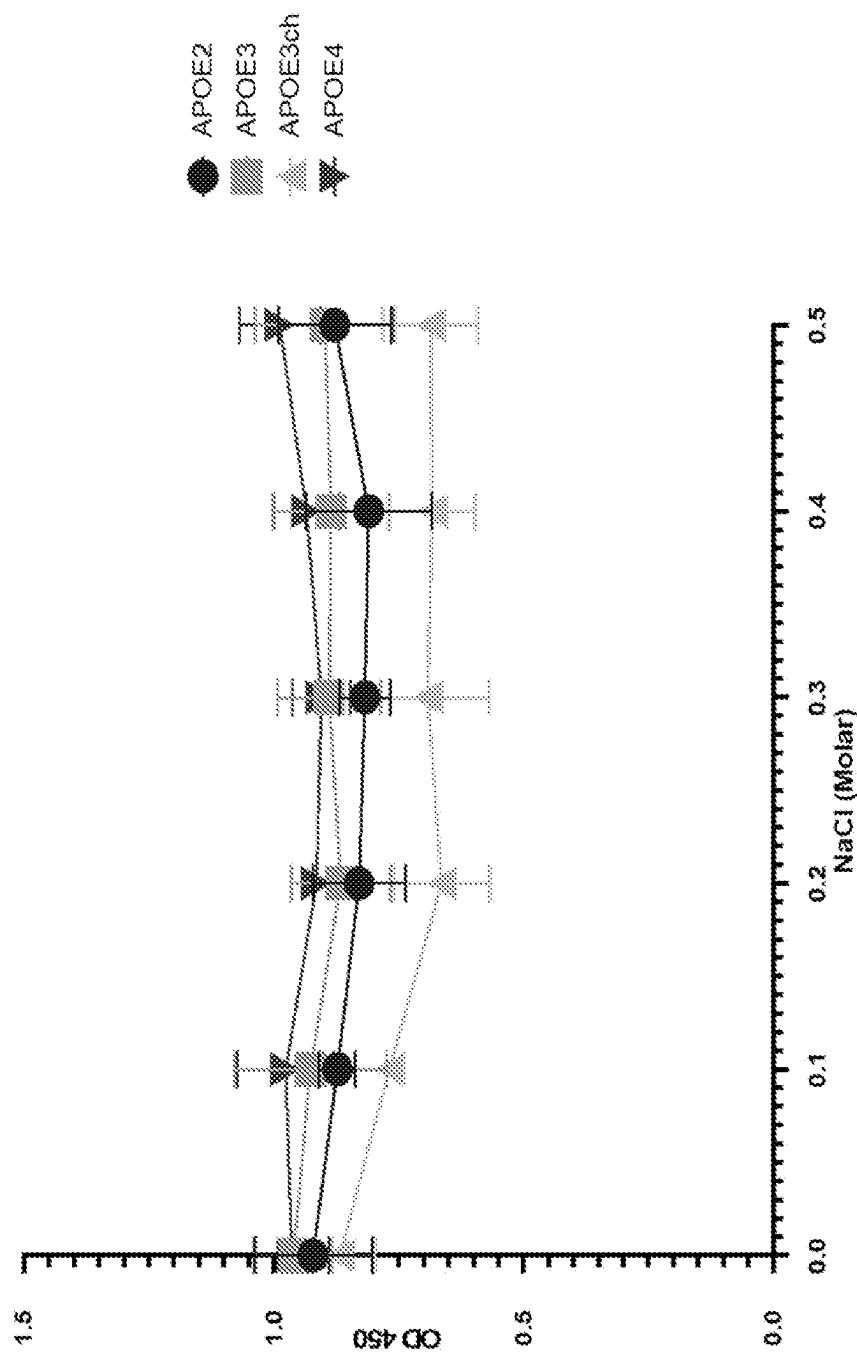


FIG. 11A

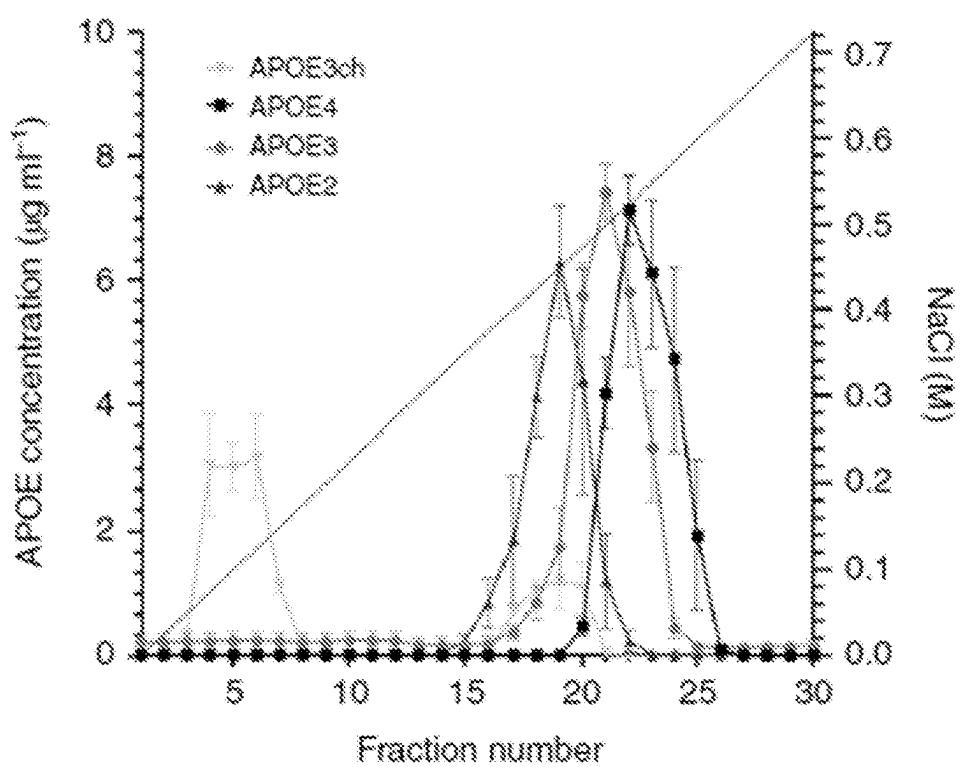
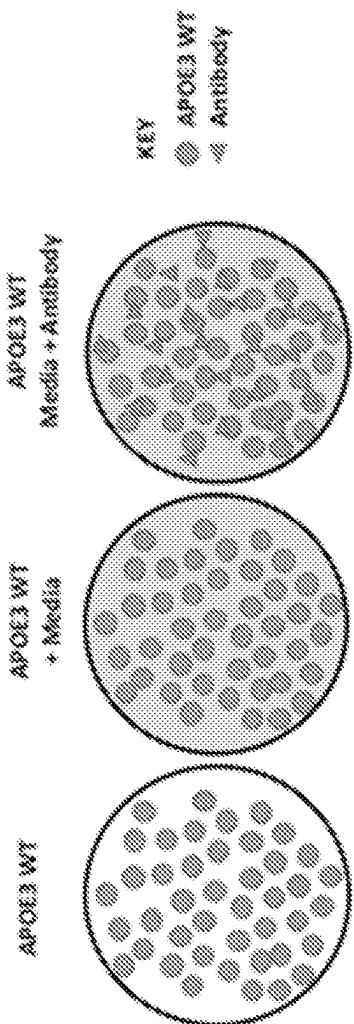
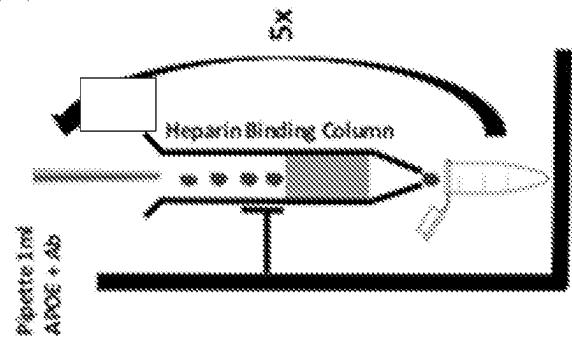
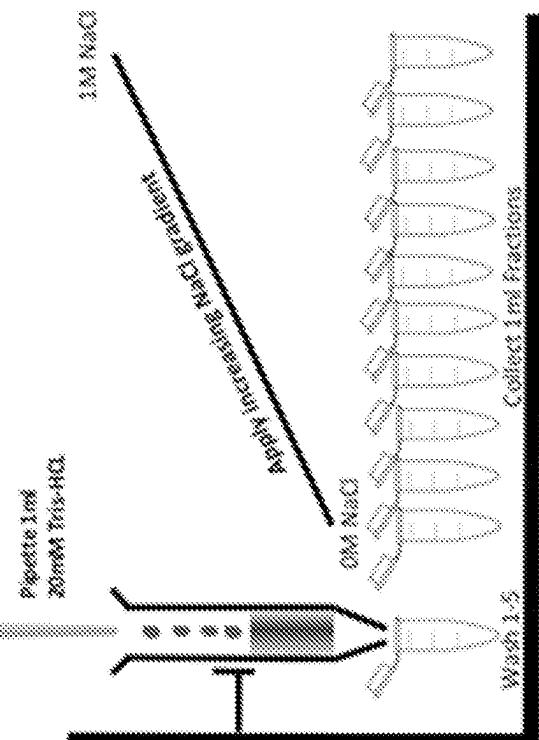


FIG. 11B

**FIG. 12A****FIG. 12B****FIG. 12C**

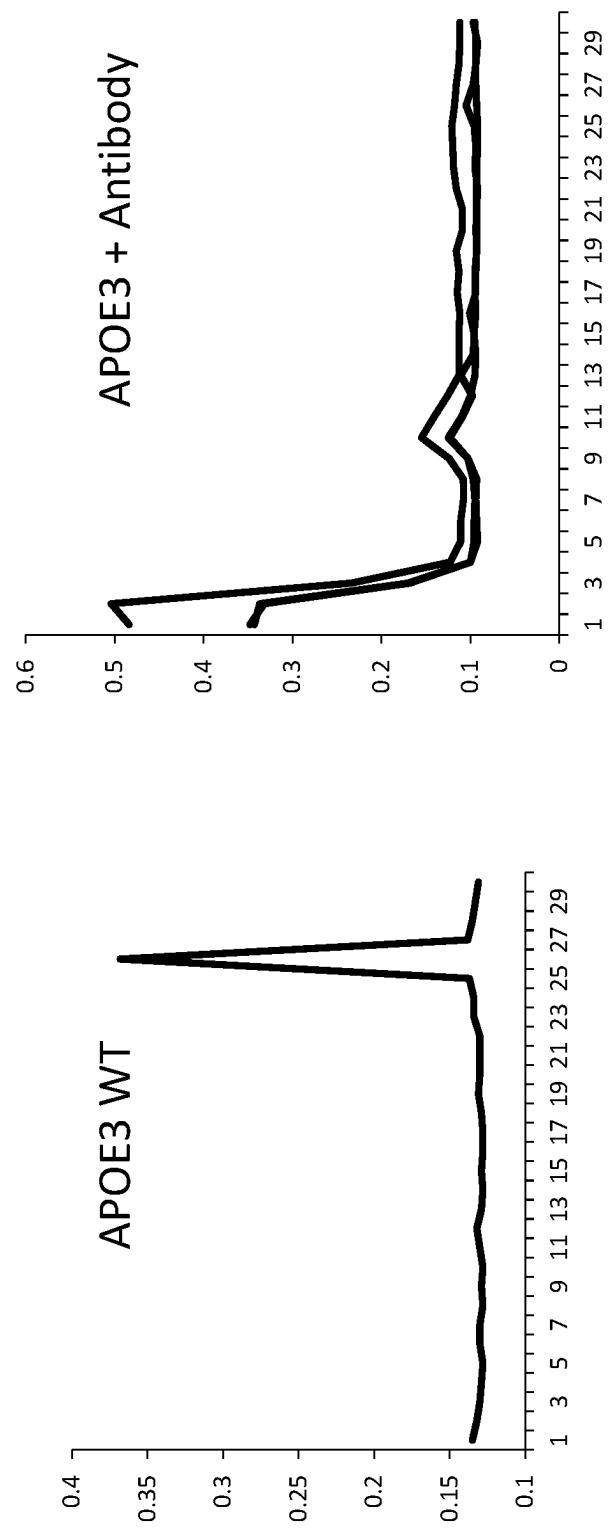


FIG. 13A

FIG. 13B

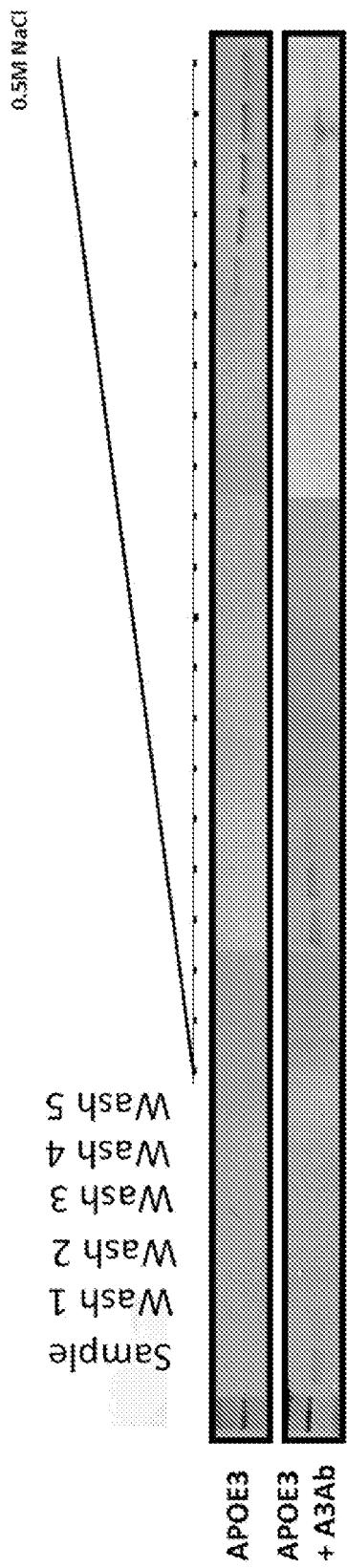


FIG. 14

19G10-2

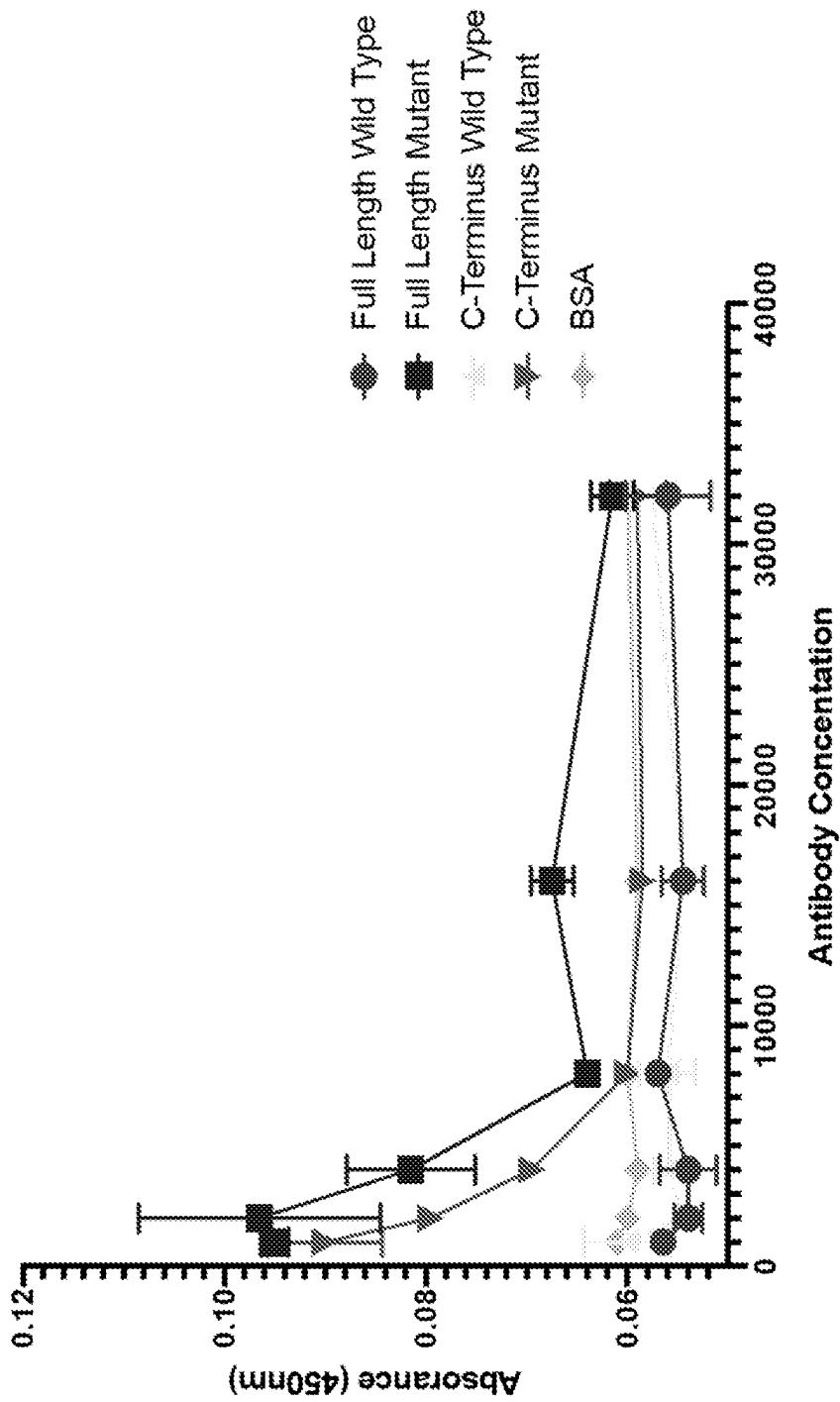


FIG. 15A

23B2

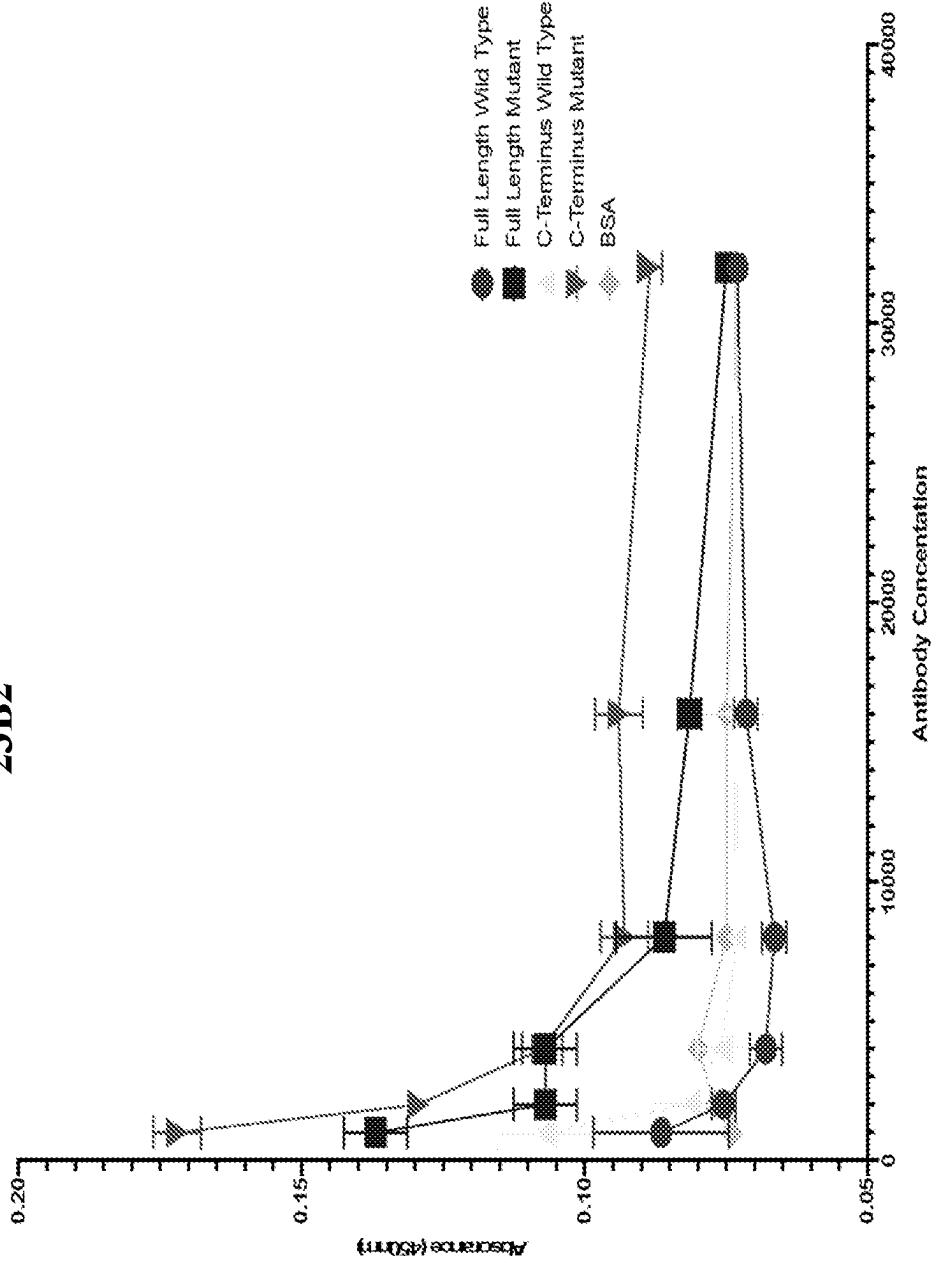


FIG. 15B

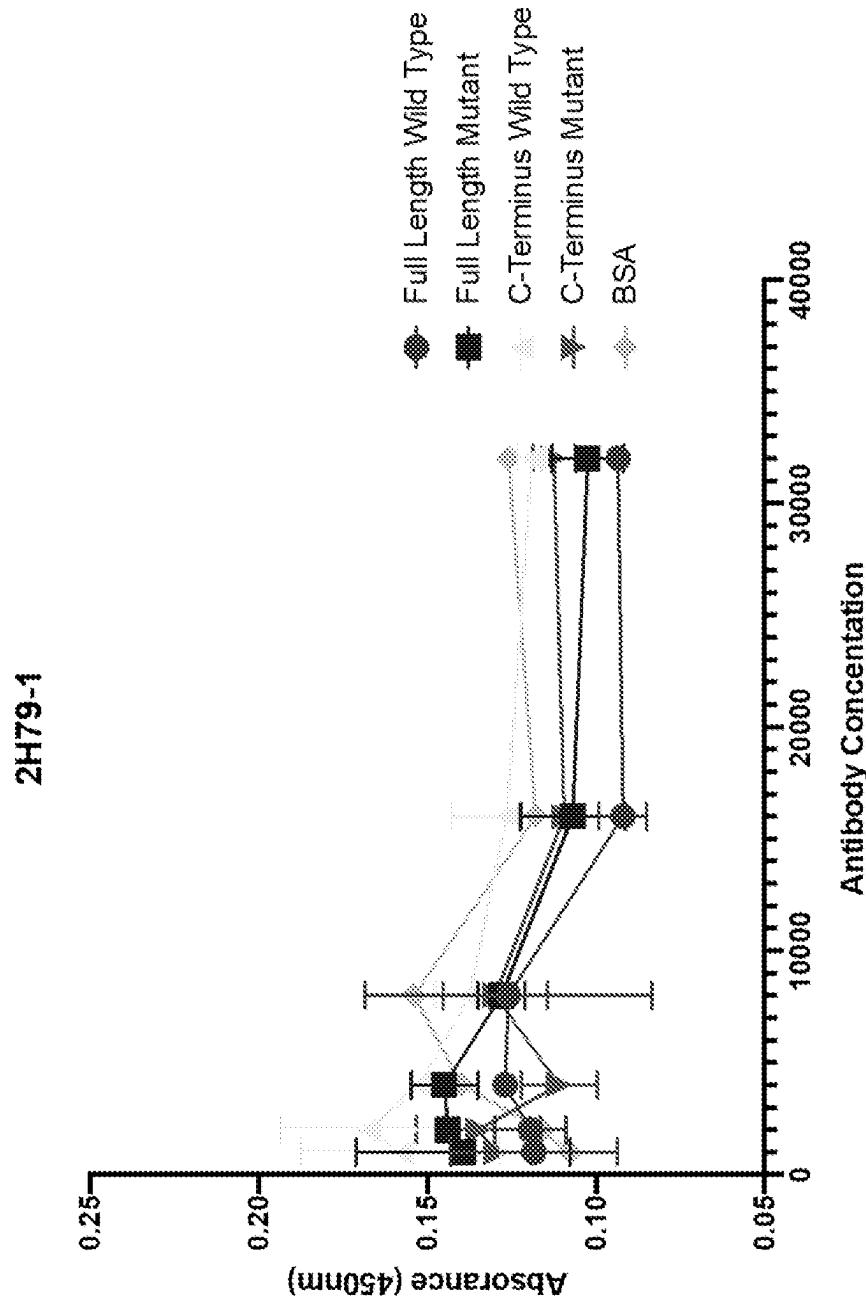


FIG. 15C

30E1-2

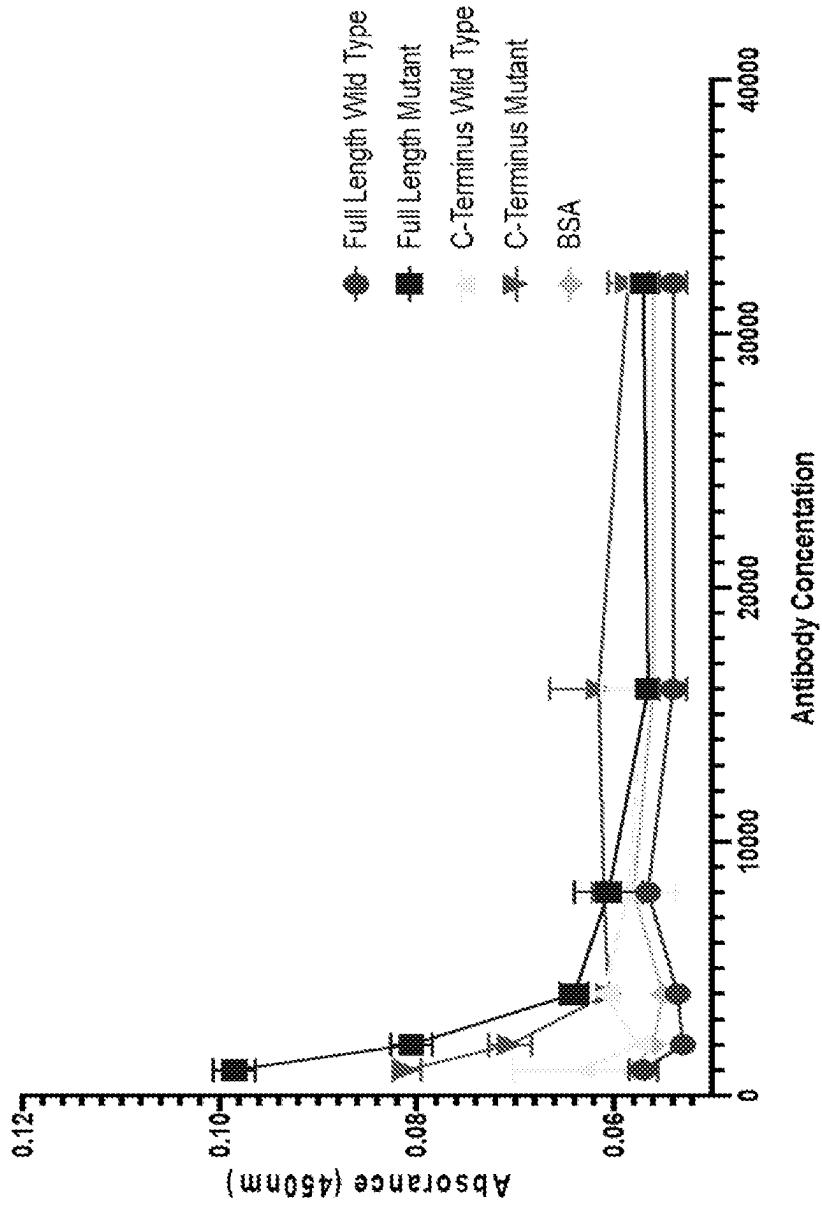


FIG. 15D

16H8

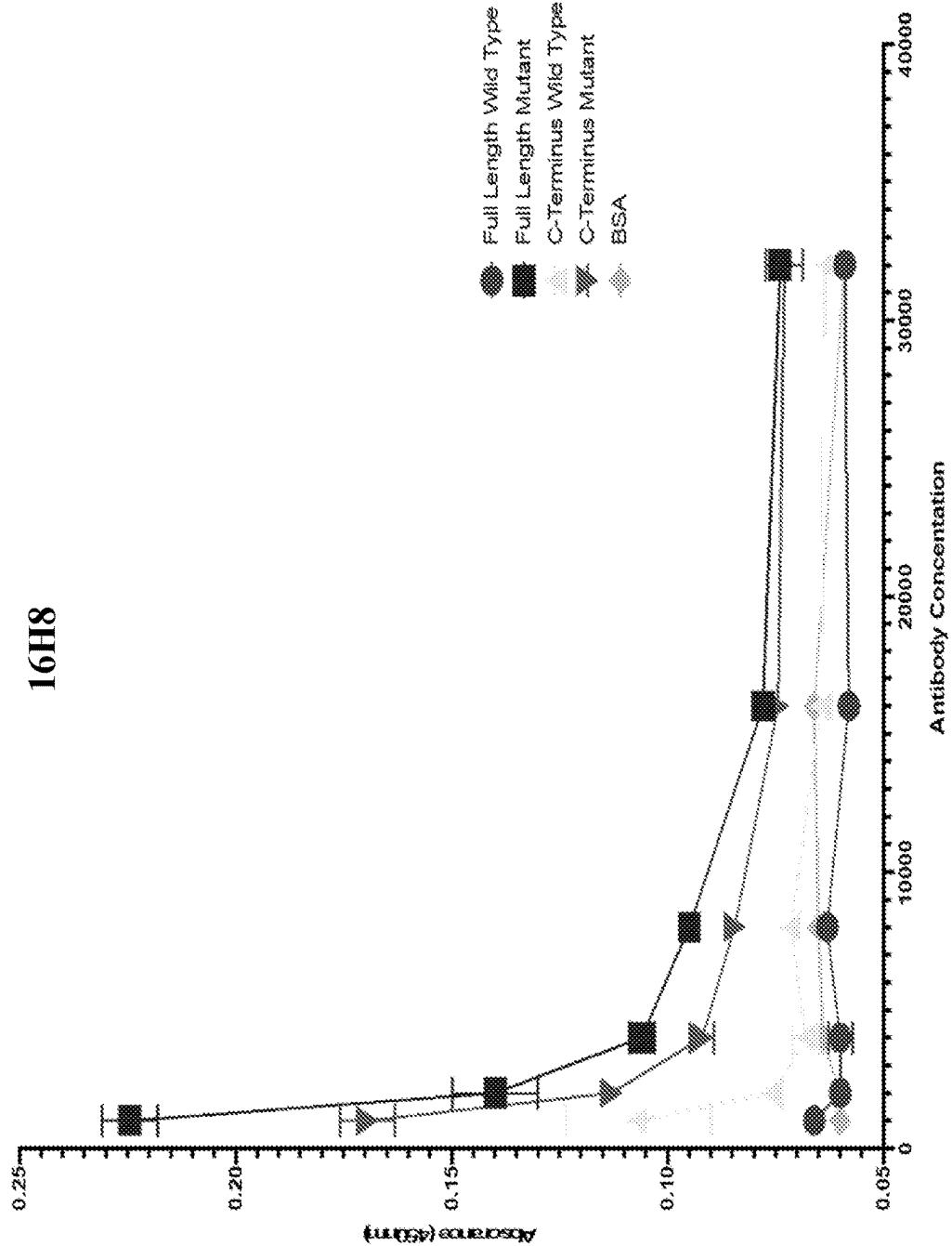


FIG. 15E

25F1-2

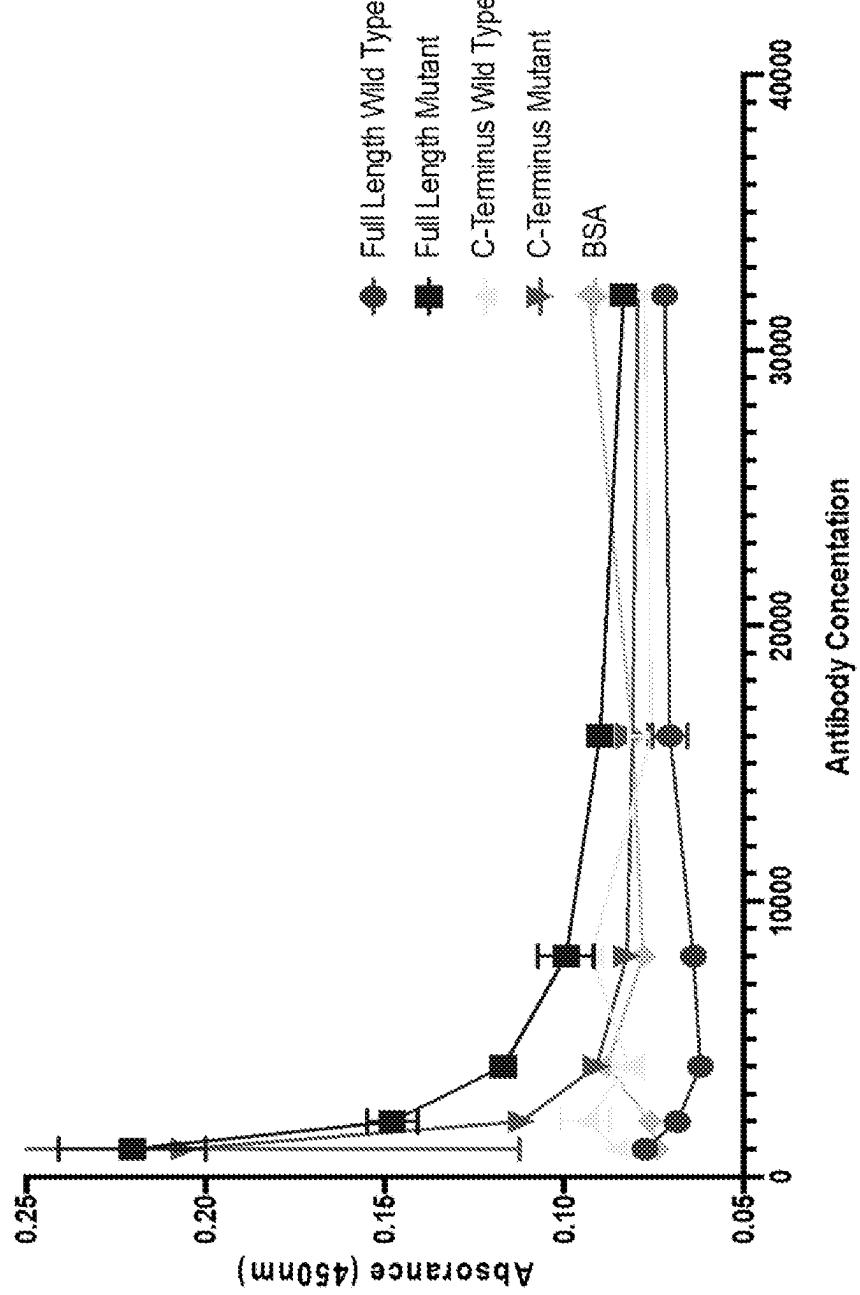


FIG. 15F

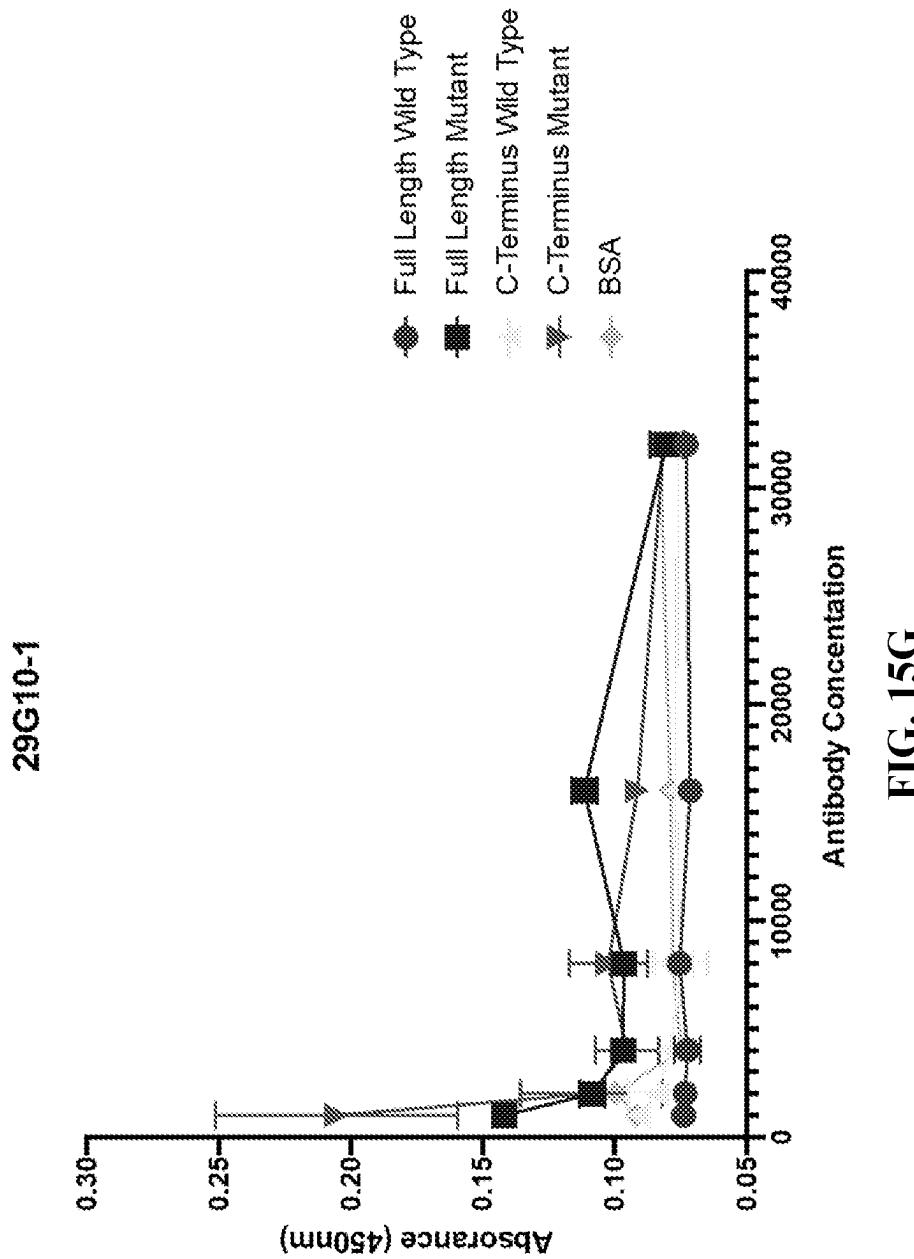


FIG. 15G

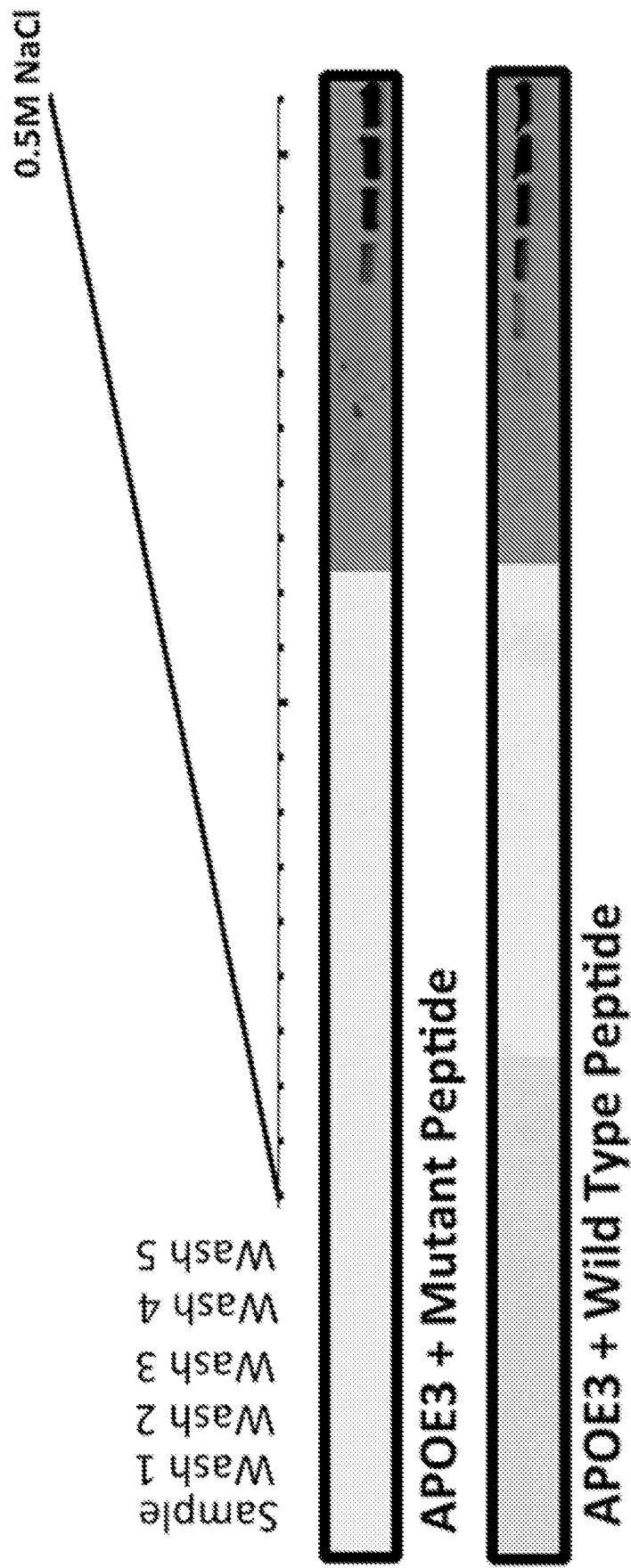


FIG. 16

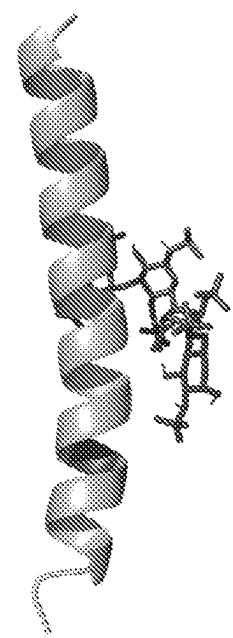


FIG. 17A

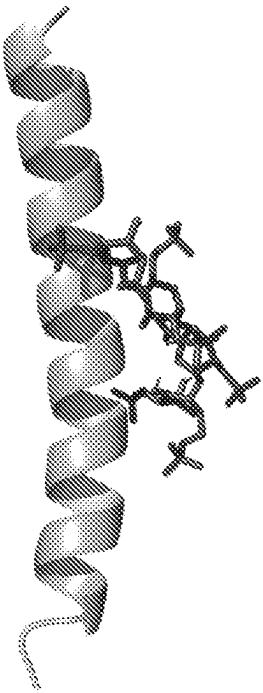


FIG. 17B

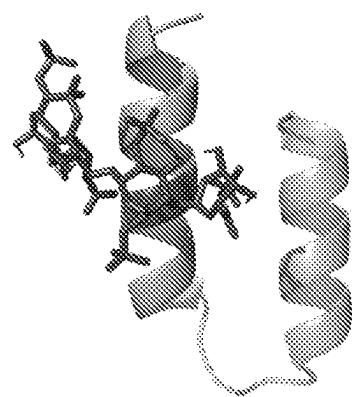


FIG. 17C

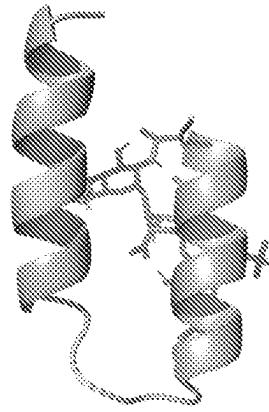


FIG. 17D

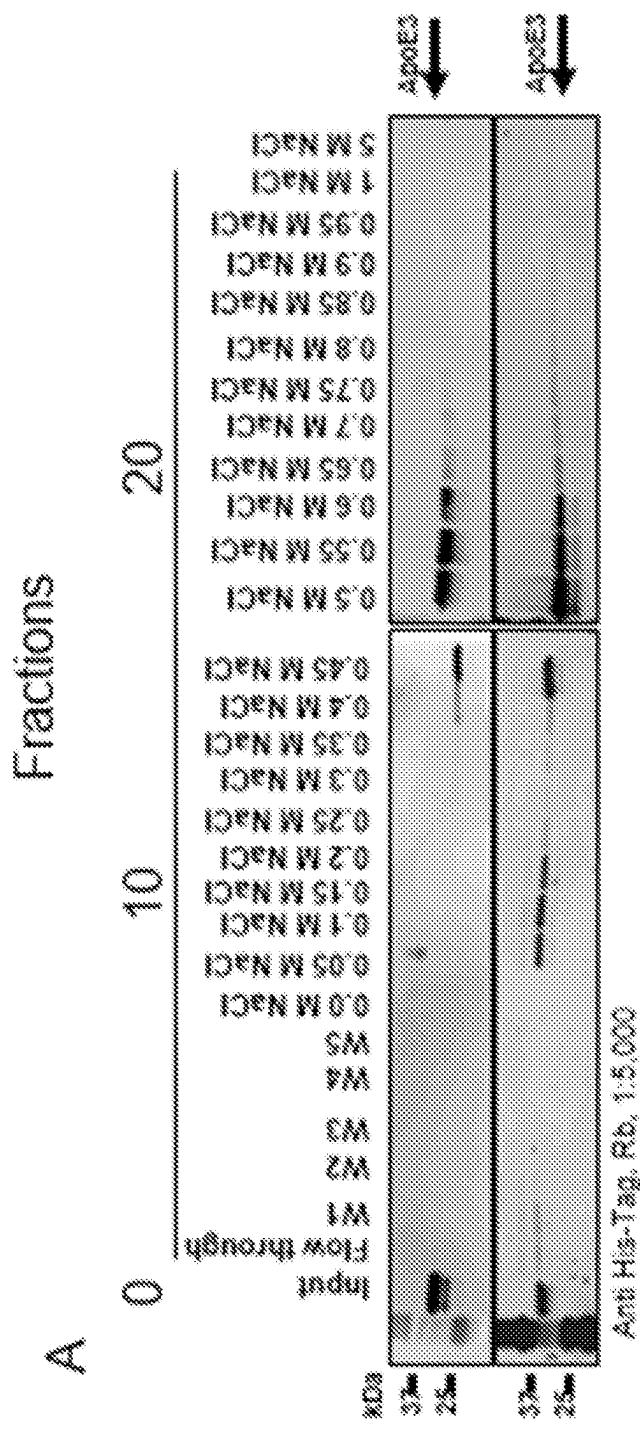


FIG. 18A

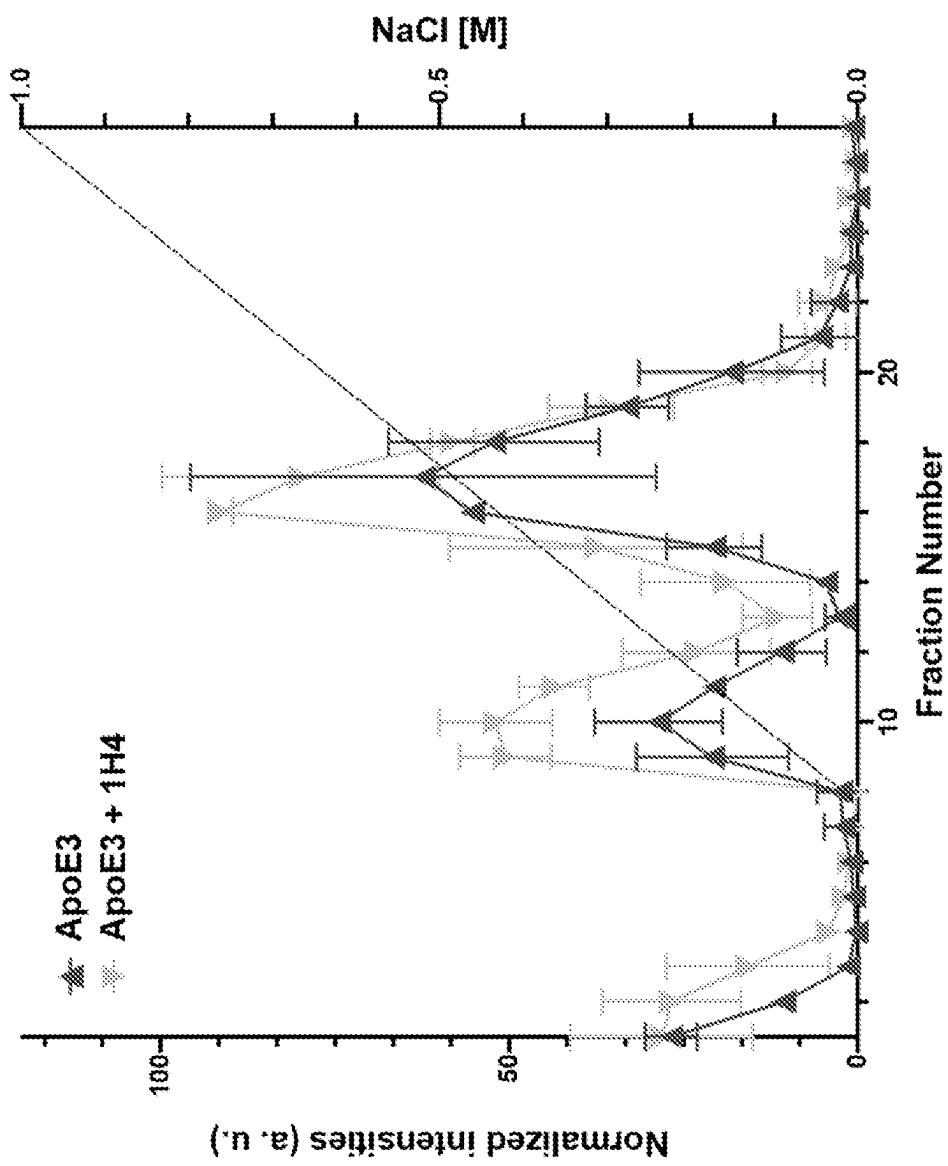


FIG. 18B

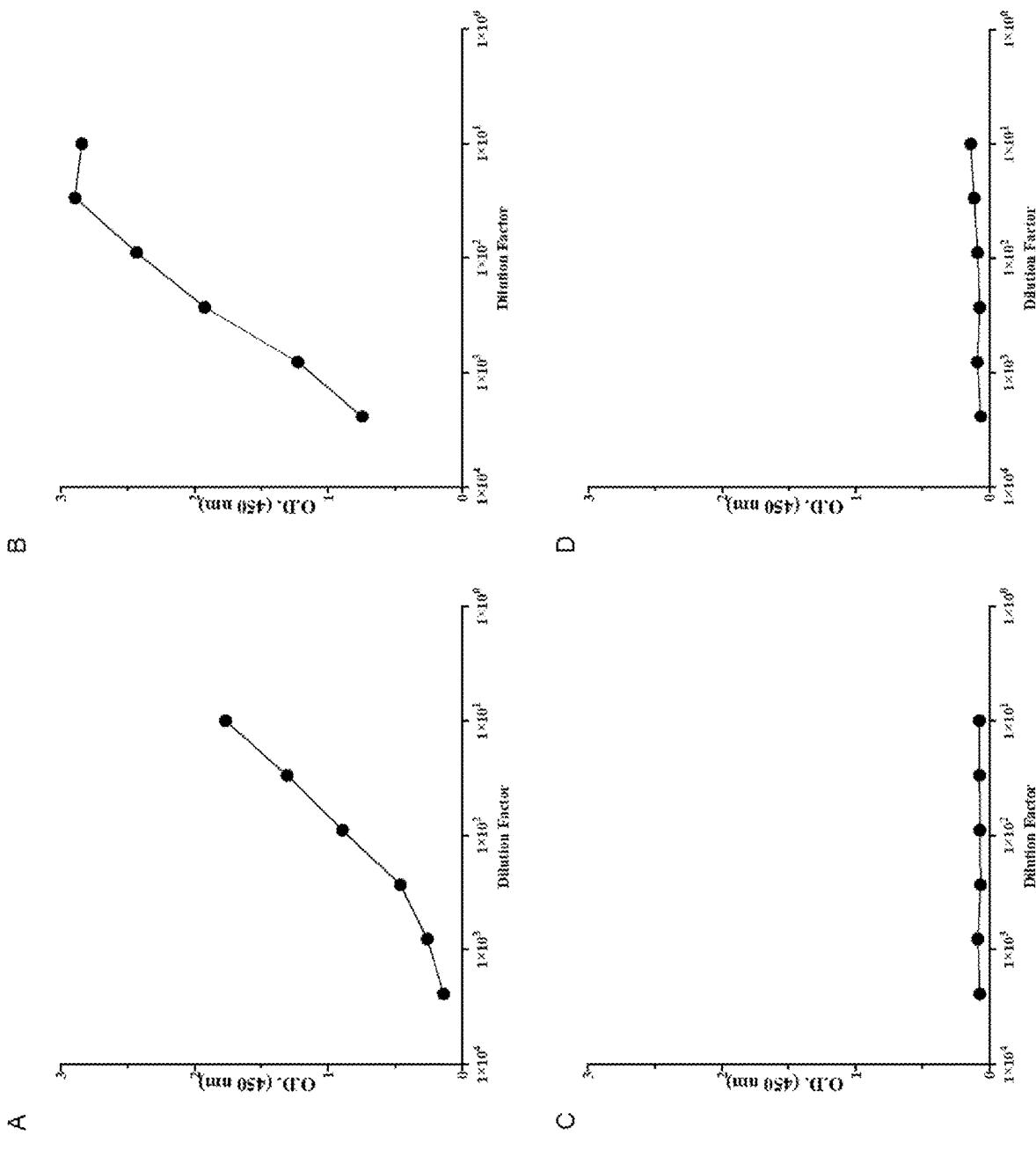


FIG. 19

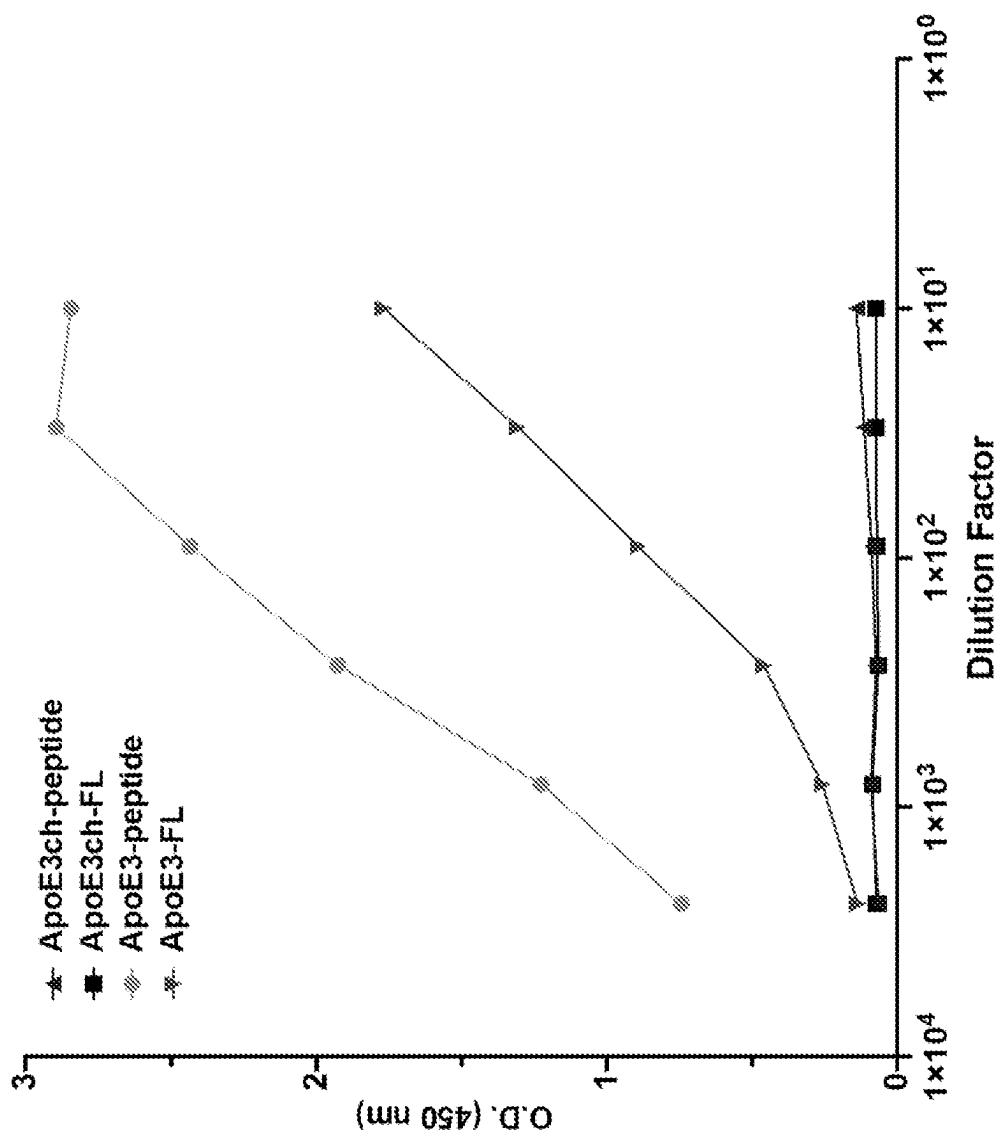


FIG. 20

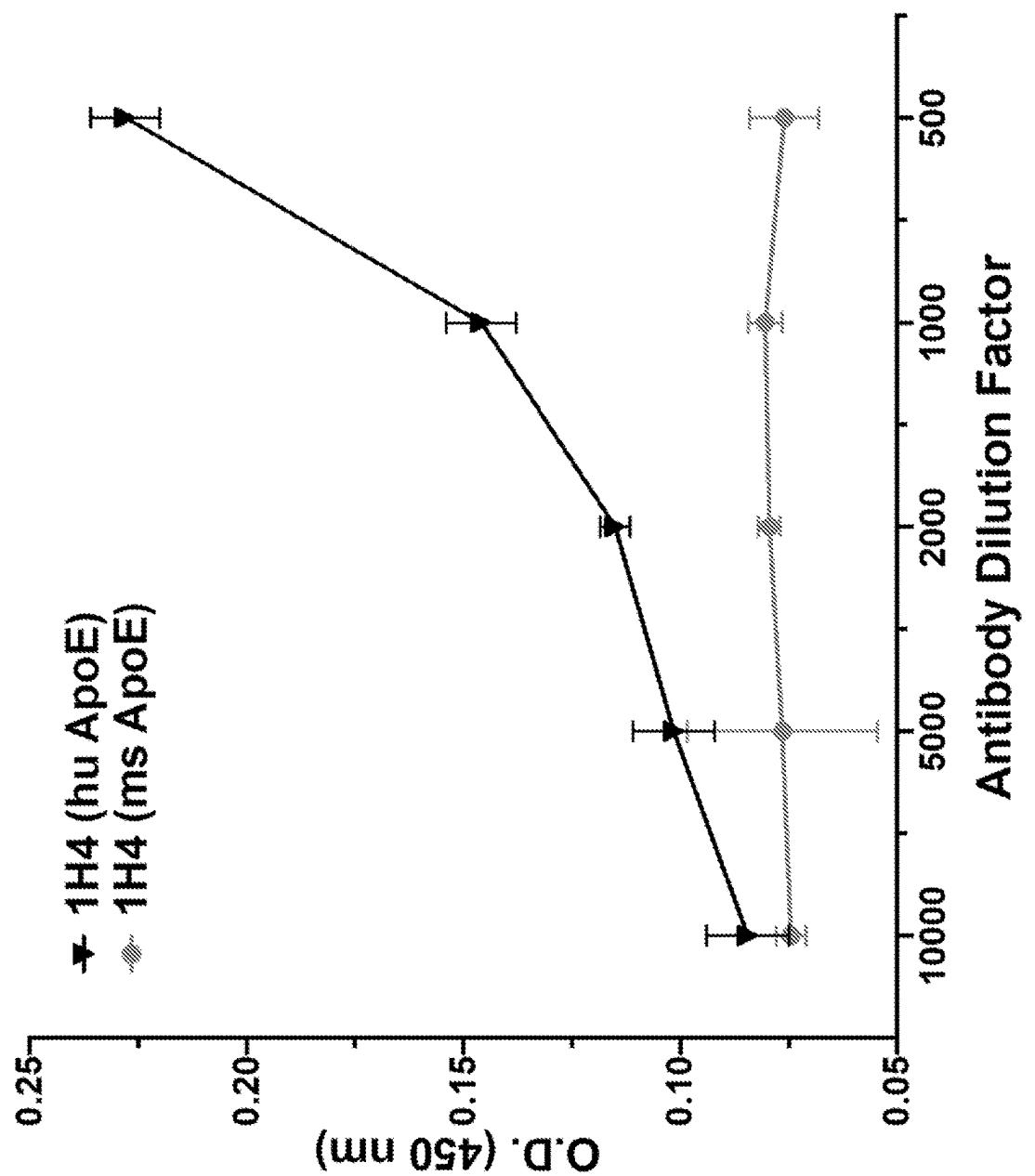


FIG. 21

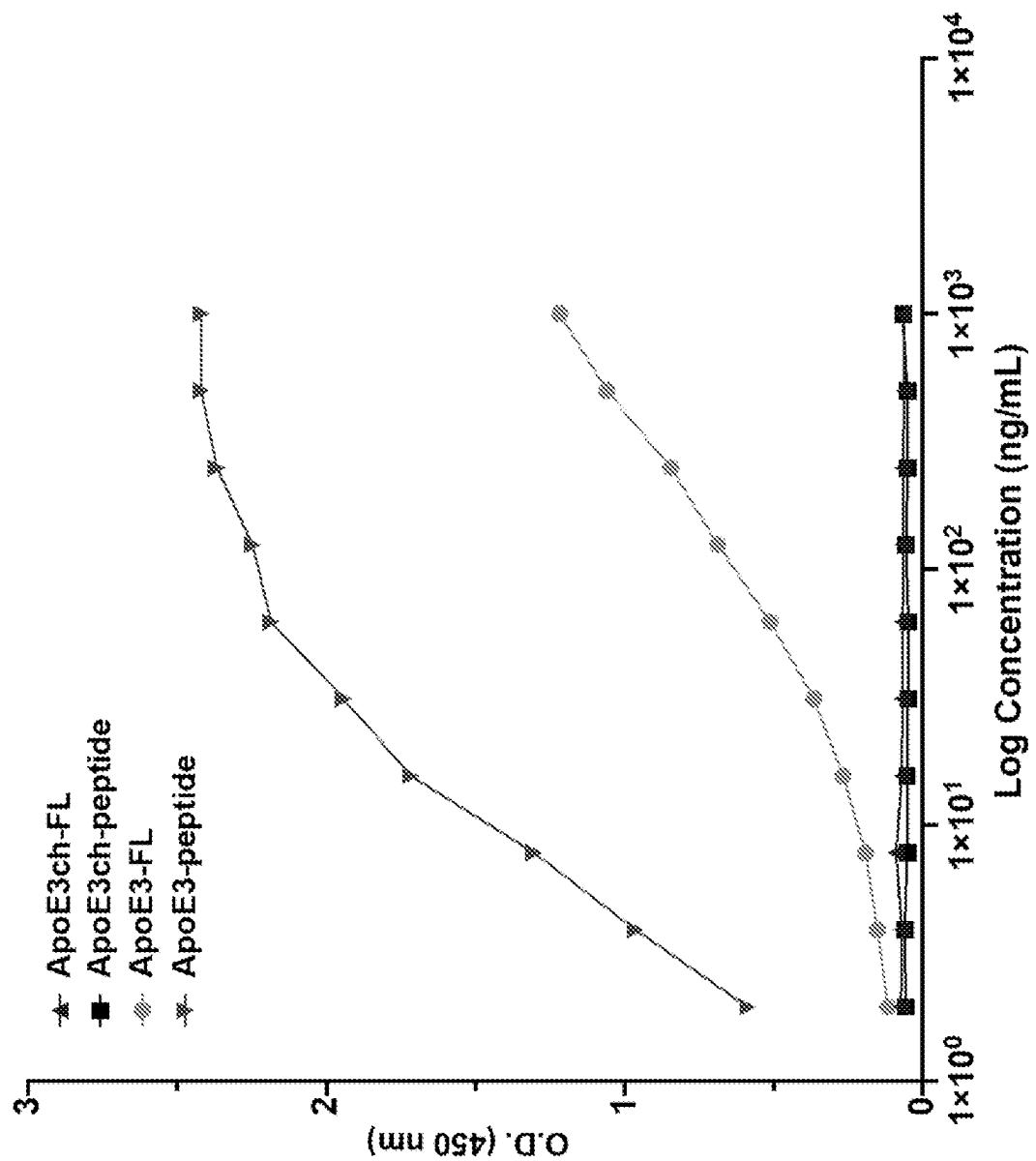


FIG. 22

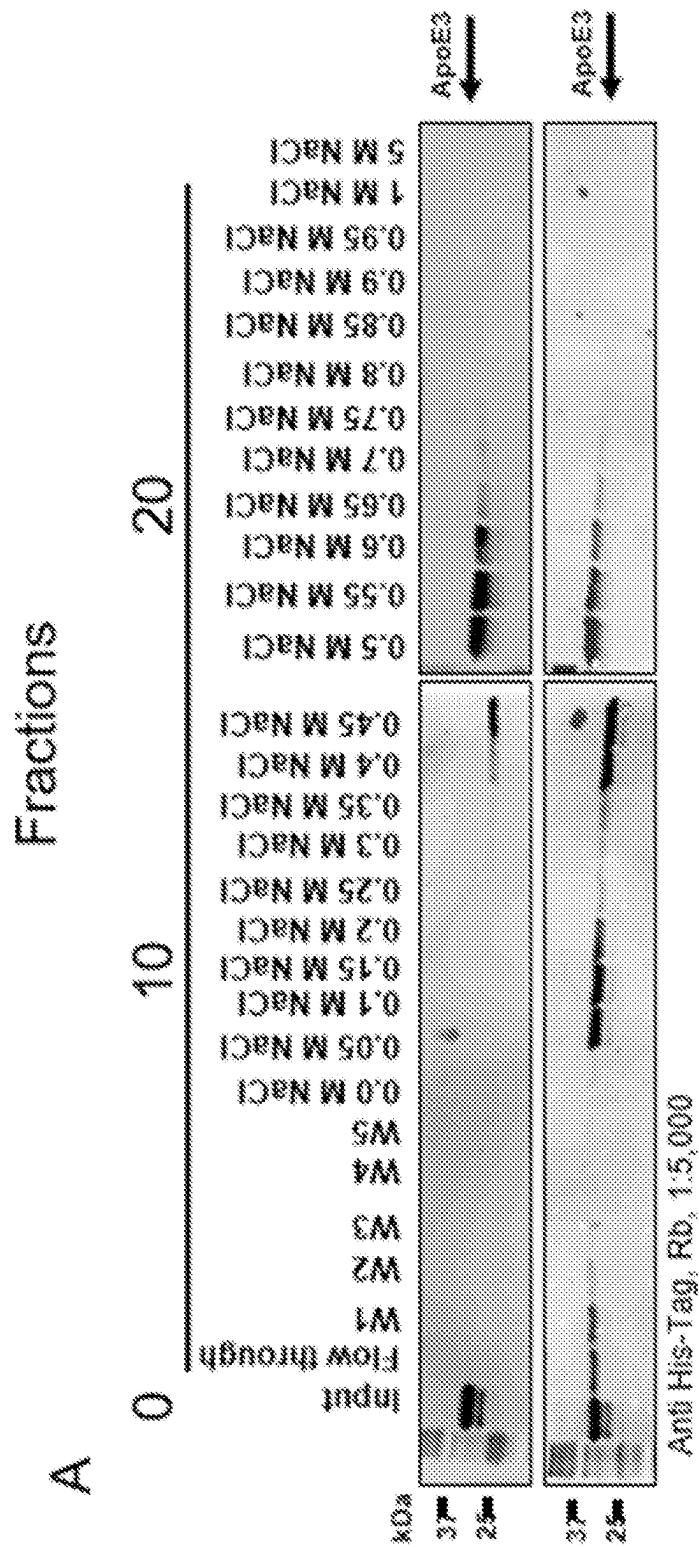


FIG. 23A

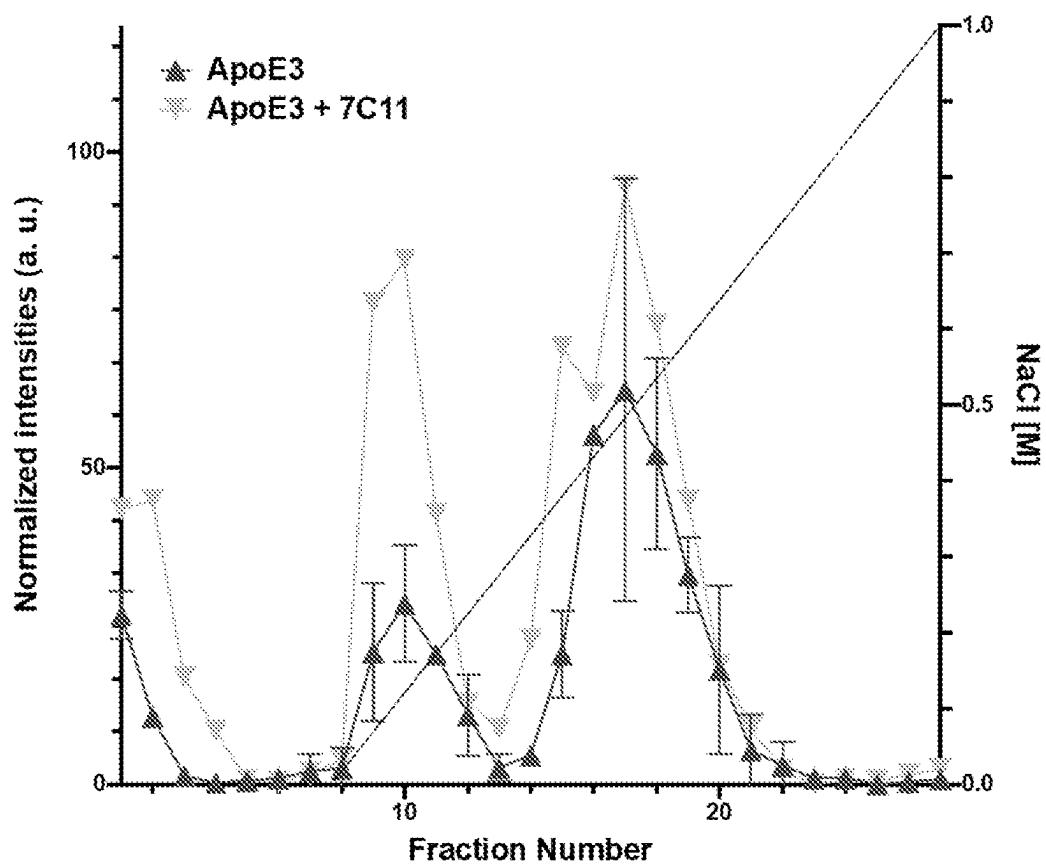
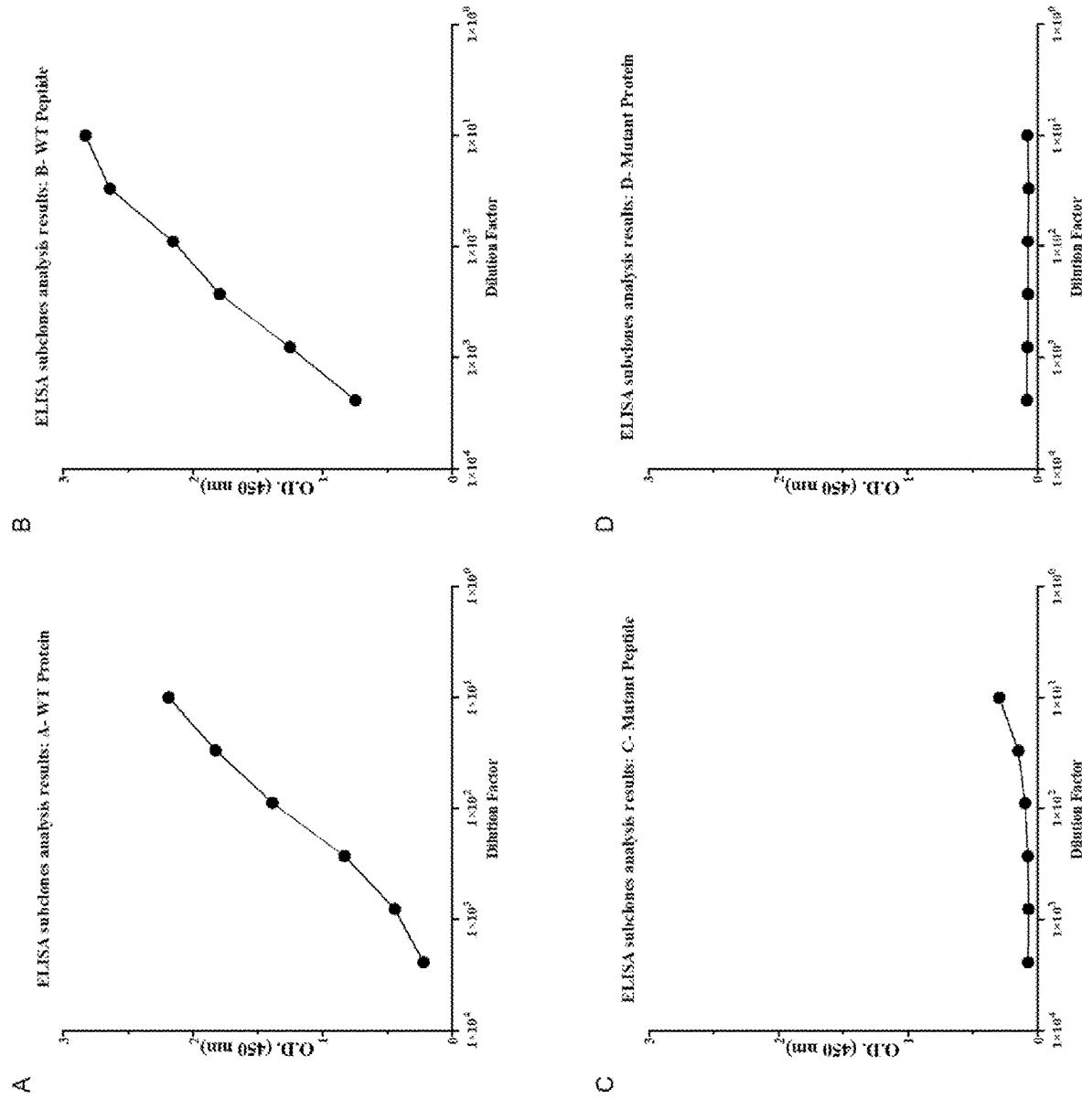


FIG. 23B



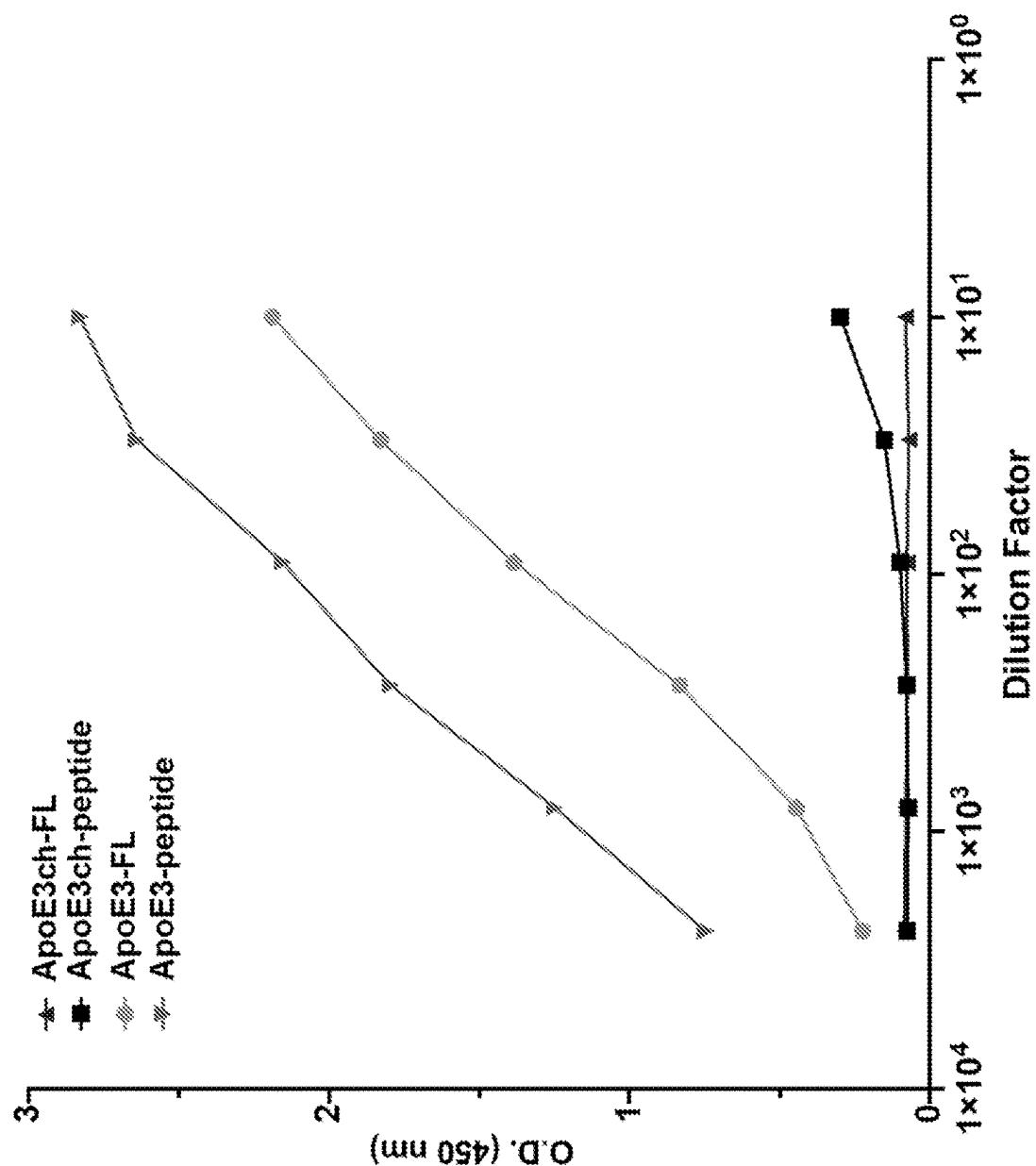


FIG. 25

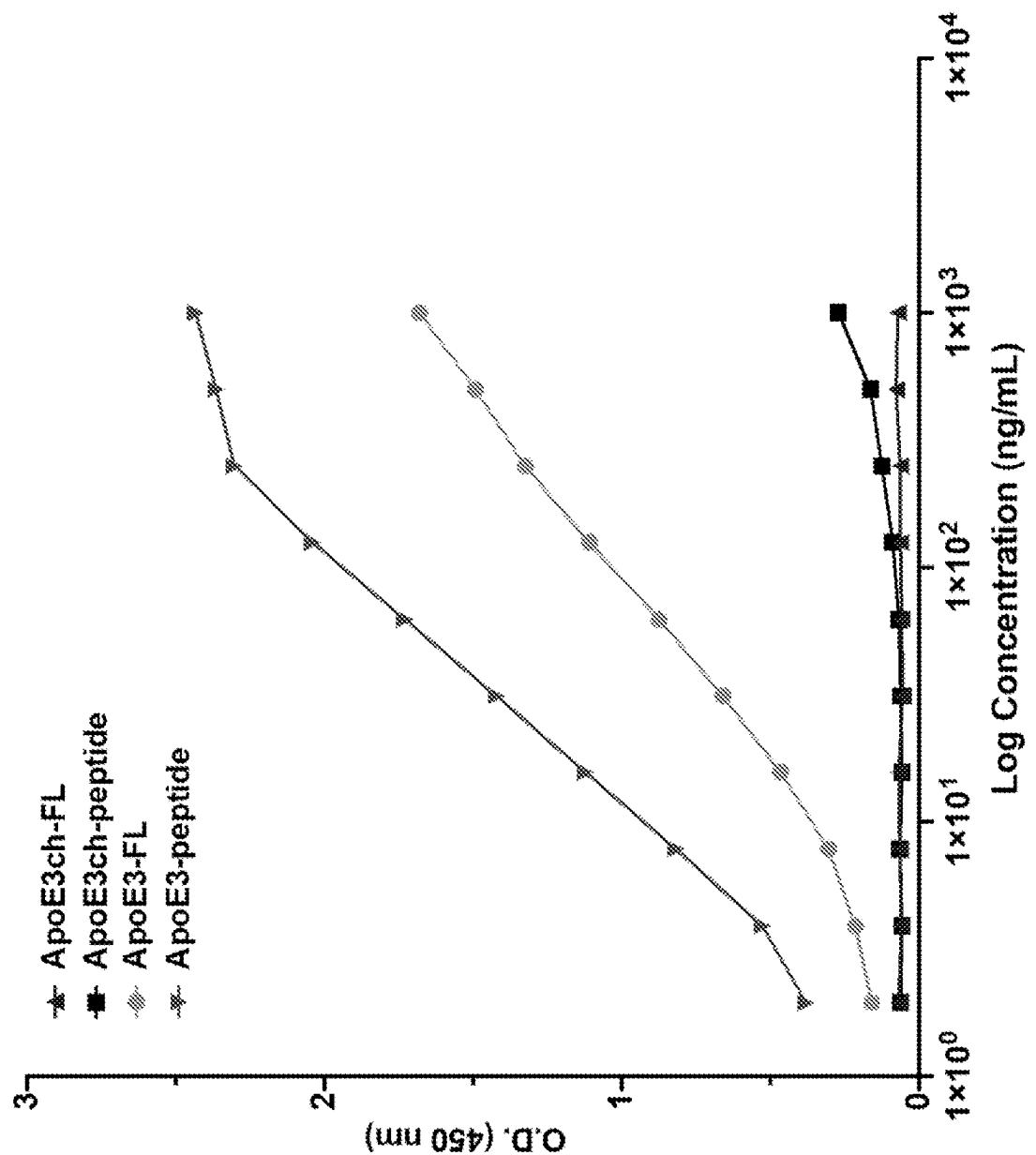


FIG. 26

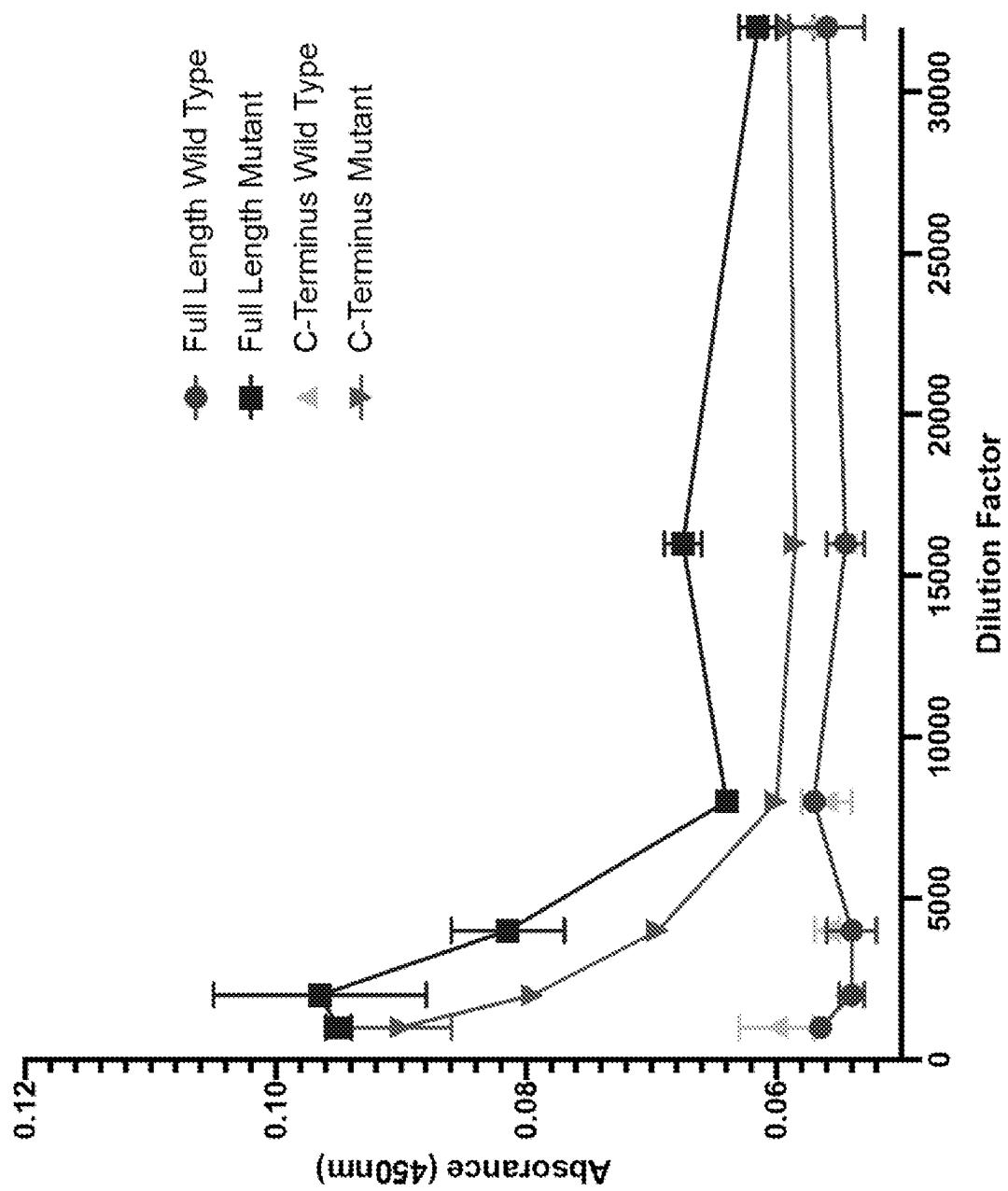


FIG. 27

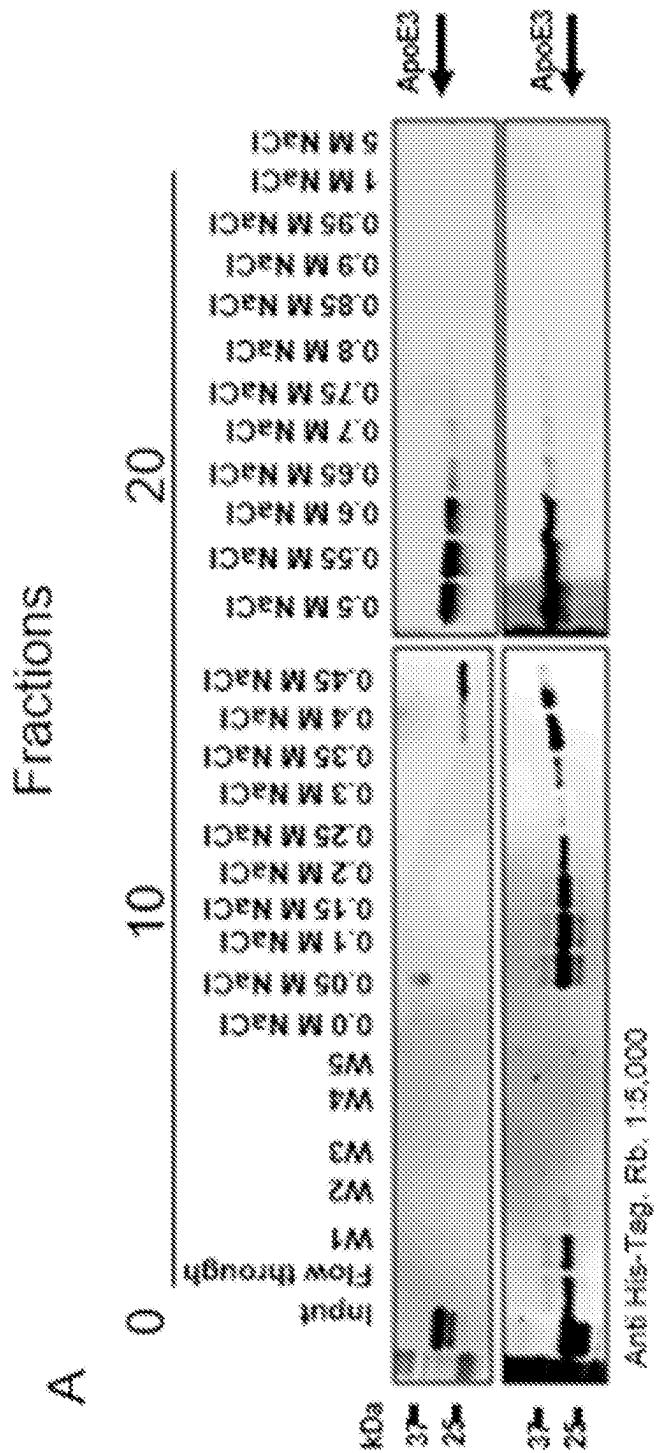


FIG. 28A

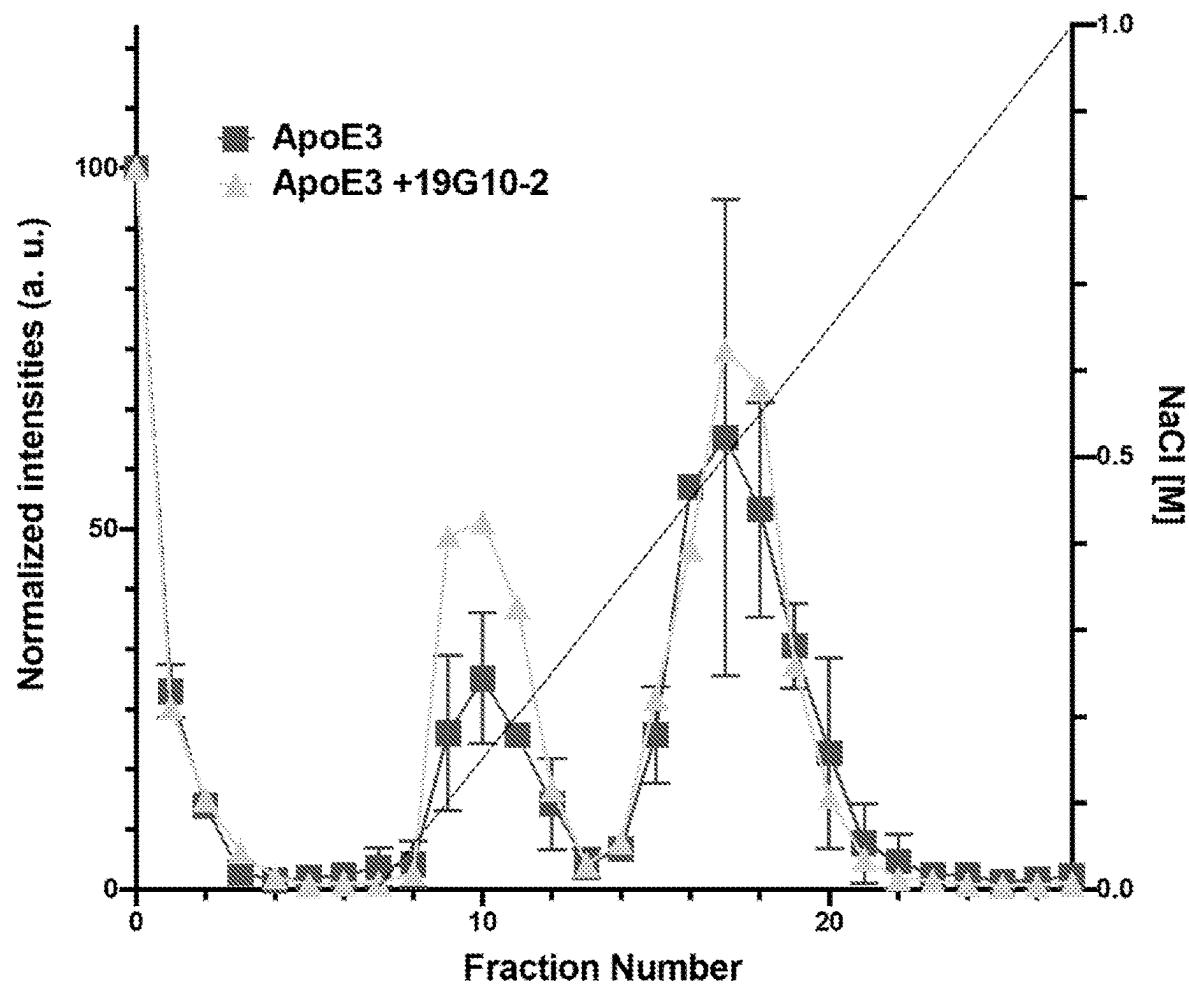


FIG. 28B

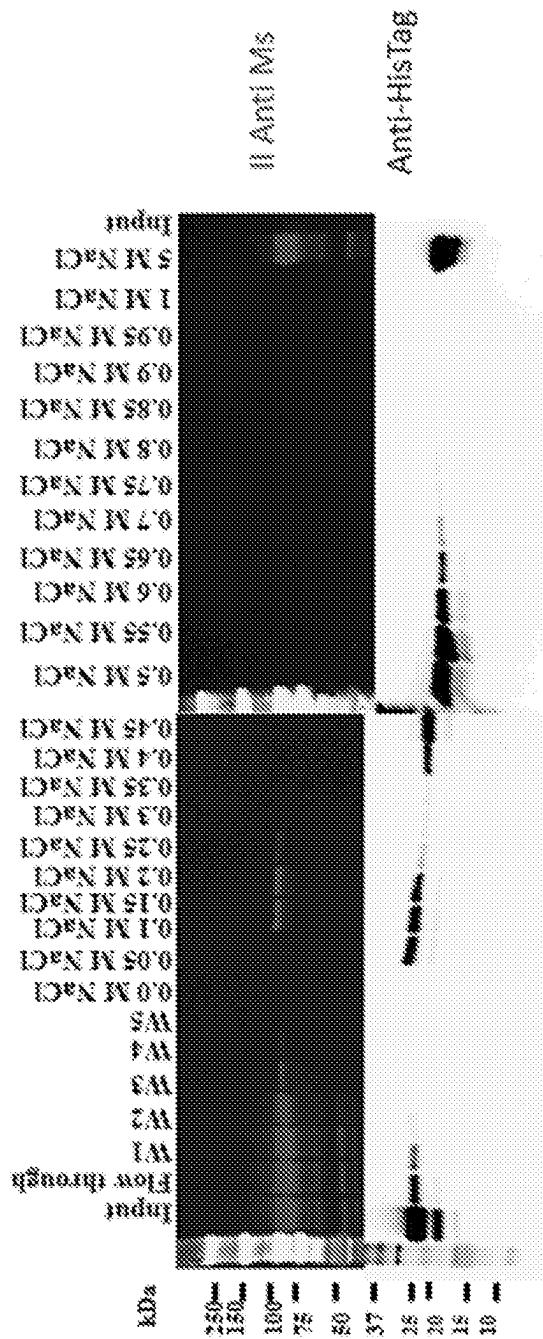


FIG. 29

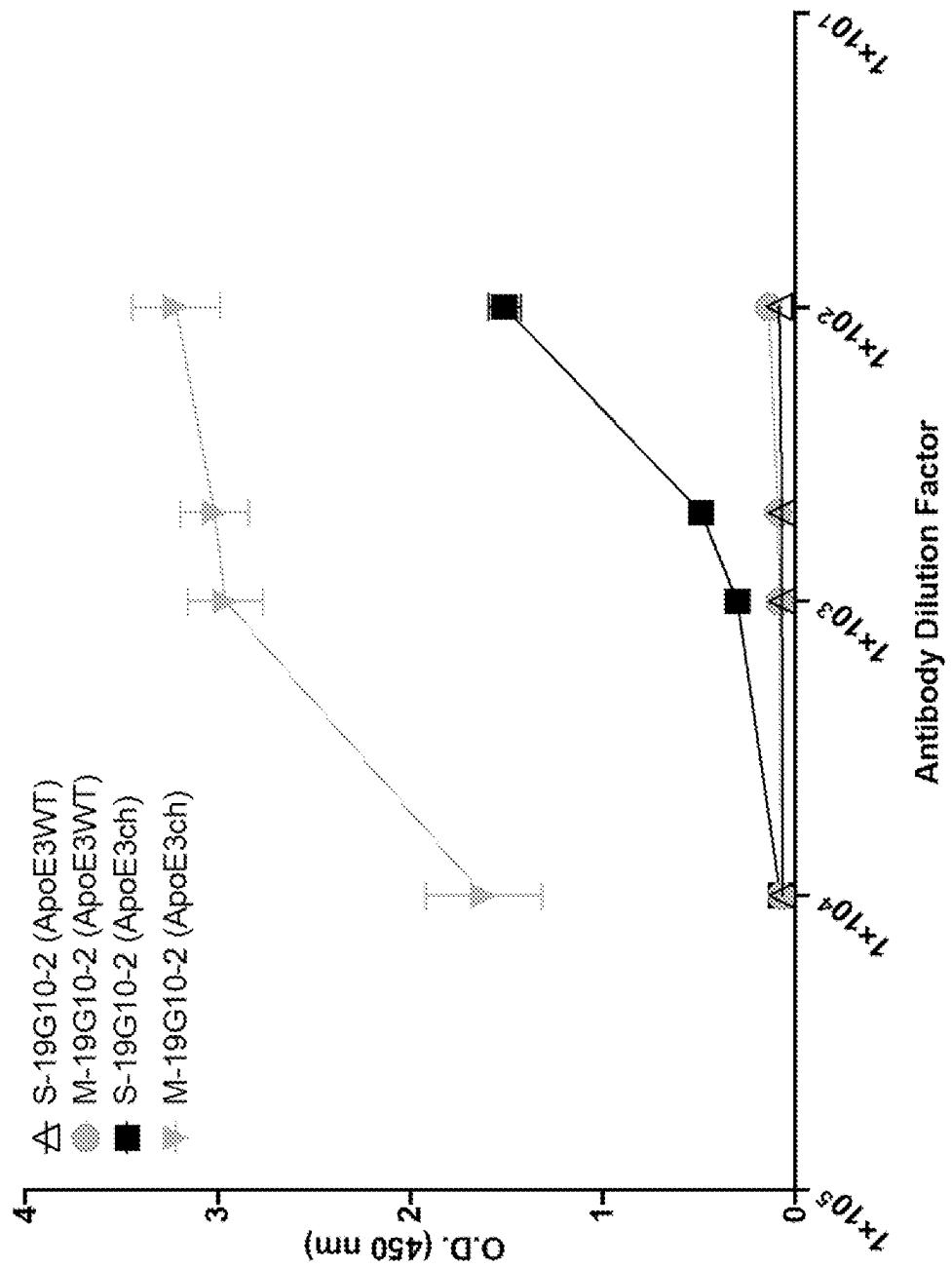


FIG. 30

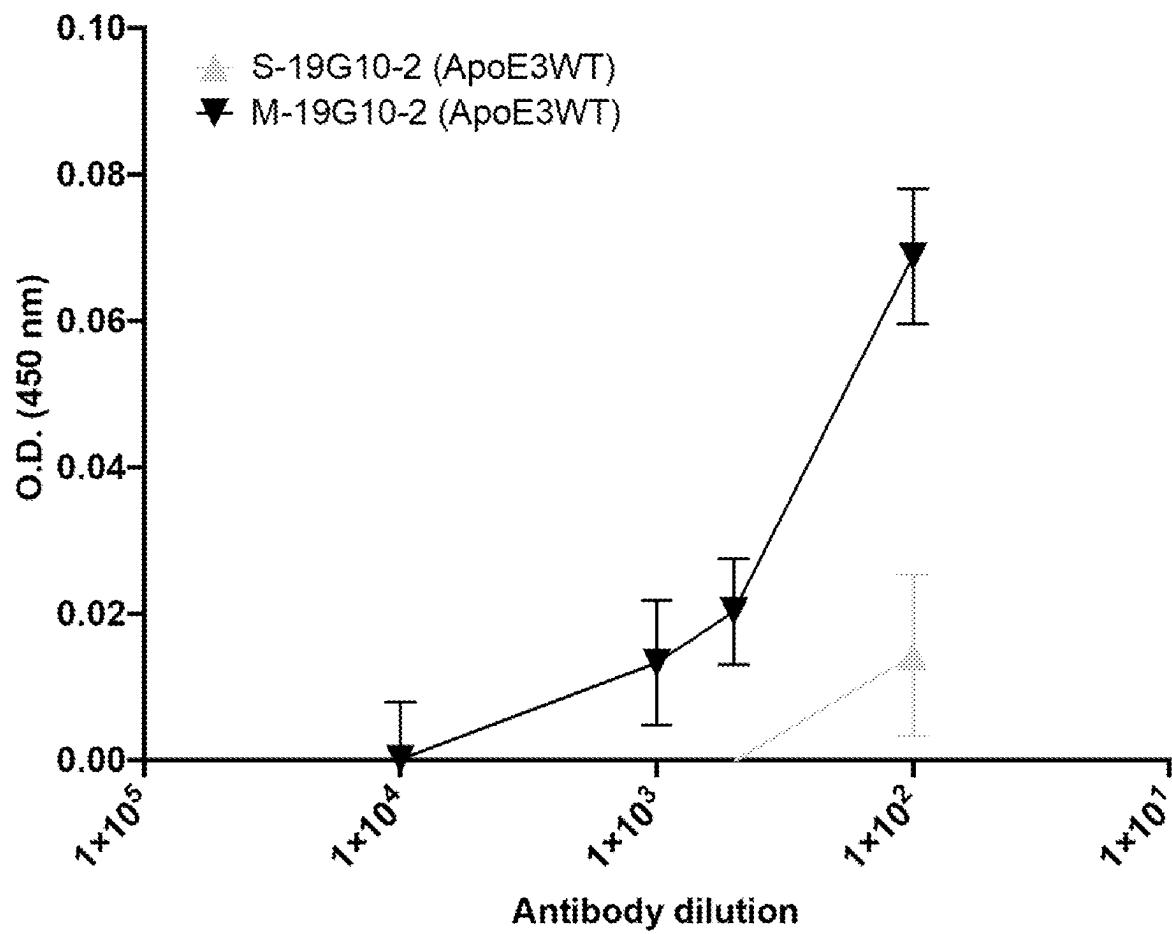


FIG.  
31

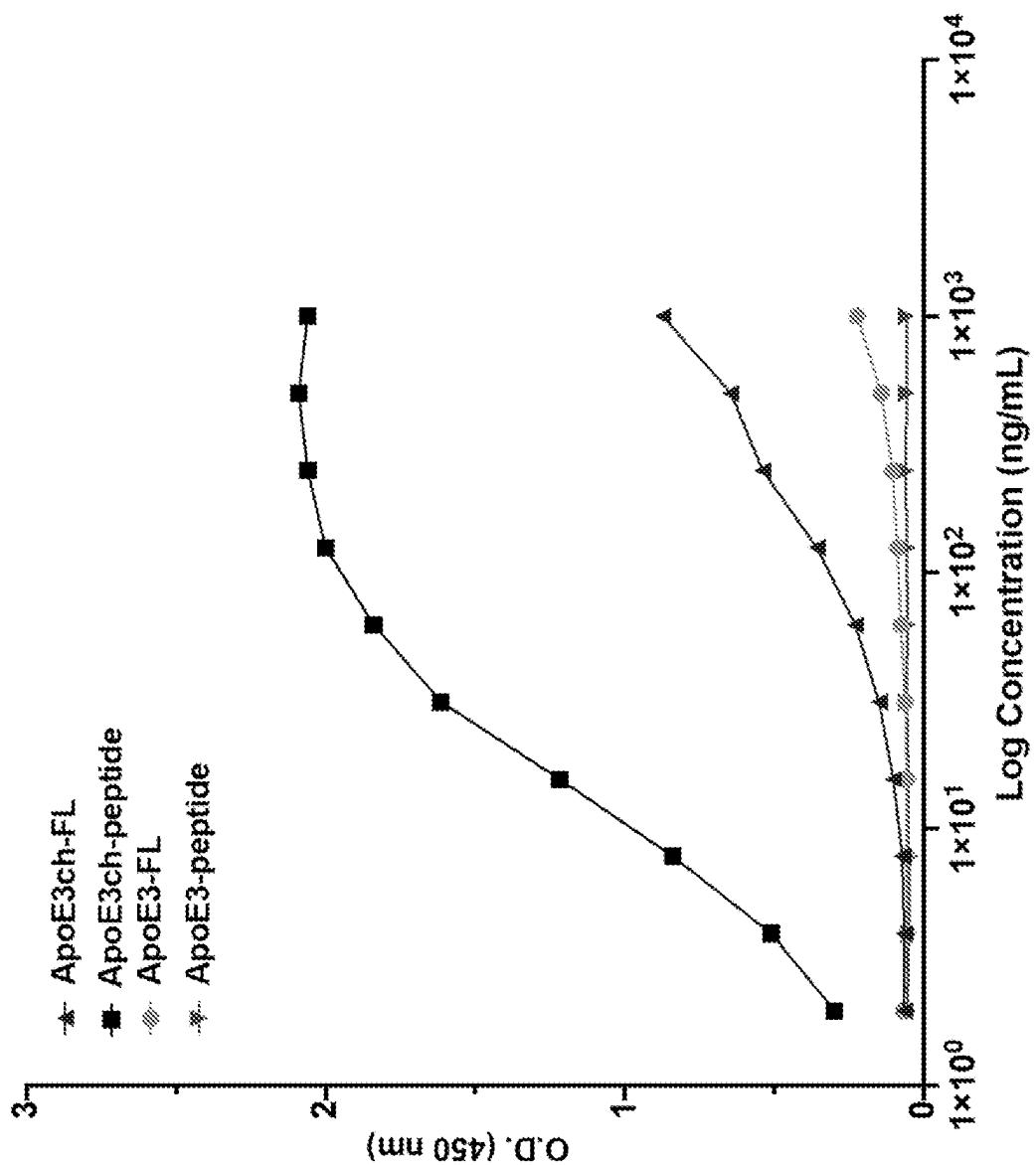


FIG. 32

25F1-2

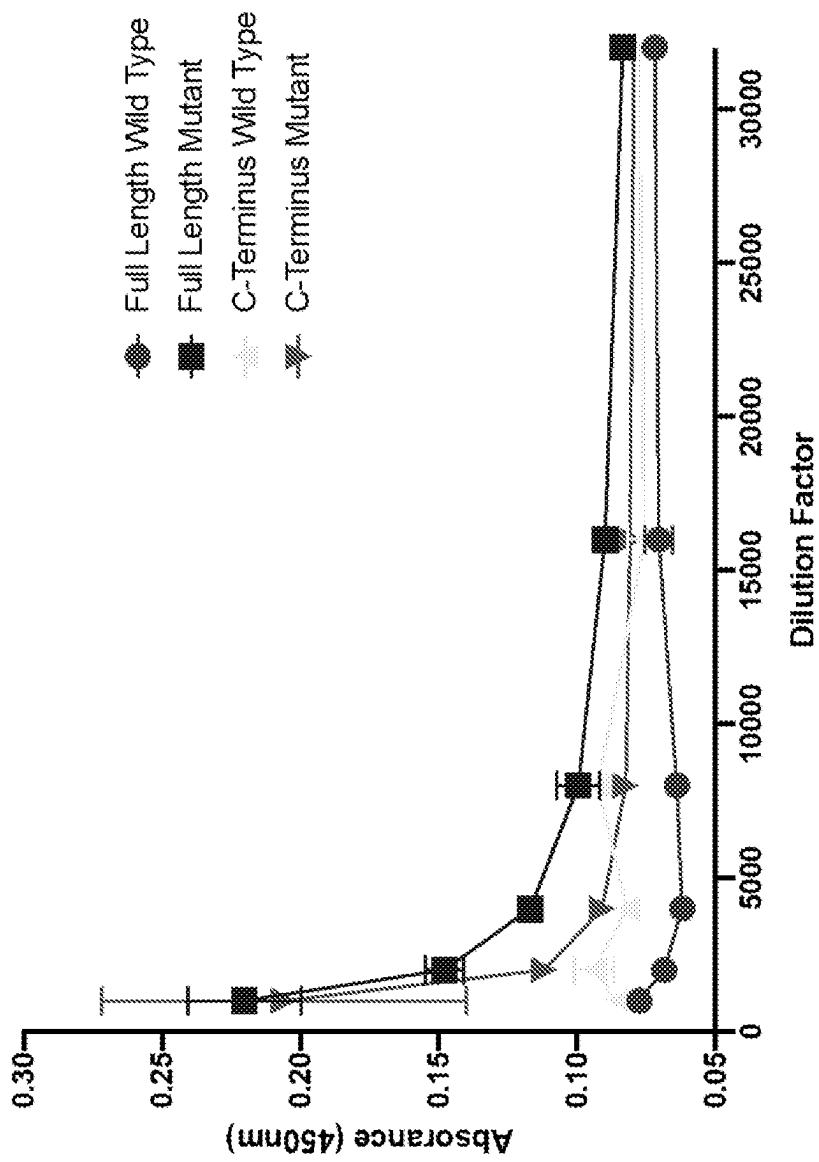


FIG. 33

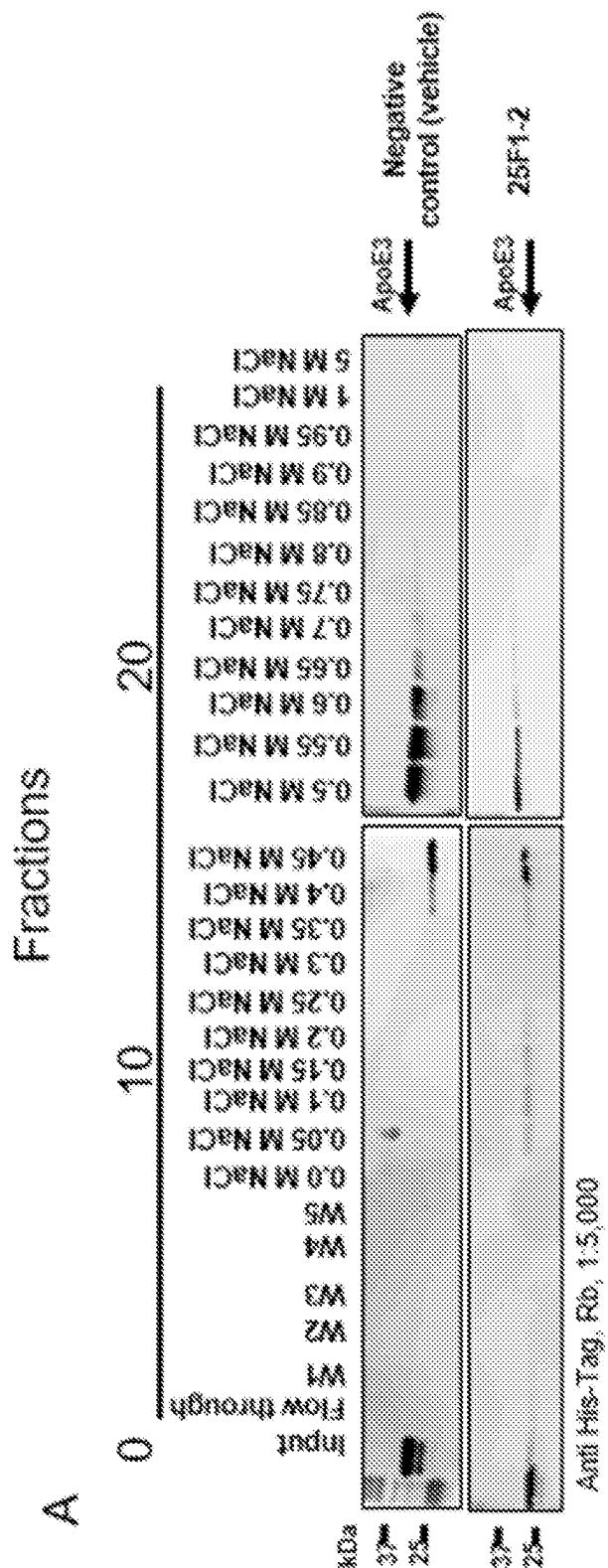


FIG. 34A

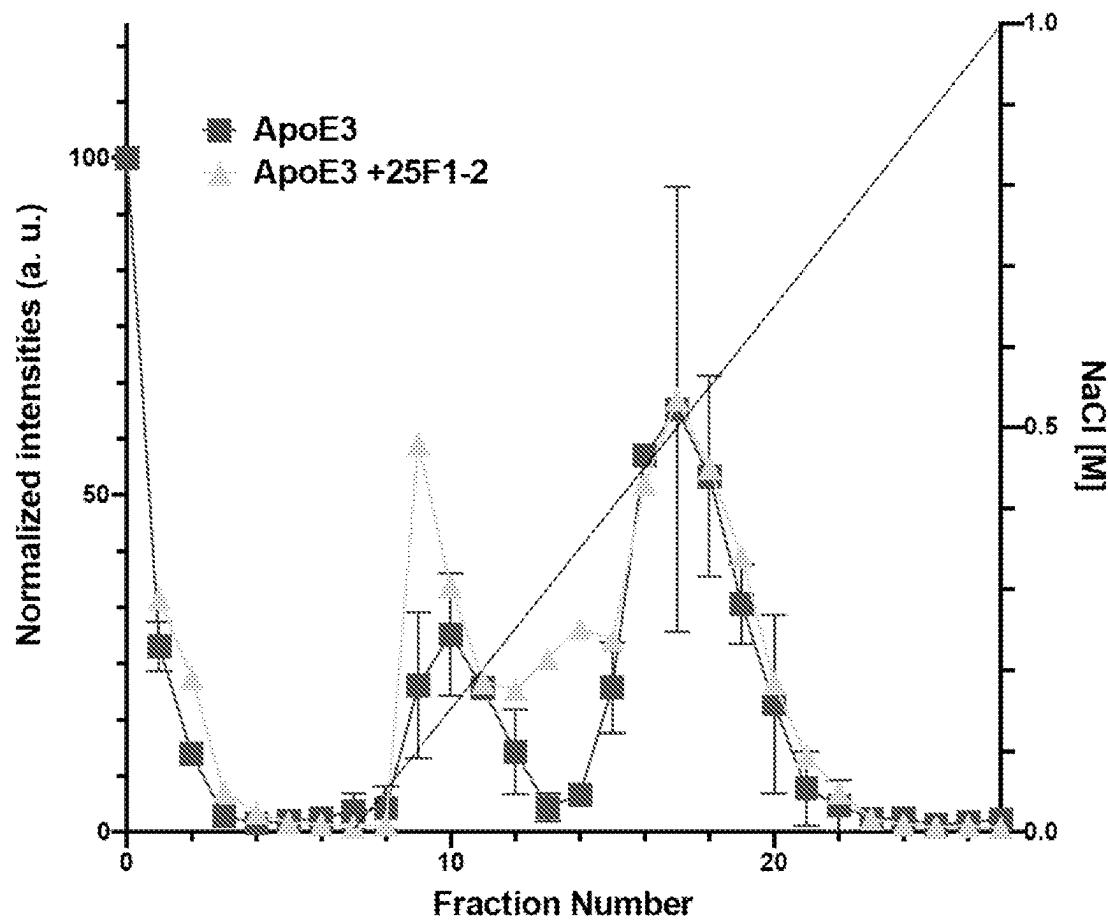


FIG. 34B

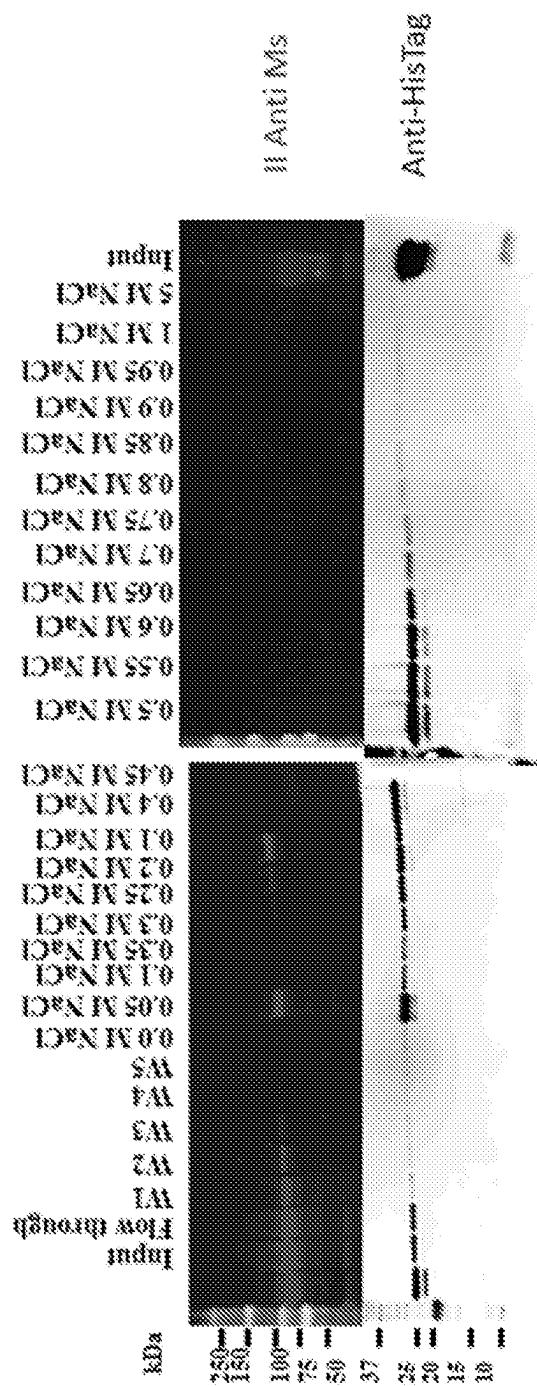


FIG. 35

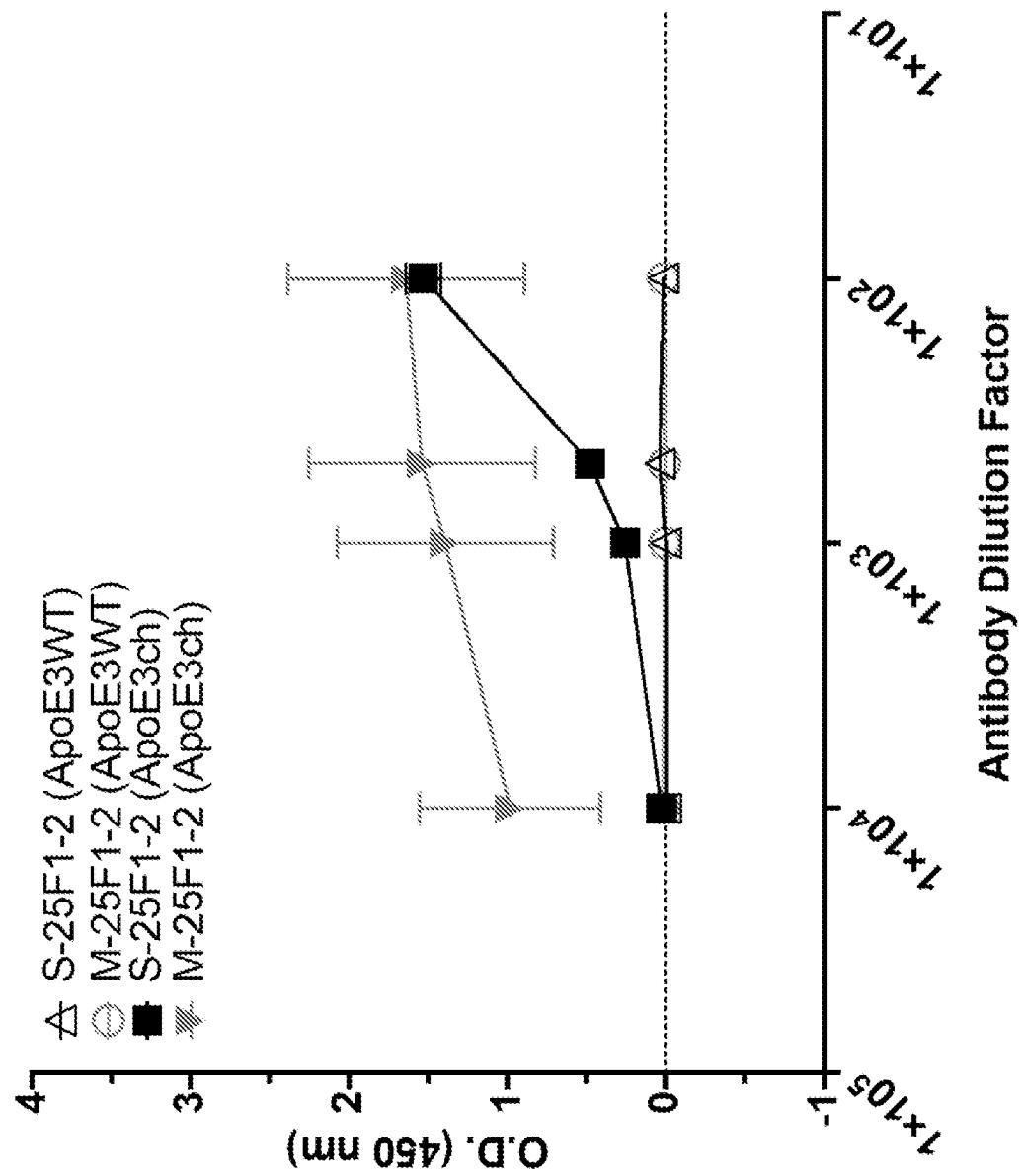
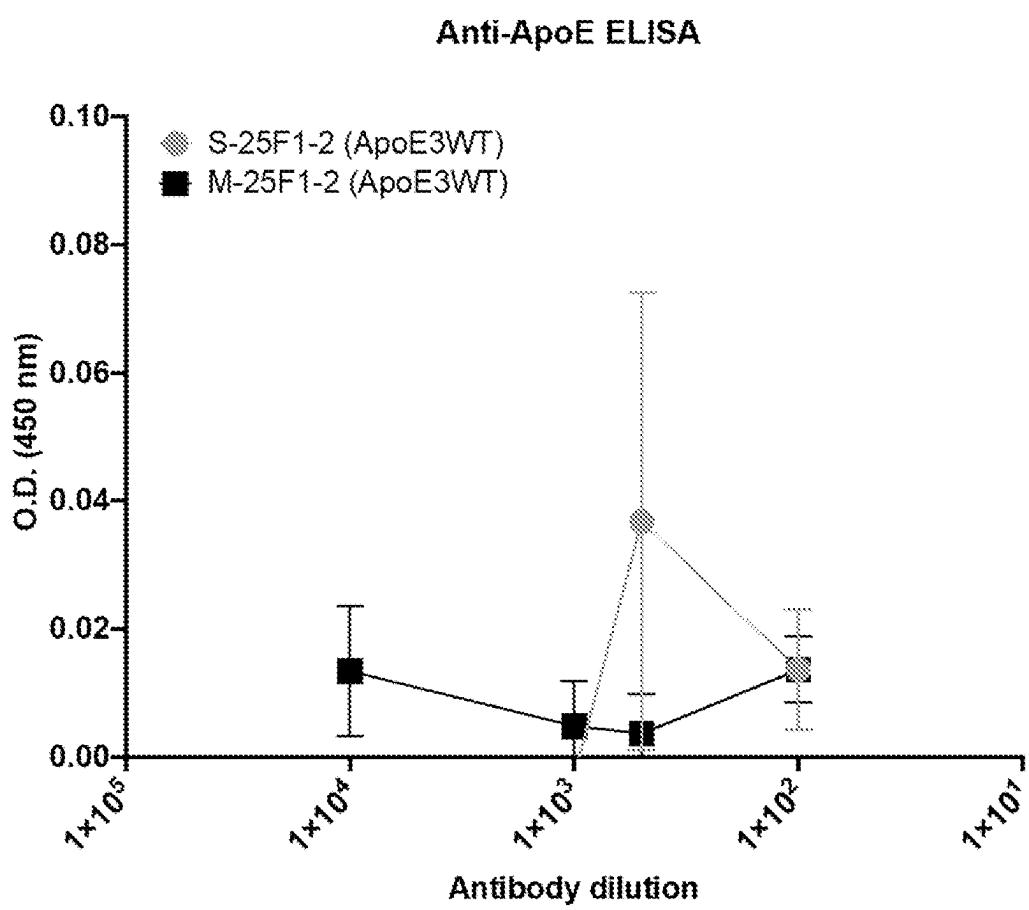


FIG. 36



**FIG. 37**

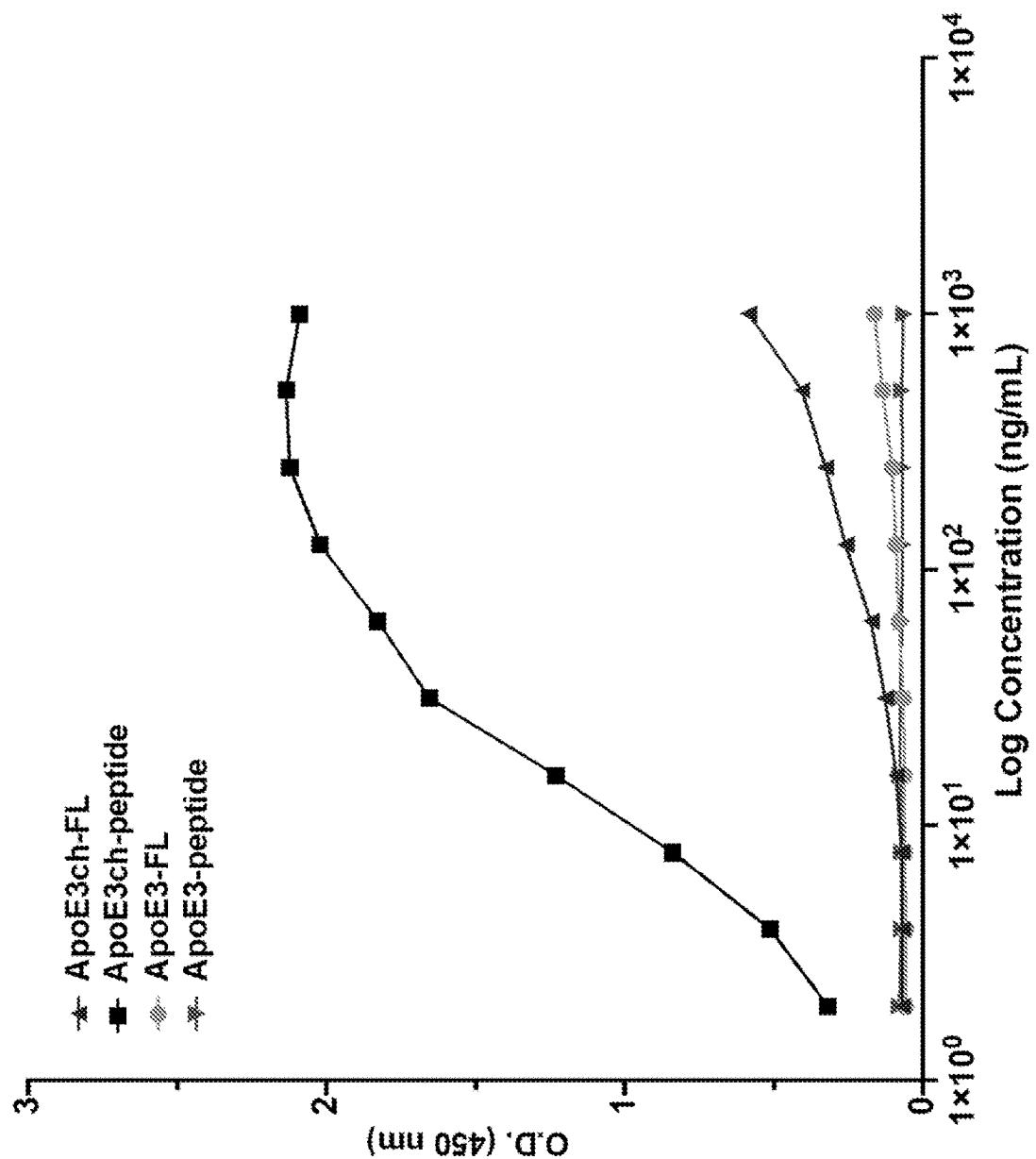


FIG. 38

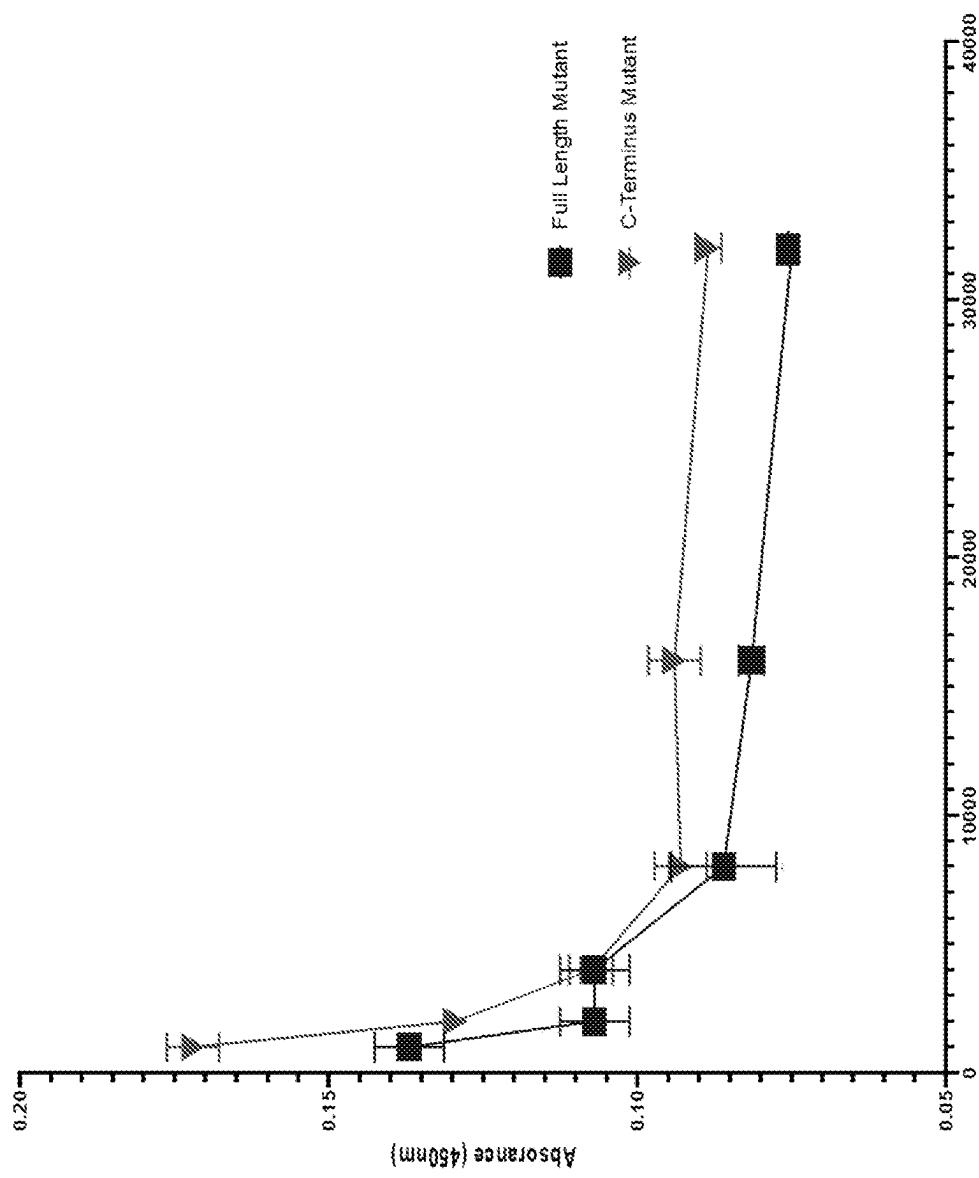


FIG. 39

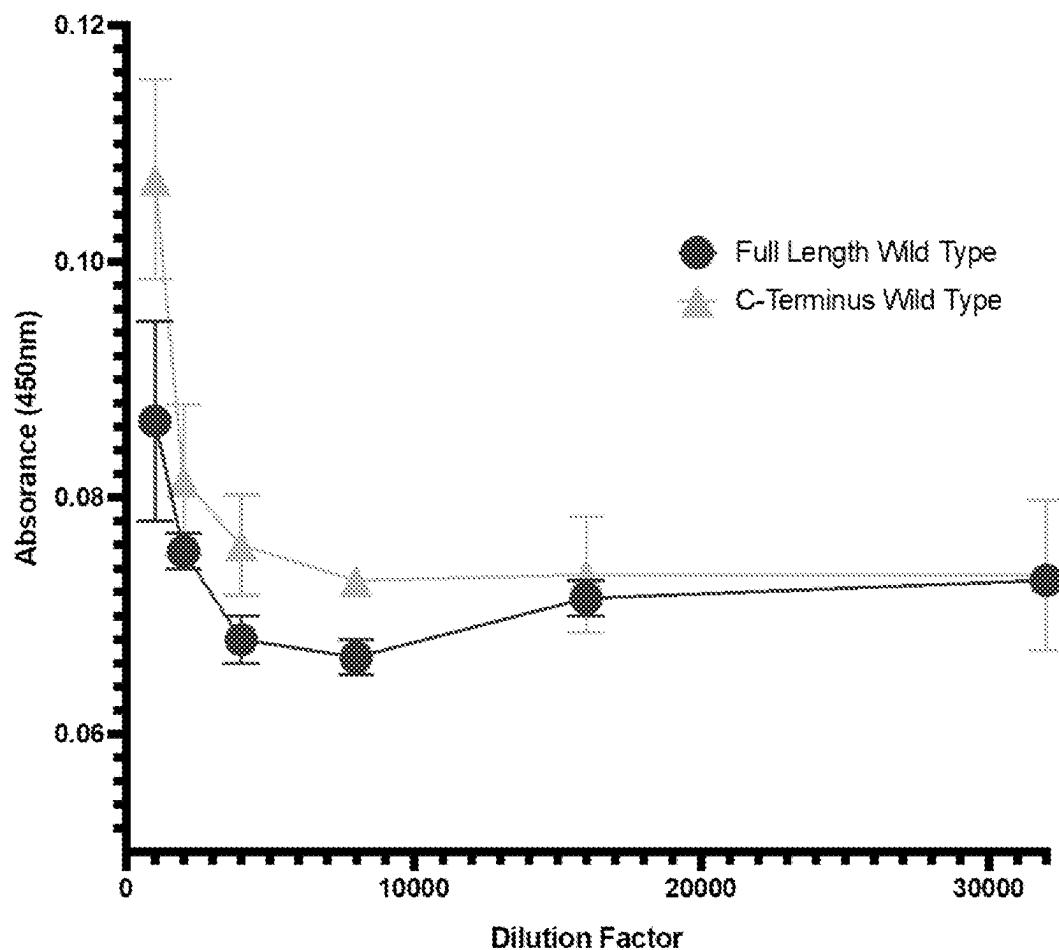


FIG. 40

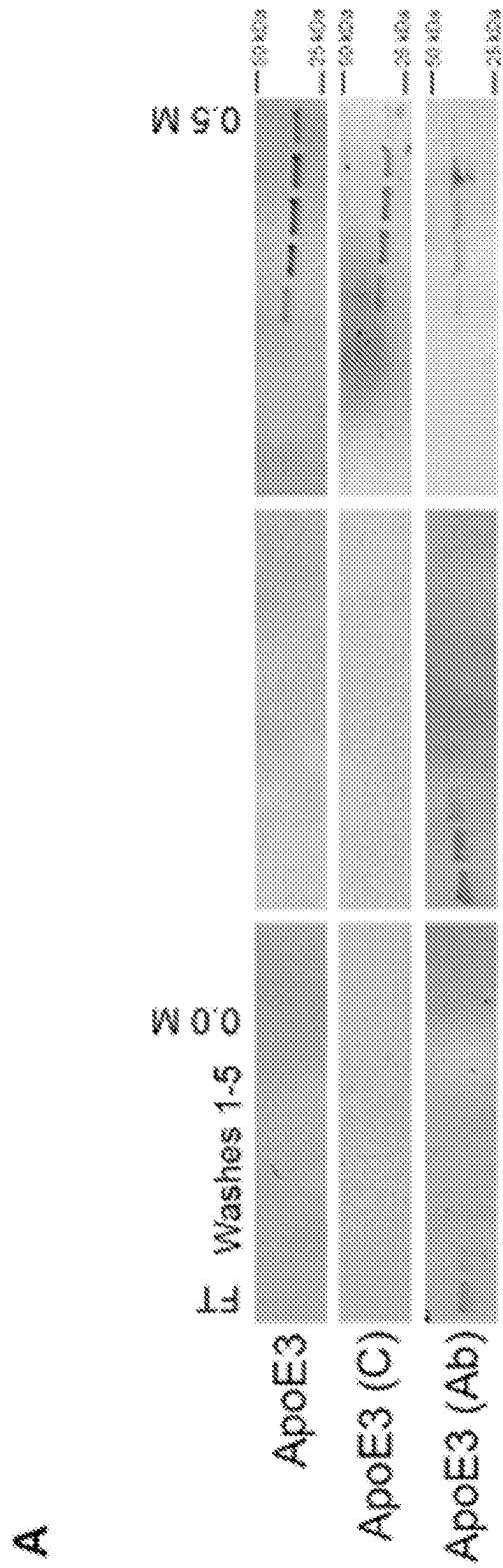


FIG. 41A

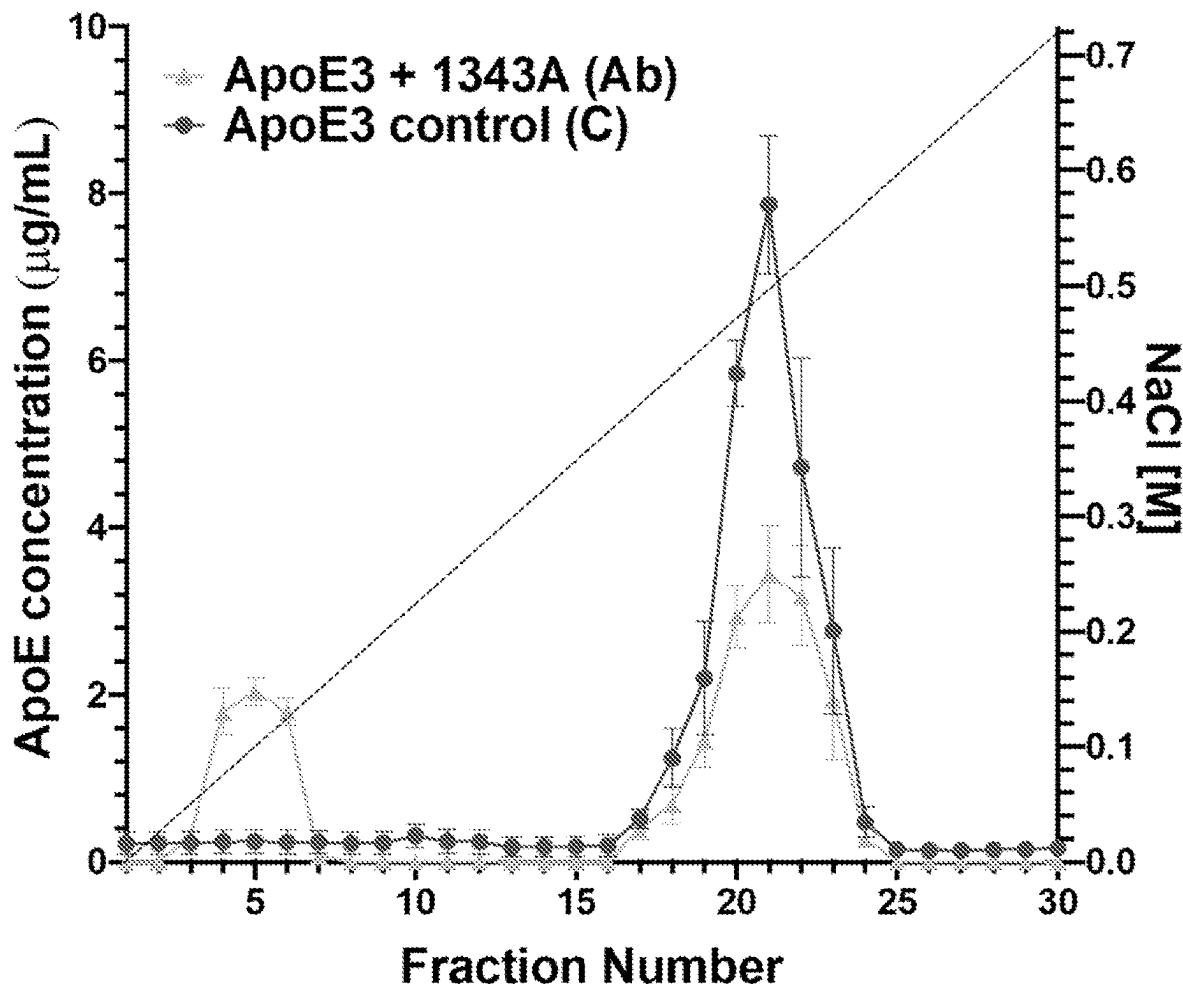


FIG.  
41B

DAY 1 →  
Intravitreal  
Injections

DAY 3 →  
Eye collection  
Fixation and Dissection

DAY 4 →  
Primary Antibody  
Incubation

DAY 5 →  
Secondary Ab  
Incubation

DAY 6 →  
Retinal Flat-mounts  
Confoocal Imaging

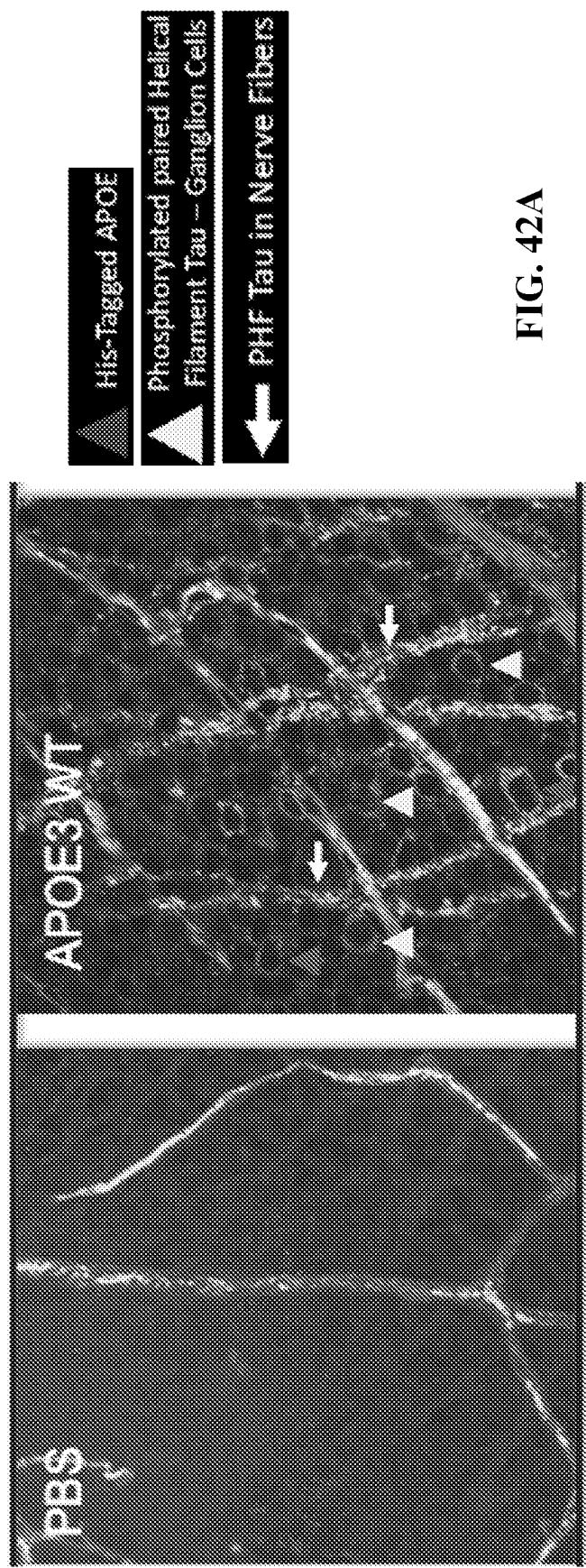


FIG. 42A

FIG. 42B

FIG. 42C

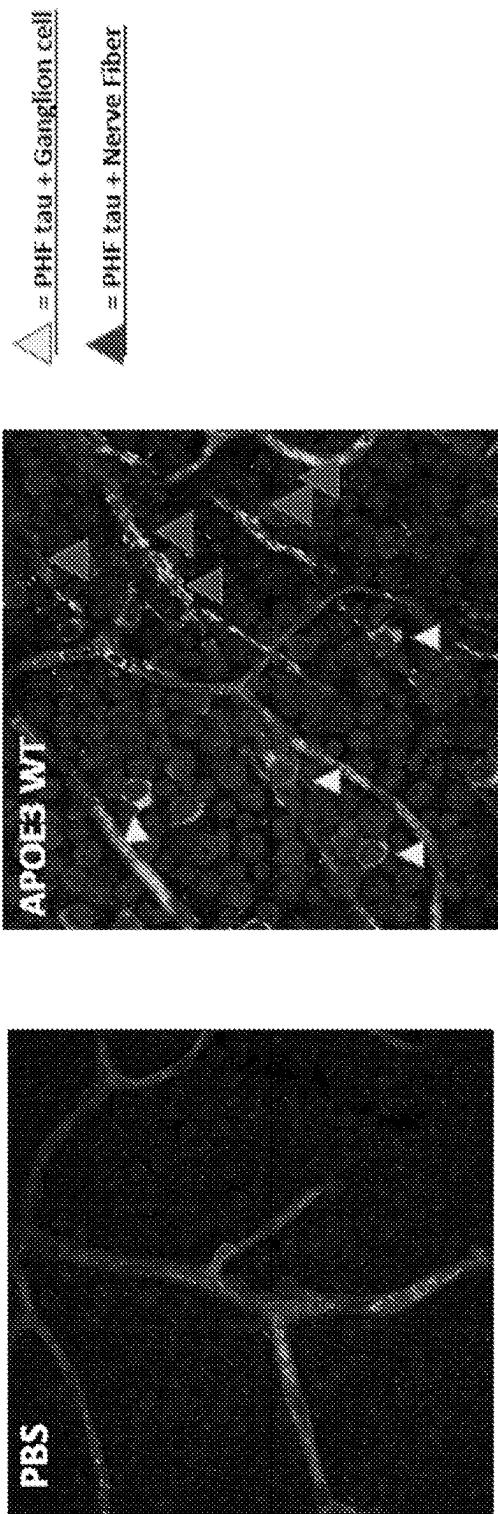


FIG. 43A

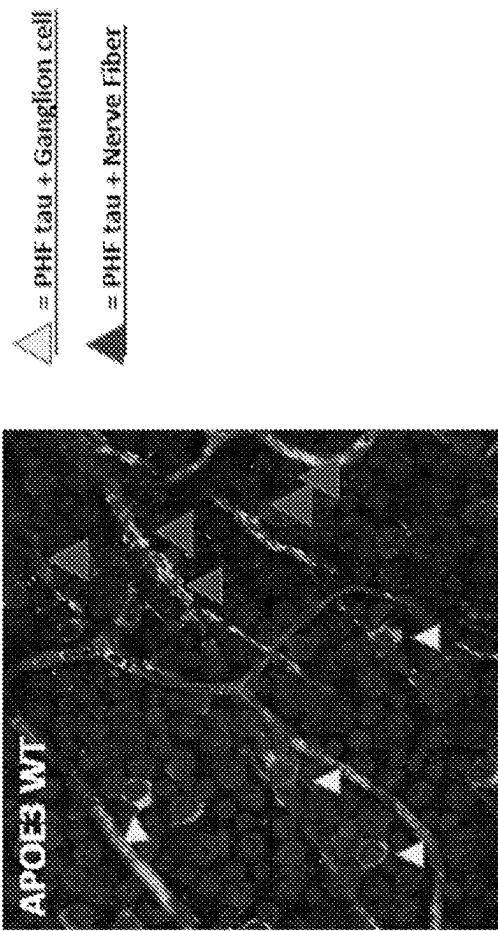


FIG. 43B

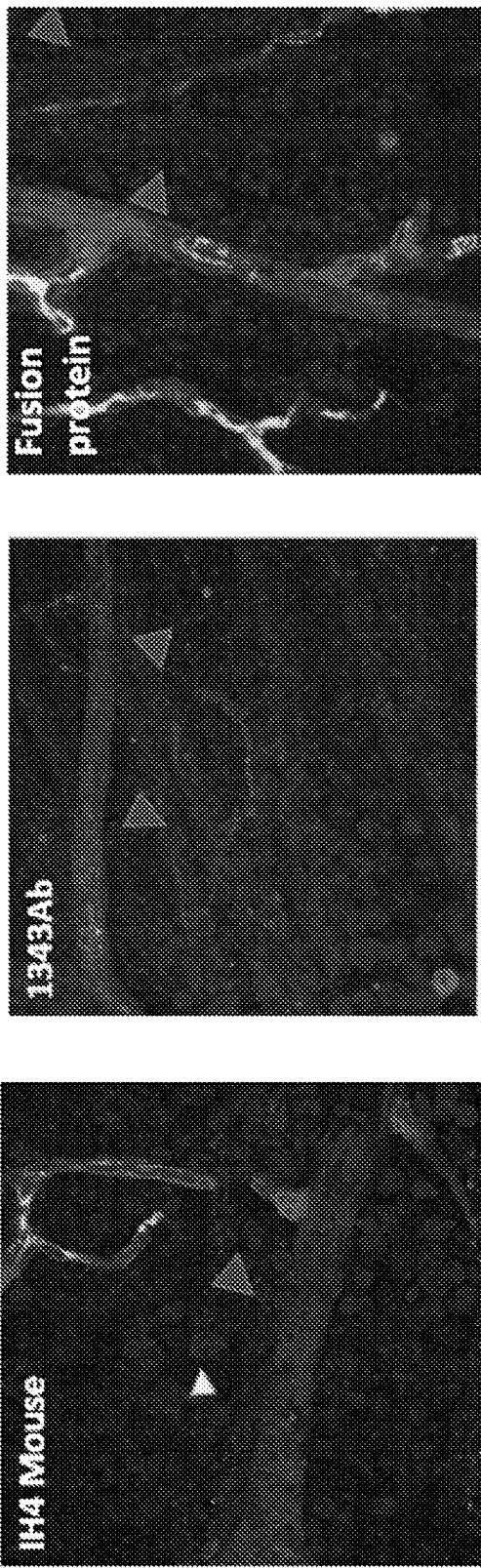


FIG. 43C

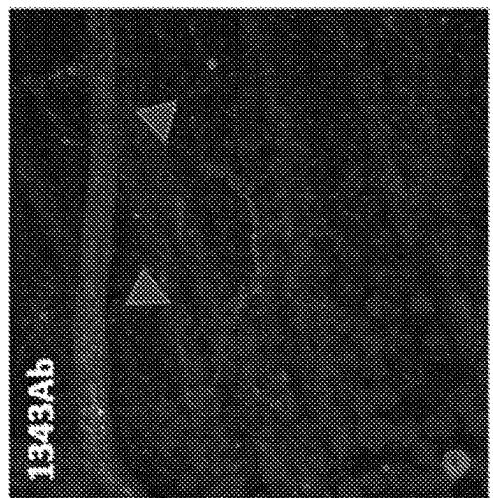


FIG. 43D

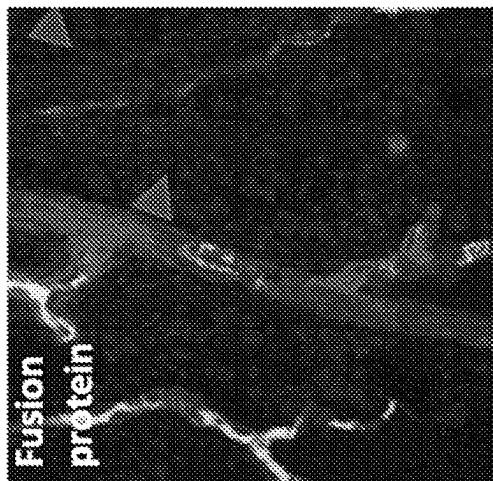


FIG. 43E

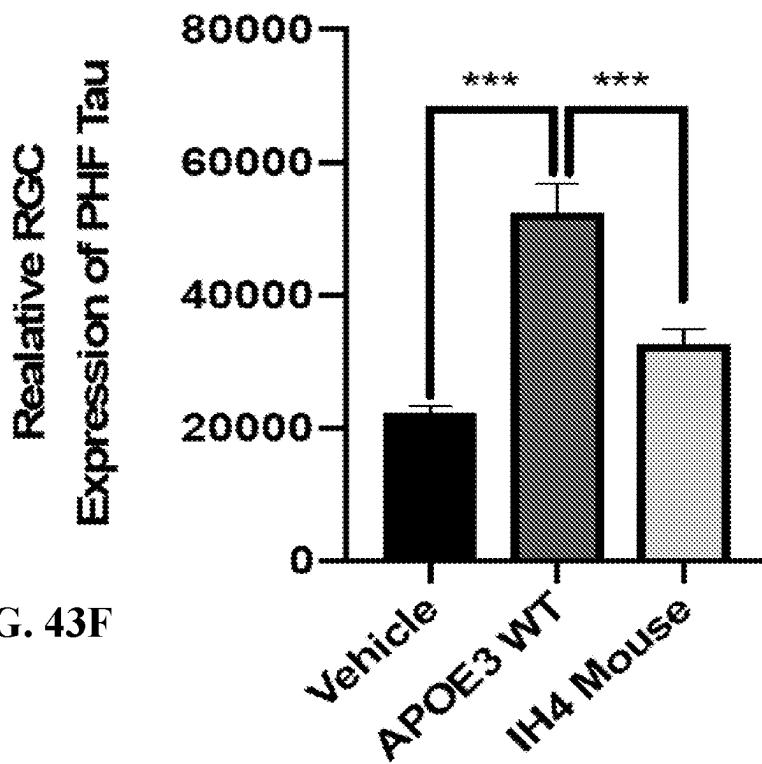


FIG. 43F

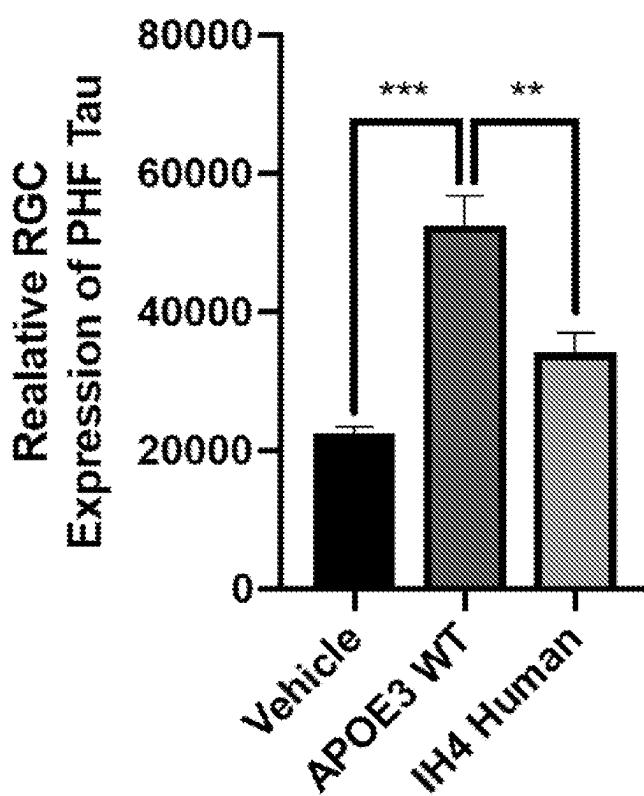


FIG. 43G

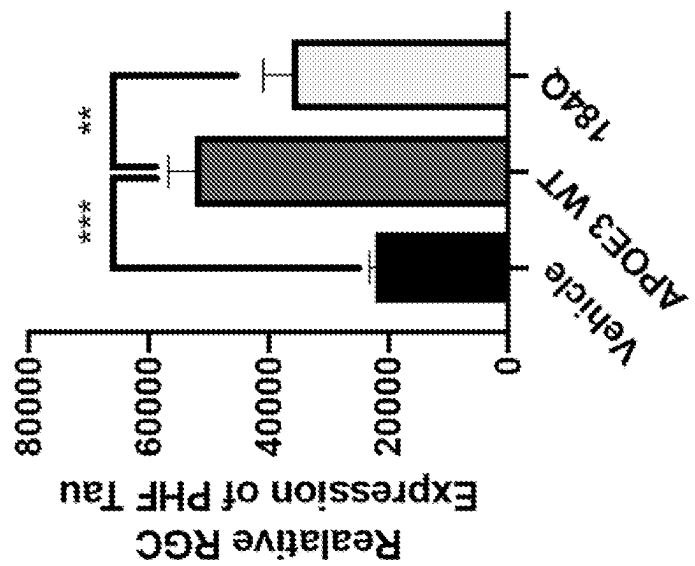


FIG. 43I

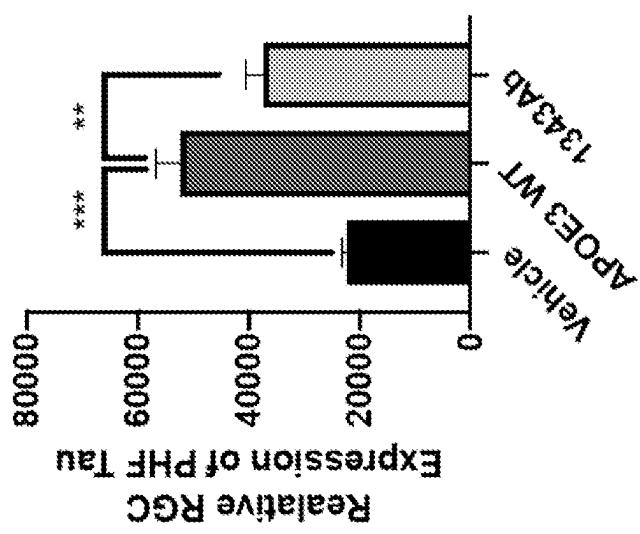


FIG. 43H

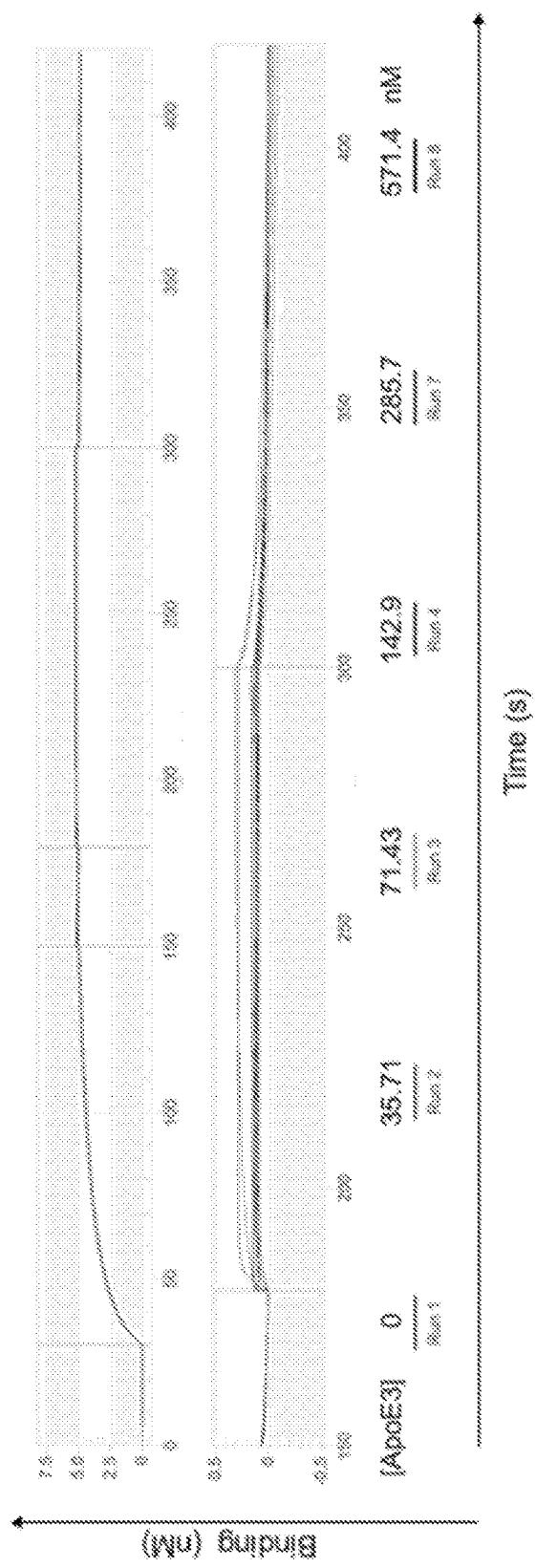


FIG. 44

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**ANTI-APOE ANTIBODIES AND POLYNUCLEOTIDES THEREOF****CLAIM OF PRIORITY**

This application is a § 371 National Stage Application of PCT/US2020/034978, filed May 28, 2020, which claims the benefit of U.S. Provisional Application No. 62/853,676, filed May 28, 2019, and U.S. Provisional Application No. 62/873,019, filed Jul. 11, 2019. The entire contents of the foregoing are incorporated by reference herein.

**FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT**

This invention was made with Government support under Grant No. OD019833 awarded by the National Institutes of Health, Grant Nos. AG054671, AG031581, and AG19610 awarded by the National Institute on Aging, and Grant Nos. NS100121 and NS110048 awarded by the National Institute of Neurological Disorders and Stroke. The Government has certain rights in the invention.

**SEQUENCE LISTING**

This application contains a Sequence Listing that has been submitted electronically as an ASCII text file named '29539\_0386US1\_Sequence\_Listing.txt'. The ASCII text file, created on Nov. 23, 2021, is 202 kilobytes in size. The material in the ASCII text filed is hereby incorporated by reference in its entirety.

**TECHNICAL FIELD**

Described herein are methods and compositions for preventing or treating cognitive decline associated with dementia and/or mild cognitive impairment by modulating the heparan sulfate proteoglycans (HSPG)/glycosaminoglycan (GAG) heparin-binding affinity of Apolipoprotein E (ApoE).

**BACKGROUND**

Alzheimer's disease (AD) is a chronic neurodegenerative disease that usually starts slowly and gradually worsens over time. It is the cause of 60-70% of cases of dementia. The disease process is associated with plaques and neurofibrillary tangles in the brain. There are presently no treatments to stop or reverse its progression, though some may temporarily improve symptoms. The accumulation, aggregation and deposition of amyloid- $\beta$  (A $\beta$ ) peptides in the brain are central to the pathogenesis of Alzheimer's disease (AD). Growing evidence has demonstrated that ApoE strongly influences AD pathogenesis by controlling A $\beta$  aggregation and metabolism (Fu et al., Mol Neurodegener 11:37, 2016). APOE impacts amyloid production, aggregation, and clearance, is a component of amyloid plaques, and exacerbates tau-mediated neurodegeneration. ApoE is 299 amino acids long and is polymorphic with three major alleles (epsilon 2, epsilon 3, and epsilon 4) which differ from each other by only one or two amino acids at positions 112 and 158: ApoE2 (cys112, cys158), ApoE3 (cys112, arg158), and ApoE4 (arg112, arg158). Accordingly, there is a need of therapeutics targeting and modulating the function of ApoE proteins for treating or preventing AD and cognitive decline associated with dementia or mild cognitive impairment.

**SUMMARY**

In one aspect, this disclosure features an isolated monoclonal antibody that specifically binds to one or more (e.g.

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1, 2, 3 or 4) HSPG-binding sites or one or more (e.g. 1, 2, 3, or 4) sites of allosteric modulation of HSPG binding of a wild type or mutant Apolipoprotein E (ApoE). In some embodiments, the antibody binds to a polypeptide having an amino acid sequence at least 95% (e.g. 96%, 97%, 98%, 99% or 100%) identical to TEELRVRLASHLRK (SEQ ID NO:3). In some embodiments, the antibody binds to a polypeptide having an amino acid sequence at least 95% (e.g. 96%, 97%, 98%, 99% or 100%) identical to TEELRVSLASHLRK (SEQ ID NO:2). In some embodiments, the antibody binds to one or more (e.g. 1, 2, 3 or 4) HSPG-binding sites of a wild type or mutant ApoE2, ApoE3, or ApoE4.

In some embodiments, the antibody competes with and/or binds the same epitope as a reference anti-ApoE antibody comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL of the reference antibody comprise: (i) the amino acid sequence set forth in SEQ ID NO: 13 and the amino acid sequence set forth in SEQ ID NO:12, respectively; (ii) the amino acid sequence set forth in SEQ ID NO:23 and the amino acid sequence set forth in SEQ ID NO: 22, respectively; (iii) the amino acid sequence set forth in SEQ ID NO:33 and the amino acid sequence set forth in SEQ ID NO:32, respectively; or (iv) the amino acid sequence set forth in SEQ ID NO:43 and the amino acid sequence set forth in SEQ ID NO: 42, respectively. In some embodiments of any of the antibodies described herein, the antibody competes with and/or binds the same epitope as a reference anti-ApoE antibody comprising a heavy chain and a light chain, wherein the heavy chain and light chain of the reference antibody comprise the amino acid sequence set forth in SEQ ID NO: 53 and the amino acid sequence set forth in SEQ ID NO: 52.

In another aspect, provided herein are anti-ApoE antibodies comprising a VH comprising VHCDR1, VHCDR2, and VHCDR3, and a VL comprising VLCDR1, VLCDR2, and VLCDR3, wherein VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 comprise: (i) SEQ ID Nos: 7, 8, 9, 4, 5, 6, respectively; (ii) SEQ ID Nos: 17, 18, 19, 14, 15, 16, respectively; (iii) SEQ ID Nos: 27, 28, 29, 24, 25, 26, respectively; (iv) SEQ ID Nos: 37, 38, 39, 34, 35, 36, respectively; or (v) SEQ ID Nos: 47, 48, 49, 44, 45, 46, respectively. In some embodiments of any of the antibodies described herein, (i) the VH and the VL comprise an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to the amino acid sequences set forth in SEQ ID NOS: 13 and 12, respectively; (ii) the VH and the VL comprise an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to the amino acid sequences set forth in SEQ ID NOS: 23 and 22, respectively; (iii) the VH and the VL comprise an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to the amino acid sequences set forth in SEQ ID NOS: 33 and 32, respectively; or (iv) the VH and the VL comprise an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to the amino acid sequences set forth in SEQ ID NOS: 43 and 42, respectively. In some embodiments of any of the antibodies described herein, the antibody comprises a heavy chain and a light chain comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to the amino acid sequence set forth in SEQ ID Nos: 53 and 52, respectively. In some embodiments, the antibody includes a mouse IgG1, IgG2a, IgG2b, IgG2c, or IgG3 heavy chain constant region. In some embodiments, the antibody includes a human IgG1, IgG2, IgG3, or IgG4 heavy chain constant region. In some embodiments, the antibody includes a human kappa or human

lambda light chain constant region. In some embodiments, the antibody is a whole antibody, a single domain antibody, a humanized antibody, a chimeric antibody, a bispecific antibody, a Fv, a scFv, an sc(Fv)2, a diabody, an Fab, or an F(ab')2. In some embodiments, the antibody further includes a half-life extending moiety. In some embodiments, the antibody further includes a blood-brain barrier penetrating moiety. In some embodiments, the antibody further includes a detectable label. In some embodiments, provided herein are pharmaceutical compositions comprising any of the antibodies described herein. In some embodiments, provided herein are polynucleotide or polynucleotides encoding any of the antibodies described herein. In some embodiments, provided herein are vector or vectors comprising the polynucleotide or polynucleotides described herein. In some embodiments provided herein are host cells comprising the polynucleotide or polynucleotides described herein, or the vector or vectors described herein. In another aspect, provided herein are methods of making an anti-ApoE antibody, the methods include: (a) culturing any of the host cells described herein under conditions that permit expression of the antibody; and (b) isolating the antibody. In some embodiments, the methods further include formulating the antibody as a sterile formulation suitable for administration to a human.

In another aspect, provided herein is an Fc-fusion protein that includes: a HSPG-binding domain of a wild type ApoE or mutant ApoE comprising an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of STEELRVRLASHLRKLRKRLRLLRDADDLQK (SEQ ID NO:57), STEELRVSLASHLRKLRKRLRLLRDADDLQK (SEQ ID NO:58), RLVQYRGEVQAMLGQSTEELRVR-LASHLRKL (SEQ ID NO:59), and RLVQYR-GEVQAMLGQSTEELRVSLASHLRKL (SEQ ID NO:60). In some embodiments, the Fc-fusion protein includes an Fc region of a human antibody. In some embodiments, the human antibody is selected from the group consisting of a human IgG1, IgG2, IgG3 and IgG4 molecule. In some embodiments, provided herein are pharmaceutical compositions comprising any of the Fc-fusion proteins described herein. In some embodiments, provided herein are polynucleotide or polynucleotides encoding the Fc-fusion proteins described herein. In some embodiments, provided herein are vector or vectors comprising any of the polynucleotide or polynucleotides described herein. In some embodiments, provided herein are host cells comprising the polynucleotide or polynucleotides described herein, or the vector or vectors described herein.

In another aspect, provided herein are pharmaceutical composition for eliciting an immune response that include: (i) a HSPG-binding domain of a wild type ApoE or mutant ApoE comprising an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of STEELRVRLASHLRKLRKRLRLLRDADDLQK (SEQ ID NO:57), STEELRVSLASHLRKLRKRLRLLRDADDLQK (SEQ ID NO:58), RLVQYRGEVQAMLGQSTEELRVR-LASHLRKL (SEQ ID NO:59), and RLVQYR-GEVQAMLGQSTEELRVSLASHLRKL (SEQ ID NO:60); and (ii) a pharmaceutically acceptable adjuvant.

In another aspect, provided herein is a pharmaceutical composition comprising a human cell expressing any of the antibodies described herein or any of the Fc-fusion proteins described herein.

In another aspect, provided herein is a method of improving, slowing down, delaying the onset of, preventing or

reversing cognitive decline associated with dementia and/or mild cognitive impairment and/or neurodegeneration in a human subject in need thereof, comprising administering to the human subject a therapeutically effective amount of any of the antibody, the Fc-fusion protein, or the pharmaceutical compositions described herein.

In another aspect, provided herein is a method of improving, slowing down, delaying the onset, preventing or reversing cognitive decline associated with dementia and/or mild cognitive impairment and/or neurodegeneration in a human subject in need thereof, the method comprising administering to said subject: (i) a viral vector comprising a nucleotide sequence encoding a gRNA molecule comprising a targeting domain complementary with a target domain from the APOE gene; (ii) a viral vector comprising a nucleotide sequence encoding a Cas9 molecule; and (iii) a viral vector comprising a template nucleic acid, wherein the template nucleic acid comprises an Adenine to replace the Cytosine at position 19:g.45412013C>A in the APOE gene, wherein said administration results in the generation of one or more ApoE R136S alleles in one or more cells of said subject. In some embodiments, the targeting domain of the gRNA molecule includes a sequence that is the same as, or differs by no more than 3 nucleotides from, a sequence from Table 7.

As used herein, "prevent" means to reduce risk of developing the disorder.

In some embodiments, the human subject is diagnosed with or is at risk for developing Alzheimer's disease. In some embodiments, the human subject carries one or more copies of the APOE4 allele. In some embodiments, the human subject carries one or more mutations in at least one gene selected from the group consisting of: APP, PSEN1, and PSEN2. In some embodiments, the human subject carries one or more mutations in additional genes that cause autosomal-dominant Alzheimer's disease (e.g. those described in Bateman et al., *Alzheimer's Research & Therapy* 3 (1): 1, 2011). In some embodiments, the human subject carries all or a portion of a third copy of chromosome 21. In some embodiments, the human subject is diagnosed with Alzheimer's disease by established biomarkers, such as those obtained via brain imaging, or blood or CSF samples. In some embodiments, the human subject is over the age of 50 (e.g. over the age of 55, 60, 65, 70, 75, 80, 85, 90, or 95). In some embodiments, the human subject is diagnosed with or is at risk of developing a disorder selected from the group consisting of: vascular cognitive impairment, vascular dementia, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), Lewy body dementia, frontotemporal dementia, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Huntington's disease, neurodegenerative diseases, cerebrovascular diseases, brain injury, chronic traumatic encephalopathy, tauopathies, amyloidopathies, synucleinopathies, Creutzfeldt-Jakob disease, retinal degeneration, glaucoma, retinal injury, optic nerve degeneration, and aging.

In yet another aspect, provided herein is a method of identifying a human subject less susceptible to developing an early onset neurodegenerative disease, comprising: obtaining a biological sample from the subject; detecting the presence of at least one mutant allele of APOE3, or the presence of a mutant ApoE3 gene product, in the biological sample; and identifying a subject as being less susceptible to developing an early onset neurodegenerative disease, based on the presence of a mutant ApoE3 allele or gene product in

the biological sample. In some embodiments, the biological sample is blood, cerebrospinal fluid, saliva, urine, tears, vitreous humor, aqueous humor, or a tissue specimen. In some embodiments, the neurodegenerative disease is Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, retinal degeneration, or glaucoma. In some embodiments, the retinal degeneration is age-related macular degeneration. In some embodiments, the detecting comprises determining the sequence of an APOE3 allele in the subject. In some embodiments, the detecting comprises determining the presence or absence of an APOE3 sequence that encodes an ApoE3 protein with a mutation at R136 as compared to a wild type ApoE3 protein. In some embodiments, the mutation at R136 is R136S, R136H, or R136C. In some embodiments of any of the methods of identifying a human subject less susceptible to developing an early onset neurodegenerative disease described herein, the methods further include selecting a subject for inclusion in a clinical trial, and optionally administering an experimental treatment, or excluding the subject from the clinical trial, if the subject does not have a mutant APOE3 allele. In some embodiments of any of the methods of identifying a human subject less susceptible to developing an early onset neurodegenerative disease described herein, the methods further include selecting a subject for inclusion in a clinical trial, and optionally administering an experimental treatment, or excluding the subject from the clinical trial, if the subject has a mutant APOE3 allele.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

#### DESCRIPTION OF DRAWINGS

FIG. 1 shows a model of the structure of the wild-type APOE3 protein. N-terminal (residues 1-191) and C-terminal (residues 201-299) domains are shown. The amino acid positions for APOE4 (C112R), APOE3ch (R136S) and APOE2 (R158C) variants are shown.

FIG. 2 shows representative Sanger sequencing results of APOE from control, proband and descendant's samples.

FIG. 3 depicts the subject's genealogy, with circles representing females, squares representing males, diamonds representing individuals whose gender has been masked for privacy, arrowhead depicts proband individual with MCI, and shading indicates individual with history of dementia. Deceased individuals are marked with a crossed bar. The individual APOE and PSEN1 genotypes are indicated as appropriate to preserve anonymity.

FIGS. 4A and 4B are fundus photographs of the right and left eyes, respectively. FIG. 4C shows an infrared image of the right eye that depicts the cross section of the retina (line) seen in FIG. 4D. FIG. 4D shows results of optical coherence

tomography (OCT) of the right eye. FIG. 4E shows an infrared image of the left eye. FIG. 4F shows results of OCT imaging of the left eye.

FIG. 5 shows brain imaging results showing the amyloid plaque burden and PHF Tau burden in the brains of the PSEN1 mutation carrier with late onset MCI (mild cognitive impairment) and a PSEN1 mutation carrier with MCI onset at a typical age for this mutation (44 years).

FIG. 6 shows measurements of amyloid burden, tau burden, hippocampal volume, and the levels of glucose metabolism in PSEN1 E280A mutation carriers. Red dots represent the measurements for the carrier with two APOE3ch alleles and an exceptionally late onset of MCI. Black dots represent PSEN1 E280A mutation carriers with MCI at the kindred's typical, younger age at MCI onset. Gray dots represent PSEN1 E280A mutation carriers who have not yet developed MCI.

FIG. 7 shows the rate of A $\beta$ 42 fibril formation in the presence of APOE3 wild-type, APOE3ch, or in the absence of APOE as detected by Thioflavin T fluorescence. Changes in relative fluorescence units (RFU) were plotted for time in minutes (min). (\*\* P<0.001, \*\*\*\* P<0.0001)

FIG. 8 shows schematic of the split-luciferase complementation triggered by amyloid oligomerization (top) and percentage of luminescence obtained by split-luciferase complementation assay after 24 hours in culture medium from 293T cells transfected with ApoE3ch or ApoE3 wild type.

FIG. 9 shows ELISA results of APOE2 and APOE4 heparin-binding affinity.

FIG. 10 shows western blot analysis of the heparin-binding affinity of ApoE2, ApoE3, ApoE4 and ApoE3ch.

FIGS. 11A and 11B show ELISA results of the heparin-binding affinity of ApoE2, ApoE3, ApoE4 and ApoE3ch.

FIG. 12A is a schematic showing the experimental setup for testing the specificity of the monoclonal ApoE3 antibody in blocking ApoE3/heparin binding. FIGS. 12B and 12C are schematics showing the process of passing the ApoE3 protein pre-incubated with the monoclonal antibody through a heparin binding column followed by washing and eluting.

FIGS. 13A-13B show results from BCA assays performed on various fractions from the heparin binding column. FIG. 13A shows the amount of ApoE3 in various fractions in the absence of the ApoE3 antibody. FIG. 13B shows the amount of ApoE3 in various fractions in the presence of the ApoE3 antibody.

FIG. 14 shows western blot results showing the amount of ApoE3 in various fractions with or without pre-incubation with the monoclonal ApoE3 antibody.

FIGS. 15A-15G show ELISA analysis of the 19G10-2, 23B2, 2H79-1, 30E1-2, 16H8, 25F1-2, and 29G10-1 antibody, respectively.

FIG. 16 shows western blot analysis of the heparin-binding affinity of ApoE3 treated with the wild type ApoE3 peptide and the ApoE3ch mutant peptide.

FIGS. 17A-17D show modeling of the interaction of ApoE fragments with heparin. FIG. 17A shows a model of the wild type ApoE fragment containing amino acids 129-157 interacting with heparin. FIG. 17B shows a model of the fragment of ApoE R136S that contains amino acids 129-157 interacting with heparin. FIG. 17C shows a model of the wild type ApoE fragment containing amino acids 114-144 interacting with heparin. FIG. 17D shows a model of the fragment of ApoE R136S that contains amino acids 114-144 interacting with heparin.

FIGS. 18A-18B show heparin-affinity chromatography and western blot analysis of antibody 1H4.

FIGS. 19A-19D show ELISA results of 1H4-2 serum tested with ApoE3 WT full-length protein (A), ApoE3 WT peptide (B), ApoE3ch full length protein (C), and ApoE3ch peptide (D).

FIG. 20 shows ELISA results of 1H4-2 serum tested with ApoE3 WT full-length protein, ApoE3 WT peptide, ApoE3ch full length protein, and ApoE3ch peptide.

FIG. 21 shows representative ELISA profiles of serial dilutions of the antibody 1H4 incubated either with human recombinant ApoE3 or mouse recombinant ApoE3.

FIG. 22 shows ELISA results for the monoclonal 1H4 antibody purified from cloned hybridoma.

FIGS. 23A and 23B show heparin-affinity chromatography and western blot analysis of antibody 7C11.

FIGS. 24A-24D show ELISA results from testing the 7C11-1 serum with ApoE3 WT full-length protein (A), ApoE3 WT peptide (B), ApoE3ch full length protein (C), or ApoE3ch peptide (D).

FIG. 25 shows ELISA results from testing the 7C11-1 serum with ApoE3 WT full-length protein, ApoE3 WT peptide, ApoE3ch full length protein, or ApoE3ch peptide.

FIG. 26 shows ELISA results for the monoclonal 7C11-1 antibody purified from cloned hybridoma.

FIG. 27 shows results from ELISA screening of the 19G10-2 antibody against the heparin binding domain of APOE3 Wild Type (WT) and APOE3ch Mutant recombinant protein.

FIGS. 28A and 28B show heparin-affinity chromatography and western blot analysis of antibody 19G10-2.

FIG. 29 shows western blotting of ApoE3 WT incubated with 19G10-2 serum antibody.

FIG. 30 is representative ELISA showing the differences in binding of both serum and monoclonal antibody hybridoma supernatant 19G10-2 for ApoE3WT or ApoE3ch.

FIG. 31 is an enlargement of the Y axes in FIG. 30.

FIG. 32 shows ELISA results for the monoclonal 19G10-2 antibody purified from cloned hybridoma.

FIG. 33 shows results from ELISA screening of the 25F1-2 antibody against the heparin binding domain of APOE3 Wild Type (WT) and APOE3ch Mutant recombinant protein.

FIGS. 34A and 34B show heparin-affinity chromatography and western blot analysis of antibody 25F1-2.

FIG. 35 shows western blotting of ApoE3 WT incubated with the 25F1-2 monoclonal antibody.

FIG. 36 is representative ELISA showing the differences in binding of both 25F1-2 serum and monoclonal antibody hybridoma supernatant 25F1-2 for ApoE3WT or ApoE3ch.

FIG. 37 is an enlargement of the Y axes of FIG. 36.

FIG. 38 shows ELISA results for the monoclonal 25F1-2 antibody purified from cloned hybridoma.

FIG. 39 shows ELISA screening of the 1343 antibody against the heparin binding domain of APOE3 Wild Type (WT) and APOE3ch Mutant recombinant protein.

FIG. 40 shows ELISA screening of the 1343 antibody against the heparin binding domain of APOE3 Wild Type (WT) and APOE3ch Mutant recombinant protein.

FIG. 41A shows western blot analysis of ApoE in protein fractions eluted from heparin columns in the presence or absence of the 1343 antibody. FIG. 41B shows ELISA analysis of the fractions.

FIG. 42A shows an exemplary experimental outline for an intraocular model of inducible APOE-dependent Tau hyperphosphorylation. FIG. 42B shows PHF tau in control retina injected with PBS. FIG. 42C shows retina injected with recombinant human APOE3.

FIGS. 43A-43I show PHF tau in control retina as compared to retina injected with either the mouse 1H4-2 antibody or the humanized 1343Ah antibody.

FIG. 44 shows representative binding measurements of increasing concentrations (nM) of ApoE3 protein to 1H4 on the protein A biosensor.

## DETAILED DESCRIPTION

The present disclosure uncovers that homozygosity for APOE3ch (having two copies of the APOE3 Christchurch (R136S) mutation) is associated with a profound resistance to the clinical onset of Alzheimer's disease, and that the R136S mutation significantly diminishes the ability of ApoE to bind heparan sulfate proteoglycans (HSPG)/heparin. Accordingly, the present disclosure is related to antibodies that bind to wild type ApoE and/or ApoE isoform(s) containing the R136S mutation (e.g. antibodies that block the interaction and/or reduces binding between ApoE and HSPG/GAG/heparin). Fusion proteins containing peptide fragments (e.g. HSPG/GAG/heparin-binding domain) of wild type and mutant ApoE containing the R136S mutation are also contemplated. These proteins may be administered via human cells expressing such compositions. The present disclosure is further related to small molecules that block the interaction between ApoE and HSPG/heparin, and methods of screening for small molecules of the same. Also provided are compositions and methods of editing the ApoE locus with a genome editing system. The antibodies, fusion proteins, small molecules, and genome editing systems described herein are useful in the treatment or prevention of cognitive decline associated with dementia and/or mild cognitive impairment (MCI) and/or neurodegeneration, e.g. Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, or Huntington's disease. The antibodies, fusion proteins, small molecules, and genome editing systems described herein are also useful in the treatment or prevention of neurodegenerative diseases, cerebrovascular conditions, brain injuries, retinal degeneration, optic nerve degeneration, or retinal injury.

### Apolipoprotein E (ApoE)

Apolipoprotein E variants are the major genetic modifier of AD contributing to the susceptibility to late-onset AD. APOE4 allele leads to a change of cysteine to arginine at position 112 and is associated with a 5 fold increase in AD risk in single allele carriers, reaching a 20 fold increase in homozygote carriers. APOE2 leads to an amino acid change of arginine to cysteine at position 158 and is protective for AD whereas the APOE3 allele is thought to be neutral (Corder et al., Nat Genet (7) 180-184, 1994; Hauser et al., Cure Alzheimer Res (10): 808-817, 2013). APOE impacts amyloid production, aggregation, and clearance, is a component of amyloid plaques, and exacerbates tau-mediated neurodegeneration. APOE alleles also regulate lipid metabolism and cardiovascular risk. About 5-10% of APOE2 homozygote individuals develop hyperlipoproteinemia type III (HLP III), whereas other APOE rare variants are linked to autosomal dominant HLP III. HLP III is characterized by increased plasma cholesterol and triglycerides levels and by the presence of tuberous or striated palmar xanthomas. The mechanisms by which APOE alleles modify AD risk and cause HLP III are not completely understood. Salient APOE properties impacted by specific mutations include differences in 1) binding affinities to lipids and the LDL receptor; 2) nature of interdomain interactions between its N-terminus (amino acids 1 to 199) and C-terminus domains (216 to

299); and, 3) ability to form homo-oligomers mediated by the C-terminus domain (Frieden et al., PNAS (109):8913-8918, 2012; Georgiadou et al., PLOS One (6)e27037, 2011; Lalazar et al., J Biol Chem (263):3542-3545, 1988).

Heparan sulfate (HS) is a linear polysaccharide found in all animal tissues, which occurs as a proteoglycan (HSPG) in which two or three HS chains are attached in close proximity to cell surface or extracellular matrix proteins. HSPG moieties are present in hundreds of proteins located in the plasma membrane and in the extracellular matrix. Protein-protein interactions mediated via HSPG play a critical role in a multitude of processes relevant to Alzheimer's pathology including amyloid and tau pathology. Heparan sulfate is a member of the glycosaminoglycan family of carbohydrates and is very closely related in structure to heparin. Both consist of a variably sulfated repeating disaccharide unit. Heparan sulfate binds with a large number of extracellular proteins. These are often collectively called the "heparin interactome" or "heparin-binding proteins", because they are isolated by affinity chromatography on the related polysaccharide heparin.

An exemplary amino acid sequence of the human ApoE3 protein (Uniprot Accession No. P02649) is shown below:

(SEQ ID NO: 1)  
 KVEQAVETEPEPELRRQQTEWQSGQRWELALGRFWDYLRWVQTLSEQVQEE  
 LLSSQVTQELRALMDETMKELKAYKSELEELQLTPVAEETRARLSKELQAA  
 QARLGADMEDVCGRLLQYRGEVQAMLGQSTEELRVRLASHLRLKRKLLR  
 DADDLQKRLAVYQAGAREGAERGLSAIRERLGPLVEQGRVRAATVGSLAG  
 QPLQERAQAWGERLRARMEEMGSRTDRRLDEVKEQVAEVRAKLEEQAQQI  
 RLQAEAFQARLKSWEEPVLVEDMQRQWAGLVEKVQAAVGTSAAPVPSDNH

At least two HSPG/heparin-binding domains have been identified in human ApoE, one located in the N-terminal domain and one in the C-terminal domain (Weisgraber et al. J Biol Chem, 261 (5): 2068-76, 1986; Saito et al., J Biol Chem, 278 (17): 14782-7, 2003). The HSPG/heparin-binding domain near arginine 136 (R136) (the N-terminal HSPG/heparin-binding domain) is functional in the full-length lipidated and delipidated ApoE, while the HSPG/heparin-binding domain in the C-terminal domain is functional only in the absence of the N-terminal domain and in delipidated ApoE. The N-terminal HSPG/heparin-binding domain is well-characterized, and comprises the amino acid residues 142 to 147 of SEQ ID NO: 1 (**bolded**). The C-terminal HSPG/heparin-binding domain is less well-characterized, and comprises the lysine (K) at position 233 and other charged amino acids in the vicinity including amino acid residues 211 to 218 and 243 to 272 of SEQ ID NO: 1. The present inventors show that the arginine at position 136 of ApoE plays a critical role in heparin binding of ApoE. Without wishing to be bound by theory, a potential mechanism is the allosteric modulation of heparin binding mediated by the arginine at position 136. Allosteric modulation as used herein is related to the modulation of ligand binding through the binding of allosteric modulators at one or more sites of allosteric modulation, which may be different from the binding site(s) of the ligand. In some embodiments, the one or more sites of allosteric modulation for ApoE and HSPG/heparin binding comprise the arginine at position 136 of ApoE as shown in SEQ ID NO: 1. "HSPG/heparin-binding domain(s)", "HSPG/heparin-binding site(s)",

"HSPG-binding domain(s)", and "HSPG-binding site(s)" are used interchangeably herein.

#### Anti-ApoE Antibodies

Provided are anti-ApoE antibodies that bind to a wild type or a mutant ApoE protein (e.g., a human ApoE protein). In some instances, the antibodies described herein bind to a wild type ApoE protein (e.g. ApoE2, ApoE3 or ApoE4), but not to a mutant ApoE protein (e.g. ApoEch). In some instances, the antibodies described herein bind to a mutant ApoE protein (e.g. ApoEch), but not to a wild type ApoE protein (e.g. ApoE2, ApoE3 or ApoE4). In some instances, the antibodies described herein bind to both a mutant ApoE protein (e.g. ApoEch), and a wild type ApoE protein (e.g. ApoE2, ApoE3 or ApoE4).

In some instances, the antibodies provided herein block the interaction between a wild type ApoE protein (e.g. ApoE2, ApoE3 or ApoE4) and HSPG. The antibodies provided herein may reduce or modulate the binding affinity of an ApoE protein (e.g. ApoE2, ApoE3 or ApoE4) to HSPG.

In some instances, the antibodies provided herein bind to the HSPG-binding domain of a wild type ApoE protein. In some instances, the antibodies provided herein bind to one or more sites of allosteric modulation of HSPG/ApoE binding (e.g., amino acid position 136 of ApoE). In some instances, the antibodies described herein reduces fibril formation and/or amyloid oligomerization.

In some instances, the antibodies provided herein bind to an amino acid sequence in a wild type or mutant ApoE that comprises or consists of TEELRVSLASHLRK (SEQ ID NO:2). In some instances, the antibodies provided herein bind to an amino acid sequence in a wild type or mutant ApoE that comprises or consists of TEELRVRLASHLRK (SEQ ID NO:3). In some instances, the amino acid sequence TEELRVSLASHLRK (SEQ ID NO:2) comprises or consists of an epitope for the antibodies provided herein. In some instances, the amino acid sequence TEELRVRLASHLRK (SEQ ID NO:3) comprises or consists of an epitope for the antibodies provided herein. Variants of these sequences can also be used, e.g., those that are at least 80%, 85%, 90%, or 95% identical to these sequences.

Calculations of "identity" between two sequences can be performed as follows. The sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second nucleic acid sequence for optimal alignment and non-identical sequences can be disregarded for comparison purposes). The length of a sequence aligned for comparison purposes is at least 70% (e.g., at least 80%, 90% or 100%) of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In some embodiments, the percent identity between two nucleotide sequences is determined using the Needleman and Wunsch ((1970) J. Mol. Biol. 48:444-453) algorithm, which has been incorporated into the GAP program in the GCG software package (available at [gcb.com](http://gcb.com)), using either a Blossum 62 matrix, a PAM250 matrix, a NWSgapdna.CMP matrix. In some embodiments, the percent identity between two amino acid

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or nucleotide sequences can be determined using the algorithm of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

Usage of the term “antibody” in this disclosure is meant to cover a whole antibody (as opposed to a minibody or antibody fragment), a bispecific antibody, a trivalent antibody, a multispecific antibody, a minibody, and antibody fragments. In some instances, the anti-ApoE antibody of this disclosure is a whole antibody. In some instances, the anti-ApoE antibody of this disclosure is a chimeric, human, or humanized antibody. In certain instances, the heavy chain constant region of the anti-ApoE antibody is a human IgG1, human IgG2, human IgG3, or human IgG4 constant region. In certain instances, the light constant region is a human

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Any of the anti-ApoE antibodies described herein are useful for treating or preventing disorders associated with dementia or mild cognitive impairment (MCI) (e.g. Alzheimer’s disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson’s disease, or Huntington’s disease), neurodegenerative diseases, cerebrovascular diseases, brain injury, retinal degeneration, or retinal injury.

## 10 Exemplary Antibody 1H4-2

Antibody 1H4-2 was generated by immunizing with APOE: KLH-CTEELRVRLASHLRK-CONH2 (SEQ ID NO: 54). The amino acid sequences of the complementarity determining regions (CDRs) and the heavy chain variable region and light chain variable regions of 1H4-2 are provided below.

Variable region	Chain type	CDR-1	CDR-2	CDR-3
1H4-2 VL	Light chain	KASQSVYDGD SYMN (SEQ ID NO: 4)	AASNLES (SEQ ID NO: 5)	QQSNEDPWT (SEQ ID NO: 6)
1H4-2 VH	Heavy chain	SYTMS (SEQ ID NO: 7)	KIRNGGGITYYLDLTKG (SEQ ID NO: 8)	HYYGSEDYFDY (SEQ ID NO: 9)

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kappa constant region. In other instances, the light constant region is a human lambda constant region. In some instances, the antibodies of this disclosure are designed to have low effector functionality (e.g., by Fc modifications such as N297Q, T299A, etc. See, also, Wang, X., Mathieu, M. & Brezski, R. J. *Protein Cell* (2018) 9: 63. doi.org/10.1007/s13238-017-0473-8 (incorporated by reference herein)). In some cases, the Fc moiety of the antibody is a hIgG1 Fc, a hIgG2 Fc, a hIgG3 Fc, a hIgG4 Fc, a hIgG1 agly Fc, a hIgG2 SAA Fc, a hIgG4 (S228P) Fc, or a hIgG4 (S228P)/G1 agly Fc (in this format—that minimizes effector function—the CH1 and CH2 domains are IgG4 with a ‘fixed’ hinge (S228P) and is aglycosylated. The CH3 domain is hIgG1, or a hIgG4 (S228P) agly Fc). In one case, the antibody has one of the following three scaffolds with reduced effector function: hIgG1 agly (N297Q); hIgG2 SAA (see, Vafa et al. *Methods*, 65(1):114-26 (2014); and hIgG4/P/G1 agly (see, US 2012/0100140 A1).

In some embodiments, an antibody or ApoE-binding fragment thereof described herein demonstrates the binding characteristics and/or biological properties as outlined for the antibodies 1H4-2, 7C11-1, 19G10-2, 23B2 (1343), 2H79-1, 30E1-2, 16H8, 25F1-2, and 29G10-1 illustrated in the Examples section below.

In some embodiments, the present disclosure provides an antibody that binds to wild type human ApoE or a portion thereof and has one or more of the following properties: (i) binds with high affinity of KD≤20 nM to wild type human ApoE; (ii) competes with wild type human ApoE for binding to heparin; and (iii) reduces Paired Helical Filament (PHF) Tau formation in retinal cells.

In some embodiments, the present disclosure provides an antibody that binds to a mutant human ApoE (e.g., those having a mutation at amino acid position 136 of the human ApoE, such as ApoEch) or a portion thereof and has one or more of the following properties: (i) binds with high affinity of KD≤20 nM to mutant human ApoE (e.g., mutation at amino acid position 136 of the human ApoE, such as ApoEch); (ii) competes with wild type human ApoE for binding to heparin; and (iii) reduces Paired Helical Filament (PHF) Tau formation in retinal cells.

## 30 Variable Light Chain:

## Nucleotide sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 10)

ATGGAGACAGACACAATCCTGCTATGGGTGCTGCTGCTCTGGGTTCCAGG

CTCCACTGGTGACAATGTGCTGACCCAATCTCAGCTCTTGGCTGTGT

35 CTCTAGGGCAGAGGCCACCATCTCCTGCAAGGCCAGCAAAGTGTGAT

TATGATGGTGTAGTTATATGAACTGGTACCAACAGAAAACCAGGACAGCC

40 ACCCAAAGTCTTCATCTATGCTGCATCCAATCTAGAATCTGGATCCCAG

CCAGGTTTAGTGGCAGTGGGCTGGGACAGACTTCACCCCTAACATCCAT

CCTGTGGAGGAGGAGGATGCTGCAACCTATTACTGTCAGCAAAGTAATGA

45 GGATCCGGGACGTTGGAGGACCAAGCTGG AAATCAA

## Amino acid sequence:

Signal peptide-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 12)

METDTILLWVLLWVPGSTGDNVLTQSPASLAVSLGQRATISCKASQSVD

50 YDGDSYMWYQQKPGQPPKVFIAASNLESGI PARFSGSGSGTDFTLNH

PVEEEADAATYYCQQSNEDPWTFGGGT KLEIK

## 55 Variable Heavy chain:

## Nucleotide sequence

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 11)

ATGAATTCTGGGCTCAGCTTGATTTCTTGCTCTGTTAAAAGGTGT

60 CCTGTGTGAAGTGAAGCTGGTGGAACTGGGGAGGTGTTGCGAGCTG

GAGGGTCCCTGAAACTCTCCTGTGCAGCCTCTGGATTCACTTCAGTAGC

TATACCATGTCCTGGGTTCGTCAGACTCCAGAGAAGAGGCTGGAGTGGT

65 CGCAAAATTCTGTAATGGTGGTGGTACACCTACTATTAGACACTTTAA

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- continued

AGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACACCCTATAACCTG  
CAAATGAGCAGTCTGAAGCTGAAGACACGGCCATTTATTCTGTGCAAG  
ACATTACTACGGTAGCGAGGACTACTTGACTACTGGGGCAAGGCACCA  
CTCTCACAGTCTCCTCA

Amino acid sequence:  
Signal peptide-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 13)  
MNFGLSLIFLVLKVLGVLCEVKLVESGGVVQPGGSLKLSCAASGFTFSS  
YTMSWVRQTPEKRLEWVAKIRNGGGITYYLDTLKGRFTISRDNAKNTLYL  
QMSSLKSEDTAIYFCARHYYGSEDYFDYWGQGTTTVSS

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13 and a VL that is identical to the amino acid sequence set forth in SEQ ID NO: 12.

In certain instances, an antibody of this disclosure that binds to ApoE is one that competes with or binds to the same epitope as a reference antibody with a VH having the amino acid sequence set forth in SEQ ID NO: 13 and a VL having the amino acid sequence set forth in SEQ ID NO: 12.

#### Exemplary Antibody 7C11-1

10 Antibody 7C11-1 generated by immunizing with APOE: KLH-CTEELRVRLASHLRK-CONH2 (SEQ ID NO: 54). The amino acid sequences of the complementarity determining regions (CDRs) and the heavy chain variable region and light chain variable regions of 7C11-1 are provided below.

Variable region	Chain type	CDR-1	CDR-2	CDR-3
7C11-1 VL	Light chain	KASQSVDYDGDSYMN (SEQ ID NO: 14)	AASNL <u>ES</u> (SEQ ID NO: 15)	QQSNEDPWT (SEQ ID NO: 16)
7C11-1 VH	Heavy chain	RYTMS (SEQ ID NO: 17)	KIRNVGGITYYPD TVKG (SEQ ID NO: 18)	HYYGSEDYFDY (SEQ ID NO: 19)

In some instances, the anti-ApoE antibody comprises a VH comprising the three VH CDRs and a VL comprising the three VL CDRs of antibody 1H4-2. The six CDRs can be based on any definition known in the art such as, but not limited to, Kabat, Chothia, enhanced Chothia, contact, IMGT, or Honegger definitions. These CDRs can be determined, e.g., by using the AbYsis database ([bioinf.org.uk/abysis/sequence\\_input/key\\_annotation/key\\_annotation.cgi](http://bioinf.org.uk/abysis/sequence_input/key_annotation/key_annotation.cgi)).

In one instance, an anti-ApoE antibody of this disclosure comprises (i) a VH comprising a VHCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 7, a VHCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 8, and a VHCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9; and (ii) a VL comprising a VLCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 4, a VLCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 5, and a VLCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 6.

In some instances, the anti-ApoE antibody comprises a VH that is at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 13. In some instances, the anti-ApoE antibody comprises a VL that is at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 12. In one instance, the anti-ApoE antibody comprises a VH that is at least 85% identical to the amino acid sequence set forth in SEQ ID NO: 13 and a VL that is at least 85% identical to the amino acid sequence set forth in SEQ ID NO: 12. In another instance, the anti-ApoE antibody comprises a VH that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 13 and a VL that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 12. In yet another instance, the anti-ApoE antibody comprises a VH that is identical to the amino acid sequence set forth in SEQ ID NO:

#### Variable Heavy Chain:

30 Nucleotide sequence  
Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 20)  
ATGAATTCTGGGCTCAGCGTGATTTCTTGTCCTTGTTAAAGGTGT

CCTGTGTGAAGTGAAGCTGGTGGAGTCTGGGGAGGTTAGTGCAGCCTG  
35 GAGGGTCCTGAAACTCCTGTGCAGCCTCTGGATTCACTTCAGTAGG  
TATACCATGTCTGGGTCGGCAGACTCCAGAGAAGAGGCTGGAGTGGGT  
CGCAAAATTCGTAATGTTGGTGGTACACCTACTATCCAGACACTGAA

40 AGGGCCGATTTCACCATCTCCAGAGACAACGCCAAGAACACCCTTACCTG  
CAAATGAGCAGTCTGAAGTCTGAAGACACGGCCATGTATTACTGTGCAAG  
ACATTATTACGGTAGCGAGGACTACTTGACTACTGGGGCAAGGCACCA

45 CTCTCACAGTCTCCTCA

Amino acid sequence:  
Signal peptide-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 22)  
MNFGLSLIFLVLKVLGVLCEVKLVESGGVVQPGGSLKLSCAASGFTFSR  
50 YTMSWVRQTPEKRLEWVAKIRNGGGITYYPDTVKGRFTISRDNAKNTLYL  
QMSSLKSEDTAMYYCARHYYGSEDYFDYWGQGTTTVSS

#### Variable Light chain:

Nucleotide sequence:  
Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 21)  
ATGGAGACAGACAATCCTGCTATGGGTGCTGCTCTGGTTCCAGG

CTCCACTGGTGACAATGTGCTGACCCAATCTCAGCTTGGCTGTG  
55 CTCTAGGGCAGAGGCCACCATCTCCTGCAAGGCCAGCCAAGGTGTTGAT

TATGATGGTGTAGTTATGAACTGGTACCAACAGAAACCAGGACAGCC

ACCCAAAGTCTTCATCTATGCTGCATCCAATCTAGAATCTGGGATCCCAG

60 CCAGGTTAGTGGCAGTGGTCTGGACAAACTTCACCCCAACATCCAT  
CTGGGTTAGTGGCAGTGGTCTGGACAAACTTCACCCCAACATCCAT

65 CCAGGTTAGTGGCAGTGGTCTGGACAAACTTCACCCCAACATCCAT

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CCTGTGGAGGAGGAGGATGCTGCAACCTATTACTGTCAGCAAAGTAATGAGGATCCGTGGACGTTCGGTGGA GGCACCAAGCTGGAAATCAA

Amino acid sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

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epitope as a reference antibody with a VH having the amino acid sequence set forth in SEQ ID NO: 23 and a VL having the amino acid sequence set forth in SEQ ID NO: 22.

Exemplary Antibody 19G10-2

Antibody 19G10-2 generated by immunizing with KLH-CTEELRVSLASHLRK-CONH2 (SEQ ID NO: 55). The amino acid sequences of the complementarity determining regions (CDRs) and the heavy chain variable region and light chain variable regions of 19G10-2 are provided below.

Variable region	Chain type	CDR-1	CDR-2	CDR-3
19G10-2 VL	Light chain	KASQSVYDGDSYMN (SEQ ID NO: 24)	AASNLES (SEQ ID NO: 25)	QQSNVDPWT (SEQ ID NO: 26)
19G10-2 VH	Heavy chain	DYHMH (SEQ ID NO: 27)	WIDPENGNTMYD PKFQG (SEQ ID NO: 28)	GTARASFDFY (SEQ ID NO: 29)

-continued

(SEQ ID NO: 23)

METDTILLWVLLLWVPGSTGDNVLTQSPASLAVSLQGRATISCKASQSVYDGDSYMNWYQQKPGQPPKVFIYAASNLESGIPARFSGSGSGTNFTLN  
IH  
PVVEEDAATYYCQOSNEDPWTFGG GTKLEIK

In some instances, the anti-ApoE antibody comprises a VH comprising the three VH CDRs and a VL comprising the three VL CDRs of antibody 7C11-1. The six CDRs can be based on any definition known in the art such as, but not limited to, Kabat, Chothia, enhanced Chothia, contact, IMGT, or Honegger definitions. These CDRs can be determined, e.g., by using the AbYsis database (bioinf.org.uk/abysis/sequence\_input/key\_annotation/key\_annotation.cgi).

In one instance, an anti-ApoE antibody of this disclosure comprises (i) a VH comprising a VHCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 17, a VHCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 18, and a VHCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 19; and (ii) a VL comprising a VLCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 14, a VLCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 15, and a VLCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 16.

In some instances, the anti-ApoE antibody comprises a VH that is at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 22. In some instances, the anti-ApoE antibody comprises a VL that is at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 23. In one instance, the anti-ApoE antibody comprises a VH that is at least 85% identical to the amino acid sequence set forth in SEQ ID NO: 22 and a VL that is at least 85% identical to the amino acid sequence set forth in SEQ ID NO: 23. In another instance, the anti-ApoE antibody comprises a VH that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 22 and a VL that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 23. In yet another instance, the anti-ApoE antibody comprises a VH that is identical to the amino acid sequence set forth in SEQ ID NO: 22 and a VL that is identical to the amino acid sequence set forth in SEQ ID NO: 23.

In certain instances, an antibody of this disclosure that binds to ApoE is one that competes with or binds to the same

20 Variable Light Chain:

Nucleotide sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 30)ATGGAGACAGACACAATCCTGCTATGGTGCTGCTGCTCTGGTTCAGGCTCCACTGGTGACATTG TGCTGACCCAATCTCCAGCTCTTGCTGTGTCTCTAGGGCAGAGGCCACCATCTCCTGCAAGGCCAGCAAAGTGTGATTATGATGGTGATAGTTATGAATTGGTACCAACAGAAAATCAGGACAGCCACCCAAACTCCTCATCTATGCTGCATCCAATCTAGAACATCTGGATCCCAGCCAGGTTTAGTGGCAGTGGTCTGGACAGACTTCACCCCTAACATCCATCCTGTGGAGGAGGAGGATGCTGCACACTTACTGTCAAGCAAAGTGTAAATGTGGATCCGTGGACGTTGGTGGAGGCACCAAGCTGGAAATCAA

40 Amino acid sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 32)METDTILLWVLLLWVPGSTGDIVLTQSPASLAVSLQGRATISCKASQSVYDGDSYMNWYQQKSGQPPKLLIYAASNLESGIPARFSGSGSGTDFTLNIH45 PVVEEDAATYYCQOSNEDPWTFGGGTKEIK

Variable Heavy chain analysis:

Nucleotide sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 31)ATGAAATGCAGCTGGTCATCTTCTCTGATGGCAGTGGTTACAGGGTCAATTTCAGAGGTTCAGCTGCAGCAGTCTGGGCTGAGCTGTGAGGCCAG55 GGGCCTTAGTCAGTTGCTCTGCAAAGCTCTGGCTCAACATTAAGACTACCATATGCACTGGTGAAGGAGAGGCCTGAAACAGGGCTGGAGTGGATTGGATGGATTGATCCTGAGAATGGTAACTATGTATGACCCGAAGTCC60 AGGGCAAGGCCAGTATAACAGCAGACACATCCTCAAACACAGCCTACCTGCAGCTTCAGCAGCTGACATCTGAGGACACTGCCGTATTACTGTGTTAGGGGGACAGCTCGGGCTCCCTTGACTACTGGGGCCAAGGCACCACTCTCA65 CAGTCCTCCTCA

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-continued

## Amino acid sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
 (SEQ ID NO: 33)

**MKCSWVIFFLMAVVTGVNSEVQLQQSGAELVRPGALVKLSCKASGFNIKD**  
**YHMHWVKERPEQGLEWIGWIDPENGNTMYDPKFQGKASITADTSSNTAYL**  
**QLSSLTSEDTAVYYCVRGTARASFDYWQGTTLTVSS**

In some instances, the anti-ApoE antibody comprises a VH comprising the three VH CDRs and a VL comprising the three VL CDRs of antibody 19G10-2. The six CDRs can be based on any definition known in the art such as, but not limited to, Kabat, Chothia, enhanced Chothia, contact, IMGT, or Honegger definitions. These CDRs can be determined, e.g., by using the AbYsis database ([bioinf.org.uk/abysis/sequence\\_input/key\\_annotation.cgi](http://bioinf.org.uk/abysis/sequence_input/key_annotation.cgi)).

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In certain instances, an antibody of this disclosure that binds to ApoE is one that competes with or binds to the same epitope as a reference antibody with a VH having the amino acid sequence set forth in SEQ ID NO: 33 and a VL having the amino acid sequence set forth in SEQ ID NO: 32.

## Exemplary Antibody 25F1-2

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Antibody 25F1-2 was generated by immunizing with KLH-CTEELRVSLASHLRK-CONH2 (SEQ ID NO: 55). The amino acid sequences of the complementarity determining regions (CDRs) and the heavy chain variable region and light chain variable regions of 25F1-2 are provided below.

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Variable region	Chain type	CDR-1	CDR-2	CDR-3
25F1-2 VL	Light chain	KASQSVVDGDYTMN (SEQ ID NO: 34)	TASNLES (SEQ ID NO: 35)	QQSNEDPWT (SEQ ID NO: 36)
25F1-2 VH	Heavy chain	DYHIH (SEQ ID NO: 37)	WIDPEIDKLYDP KFQG (SEQ ID NO: 38)	GTARASF DY (SEQ ID NO: 39)

In one instance, an anti-ApoE antibody of this disclosure comprises (i) a VH comprising a VHCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 27, a VHCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 28, and a VHCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 29; and (ii) a VL comprising a VLCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 24, a VLCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 25, and a VLCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 26.

## Variable Light Chain Analysis:

## 35 Nucleotide sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
 (SEQ ID NO: 40)

**ATGGAGACAGACACAATCCTGCTATGGGTGCTGCTGCTCTGGGTTCCAGG**

**CTCCACTGGTGACATTGCTGACCCAATCTCAGCTCTTGCTGTGT**

**CTCTAGGGCAGAGGCCACCATCTCCTGCAAGGCCAGCAAAGTGTGAT**

**TATGATGGTGTAACTTATGAACTGGTACCAACAGAAACCAGGACAGCC**

**ACCCAAACTCCTCATCTATACTGCATCCAATCTAGAACCTGGGATCCCAG**

**CCAGGTTTAGTGGCAGTGGCTGGGACAGACTTCACCCCTAACATCCAT**

**CCTGTGGAGGAGGTGGATGCTGCAACCTTAACTGTCAAGCAAAGTAATGA**

**GGATCCATGGACGTTGGTGGAGGACCAAGCTGG AAATCAAA**

## 40 Amino acid sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
 (SEQ ID NO: 42)

**METDTILLWVLLWVPGSTGDIVLTQSPASLA VSLQGRATISCKASQSVD**

**YDGDTYMNWYQQKPGQPPKLLIYTASNLESGIPARFSGSGSGTDFTLNIH**

**PVEEVDAATYYCQOSNEDPWTFGGGTKLEIK**

## 45 Variable Heavy chain analysis:

## Nucleotide sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
 (SEQ ID NO: 41)

**ATGAAATGCAGCTGGTCATCTTCTCTGATGGCAGTGGTTACAGGGT**

**CAATTCAAGGGTCAGCTGCAAGCTGGCTGAGCTTGAGGCCAG**

**GGGCCTTAGTCAGTGGCTCTGCAAAGCTCTGGCTCAACATTAAAGAC**

**TACCATATACACTGGGTGAAACAGAGGCCCTGAAACAGGGCCTGGACTGGAT**

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TGGATGGATTGATCCTGAGATTGATAAAACTCTATATGACCCGAAGTTTC  
AGGGCAAGGCCAGAATAACAGCAGACACATCCTCCAATACAGCCTACCTG  
CAGCTCAGCAGCCTGACATCTGAAGACACTGCCGTCTATTACTGTGCCAG  
GGGGACAGCTCGGGCTTCTTGACTACTGGGCCAAGGCACCCTCTCA  
CAGTCTCTCA

## Amino acid sequence:

Signal sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4  
(SEQ ID NO: 43)  
MKCSWVIFFLMAMVVTGVNSeVQLOQSGAELVRPGALVKWSCKASGFNIKD  
YHIHWVKQRPEQGLDWIGWIDPEIDKTLYDPKFQGKARITADTSSNTAYL  
QLSSLTSEDTAVYYCARGTARASFDYWQGTTLVSS

In some instances, the anti-ApoE antibody comprises a VH comprising the three VH CDRs and a VL comprising the three VL CDRs of antibody 25F1-2. The six CDRs can be based on any definition known in the art such as, but not limited to, Kabat, Chothia, enhanced Chothia, contact, IMGT, or Honegger definitions. These CDRs can be determined, e.g., by using the AbYsis database ([bioinf.org.uk/abysis/sequence\\_input/key\\_annotation/key\\_annotation.cgi](http://bioinf.org.uk/abysis/sequence_input/key_annotation/key_annotation.cgi)).

In one instance, an anti-ApoE antibody of this disclosure comprises (i) a VH comprising a VHCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 37, a VHCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 38, and a VHCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 39; and (ii) a VL comprising a VLCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 34, a VLCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 35, and a VLCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 36.

In some instances, the anti-ApoE antibody comprises a VH that is at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 43. In some instances, the anti-ApoE antibody comprises a VL that is at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 42. In one instance, the anti-ApoE antibody comprises a VH that is at least 85% identical to the amino acid sequence set forth in SEQ ID NO: 43 and a VL that is at least 85% identical to the amino acid sequence set forth in SEQ ID NO: 42. In another instance, the anti-ApoE antibody comprises a VH that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 43 and a VL that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 42. In yet another instance, the anti-ApoE antibody comprises a VH that is identical to the amino acid sequence set forth in SEQ ID NO: 43 and a VL that is identical to the amino acid sequence set forth in SEQ ID NO: 42.

In certain instances, an antibody of this disclosure that binds to ApoE is one that competes with or binds to the same epitope as a reference antibody with a VH having the amino acid sequence set forth in SEQ ID NO: 43 and a VL having the amino acid sequence set forth in SEQ ID NO: 42.

## Exemplary Antibody 1343ab

Antibody 1343ab was generated by immunizing with KLH-CTEELRVSLASHLRK-CONH2 (SEQ ID NO: 55). The amino acid sequences of the complementarity determining regions (CDRs) and the full length heavy and light chains are provided below.

Variable region	Chain type	CDR-1	CDR-2	CDR-3
5 1343 VL	Light chain	KASQSVVDYDGEN YMN (SEQ ID NO: 44)	VASNLES (SEQ ID NO: 45)	QQSNLDWPW (SEQ ID NO: 46)
	Heavy chain	GFNIKYD (SEQ ID NO: 47)	DPENGN (SEQ ID NO: 48)	GTARASFDY (SEQ ID NO: 49)

10 Full length heavy chain  
(SEQ ID NO: 53)  
15 EVQLQQSGAELVRPGALVKLSCKASGFNIKYDHLHNVKQRPEQGLE  
WIGWIDPENGNVIYDPKFQGKATMTV  
VTSSNTAYLQLRSLSLSEDTAVYFCTRGATARASFDYWQGTSLTVSSAK  
20 TPPPSVYPLAPGSAAQTNSMVTLG  
CLVKGYFPEPVTVWNNSGLSSGVHTFPAPVLQSDLYTLLSSVTVPSSST  
WPSETVTCNVAHPASSTKVDKKIV  
25 PRDCGCKPCICTVPEVSSVFIFPPPKPDVLTITLTPKVTCVVVDISKDD  
PEVQFSWFVDDDEVHTAQTQP  
EQFNSTFRSVESELPMIHQDWLNGKEFKCRVNSAAFPAPIEKTKISKTGKR  
30 PKAPQVYTI PPPKEQMAKDKVSL  
TCMITDFFPEDITVEWQWNQPAENYKNTQPIMDTDGSYFVYSKLN  
QKSNWEAGNTFTCSVVLHEGLHNHHT  
EKSLSHSPGK  
35 Full length light chain  
(SEQ ID NO: 52)  
DIVLTQSPASLA VSLGQRATISCKASQSVVDYDGENYMNWYQQKPGQS  
PKL LIYVASNLESGIPARFSGSGSG  
40 TDFTLNIHPVEEEDAAT YYCQQSNLDPWTFGGGTKLEIKRADAAPTV  
IFPPSSQEQLTSGGASVVCFLNNFY  
PKDINVWKWIDGSERQNGV LNSWTDQDSKDSTYSMSSTLTLKDEYE  
45 RHNSYTCEATHKTSTSPIVKS FNRN  
EC

N-linked glycosylation was detected on heavy chain constant region N at 292. Loss of C-terminal lysine observed on heavy chain.

In some instances, the anti-ApoE antibody comprises a VH comprising the three VH CDRs and a VL comprising the three VL CDRs of antibody 1343ab. The six CDRs can be based on any definition known in the art such as, but not limited to, Kabat, Chothia, enhanced Chothia, contact, IMGT, or Honegger definitions. These CDRs can be determined, e.g., by using the AbYsis database ([bioinf.org.uk/abysis/sequence\\_input/key\\_annotation/key\\_annotation.cgi](http://bioinf.org.uk/abysis/sequence_input/key_annotation/key_annotation.cgi)).

60 In one instance, an anti-ApoE antibody of this disclosure comprises (i) a VH comprising a VHCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 47, a VHCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 48, and a VHCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 49; and (ii) a VL comprising a VLCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 44, a VLCDR2 comprising the

amino acid sequence set forth in SEQ ID NO: 45, and a VLCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 46.

In some instances, the anti-ApoE antibody comprises a heavy chain that is at least 70%, 71%, 72%, 73%, 74%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 53. In some instances, the anti-ApoE antibody comprises a light chain that is at least 70%, 71%, 72%, 73%, 74%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 52. In one instance, the anti-ApoE antibody comprises a heavy chain that is at least 80% identical to the amino acid sequence set forth in SEQ ID NO: 53 and a light chain that is at least 80% identical to the amino acid sequence set forth in SEQ ID NO: 52. In another instance, the anti-ApoE antibody comprises a heavy chain that is at least 85% identical to the amino acid sequence set forth in SEQ ID NO: 53 and a light chain that is at least 85% identical to the amino acid sequence set forth in SEQ ID NO: 52. In yet another instance, the anti-ApoE antibody comprises a heavy chain that is identical to the amino acid sequence set forth in SEQ ID NO: 53 and a light chain that is identical to the amino acid sequence set forth in SEQ ID NO: 52.

In certain instances, an antibody of this disclosure that binds to ApoE is one that competes with or binds to the same epitope as a reference antibody with a heavy chain having the amino acid sequence set forth in SEQ ID NO: 53 and a light chain having the amino acid sequence set forth in SEQ ID NO: 52.

Chimeric, human, or humanized antibodies having the CDR sequences of any of the above antibodies can be generated based on methods described herein.

#### Antibody Fragments

Antibody fragments (e.g., Fab, Fab', F(ab')2, Fc<sub>ab</sub>, and Fv) can be prepared by proteolytic digestion of intact antibodies. For example, antibody fragments can be obtained by treating the whole antibody with an enzyme such as papain, pepsin, or plasmin. Papain digestion of whole antibodies produces F(ab)2 or Fab fragments; pepsin digestion of whole antibodies yields F(ab')2 or Fab'; and plasmin digestion of whole antibodies yields Fc<sub>ab</sub> fragments.

Alternatively, antibody fragments can be produced recombinantly. For example, nucleic acids encoding the antibody fragments of interest can be constructed, introduced into an expression vector, and expressed in suitable host cells. See, e.g., Co, M. S. et al., *J. Immunol.*, 152:2968-2976 (1994); Better, M. and Horwitz, A. H., *Methods in Enzymology*, 178:476-496 (1989); Pluckthun, A. and Skerra, A., *Methods in Enzymology*, 178:476-496 (1989); Lamoyi, E., *Methods in Enzymology*, 121:652-663 (1989); Rousseaux, J. et al., *Methods in Enzymology*, (1989) 121:663-669 (1989); and Bird, R. E. et al., *TIBTECH*, 9:132-137 (1991). Antibody fragments can be expressed in and secreted from *E. coli*, thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab)2 fragments (Carter et al., *Bio/Technology*, 10:163-167 (1992)). According to another approach, F(ab')2 fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')2 fragment with increased in vivo half-life comprising a salvage receptor binding epitope residues are described in U.S. Pat. No. 5,869,046.

#### Conjugated Antibodies

The antibodies disclosed herein can be conjugated antibodies that are bound to various molecules including macromolecular substances such as polymers (e.g., polyethylene glycol (PEG), polyethylenimine (PEI) modified with PEG (PEI-PEG), polyglutamic acid (PGA) (N-(2-Hydroxypropyl) methacrylamide (HPMA) copolymers), hyaluronic acid, radioactive materials (e.g. <sup>90</sup>Y, <sup>131</sup>I), fluorescent substances, luminescent substances, haptens, enzymes, metal chelates, and drugs.

In some embodiments, the antibodies described herein are modified with a moiety that improves its stabilization and/or retention in circulation, e.g., in blood, serum, or other tissues, including the brain, e.g., by at least 1.5, 2, 5, 10, 15, 20, 25, 30, 40, or 50-fold. For example, the antibodies described herein can be associated with (e.g., conjugated to) a polymer, e.g., a substantially non-antigenic polymer, such as a polyalkylene oxide or a polyethylene oxide. Suitable polymers will vary substantially by weight. Polymers having molecular number average weights ranging from about 200 to about 35,000 Daltons (or about 1,000 to about 15,000, and 2,000 to about 12,500) can be used. For example, the antibodies described herein can be conjugated to a water soluble polymer, e.g., a hydrophilic polyvinyl polymer, e.g., polyvinylalcohol or polyvinylpyrrolidone. Examples of such polymers include polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof, provided that the water solubility of the block copolymers is maintained. Additional useful polymers include polyoxyalkylenes such as polyoxyethylene, polyoxypropylene, and block copolymers of polyoxyethylene and polyoxypropylene; polymethacrylates; carborers; and branched or unbranched polysaccharides. In some embodiments, the antibodies described herein are modified with a moiety that improves its penetration of the blood-brain barrier (such as those described in Pardridge, *J Cereb Blood Flow Metab* 32 (11): 1959-1972, 2012). Exemplary blood-brain barrier penetrating moieties include, but are not limited to, glucose transporter type 1 (GLUT1), cationic amino-acid transporter type 1 (CAT1), monocarboxylic acid transporter type 1 (MCT1), concentrative nucleoside transporter type 2 (CNT2), active efflux transporter (AET) (e.g., p-glycoprotein, and those described in Pardridge, *J Cereb Blood Flow Metab* 32 (11): 1959-1972, 2012). Additional blood-brain barrier penetrating moieties are known in the art.

The above-described conjugated antibodies can be prepared by performing chemical modifications on the antibodies or the lower molecular weight forms thereof described herein. Methods for modifying antibodies are well known in the art (e.g., U.S. Pat. Nos. 5,057,313 and 5,156,840).

The anti-ApoE antibodies can be in the form of full length (or whole) antibodies, or in the form of low molecular weight forms (e.g., biologically active antibody fragments or minibodies) of the anti-ApoE antibodies, e.g., Fab, Fab', F(ab')2, Fv, Fd, dAb, scFv, and sc(Fv)2. Other anti-ApoE antibodies encompassed by this disclosure include single domain antibody (sdAb) containing a single variable chain such as, VH or VL, or a biologically active fragment thereof. See, e.g., Moller et al., *J. Biol. Chem.*, 285(49): 38348-38361 (2010); Harmsen et al., *Appl. Microbiol. Biotechnol.*, 77(1):13-22 (2007); U.S. 2005/0079574 and Davies et al. (1996) *Protein Eng.*, 9(6):531-7. Like a whole antibody, a sdAb is able to bind selectively to a specific antigen (e.g., ApoE2, ApoE3, ApoE4, or ApoEch). With a molecular weight of only 12-15 kDa, sdAbs are much smaller than

common antibodies and even smaller than Fab fragments and single-chain variable fragments.

In certain embodiments, an anti-ApoE antibody or antigen-binding fragment thereof or low molecular weight antibodies thereof specifically binds to the HSPG/heparin-binding domain of ApoE and reduces the severity of symptoms when administered to human patients having one or more of, or animal models of: dementia and/or mild cognitive impairment (MCI) (e.g. those associated with Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, Huntington's disease, or neurodegeneration). In certain embodiments, an anti-ApoE antibody or antigen-binding fragment thereof or low molecular weight antibodies thereof specifically binds to the HSPG/heparin-binding domain of ApoE and reduces the severity of symptoms when administered to human patients having one or more of, or animal models of: neurodegenerative diseases, cerebrovascular diseases (e.g. stroke, carotid stenosis, vertebral stenosis, or aneurysms), brain injuries (e.g. traumatic brain injury, acquired brain injury), retinal degeneration, glaucoma, or retinal injury. These features of an anti-ApoE antibody or low molecular weight antibodies thereof can be measured according to methods known in the art.

#### Nucleic Acids, Vector, Host Cells

This disclosure also features nucleic acids encoding the antibodies disclosed herein. Provided herein are nucleic acids encoding the VH CDR1, VH CDR2, and VH CDR3 of the anti-ApoE antibodies described herein. Also provided are nucleic acids encoding the VL CDR1, VL CDR2, and VL CDR3 of the anti-ApoE antibodies described herein. Provided herein are nucleic acids encoding the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of the anti-ApoE antibodies described herein. Also provided are nucleic acids encoding the heavy chain variable region (VH) of the anti-ApoE antibodies described herein, and/or nucleic acids encoding the light chain variable region (VL) of the anti-ApoE antibodies described herein. In certain instances, provided herein are nucleic acids encoding the VH and/or VL of the anti-ApoE antibodies described herein, linked to human heavy and/or human light chain constant regions, respectively. Also provided herein are nucleic acids encoding both VH and VL of the anti-ApoE antibodies described herein. In some instances, the nucleic acids described herein include a nucleic acid encoding the Fc region of a human antibody (e.g., human IgG1, IgG2, IgG3, or IgG4). In certain instances, the nucleic acids include a nucleic acid encoding the Fc region of a human antibody that has been modified to reduce or eliminate effector function (e.g., a N297Q or T299A substitution in a human IgG1 Fc region (numbering according to EU numbering)). In some cases, the nucleic acids include a nucleic acid encoding an Fc moiety that is a hIgG1 Fc, a hIgG2 Fc, a hIgG3 Fc, a hIgG4 Fc, a hIgG1agly Fc, a hIgG2 SAA Fc, a hIgG4 (S228P) Fc, or a hIgG4 (S228P)/G1 agly Fc.

Also disclosed herein are vectors (e.g. expression vectors) containing any of the nucleic acids described above.

Furthermore, this disclosure relates to host cells (e.g. bacterial cells, yeast cells, insect cells, or mammalian cells) containing the vector(s) or the nucleic acid(s) described above.

#### Methods of Obtaining Anti-ApoE Antibodies

Also provided herein are methods for making anti-ApoE antibodies useful in the present methods. General methods for making antibodies, e.g., monospecific, polyclonal, or monoclonal antibodies, are known in the art. For monoclonal antibodies, the process involves obtaining antibody-

secreting immune cells (lymphocytes) from the spleen of a mammal (e.g., mouse) that has been previously immunized with the antigen of interest (e.g., a peptide antigen as described herein) either in vivo or in vitro. The antibody-secreting lymphocytes are then fused with myeloma cells or transformed cells that are capable of replicating indefinitely in cell culture, thereby producing an immortal, immunoglobulin-secreting cell line. The resulting fused cells, or hybridomas, are cultured, and the resulting colonies screened for the production of the desired monoclonal antibodies. Colonies producing such antibodies are cloned, and grown either in vivo or in vitro to produce large quantities of antibody. A description of the theoretical basis and practical methodology of fusing such cells is set forth in Kohler and Milstein, *Nature* 256:495 (1975).

Mammalian lymphocytes can be immunized by in vivo immunization of the animal (e.g., a mouse) with a peptide antigen, e.g., a peptide antigen that is at least 80%, 85%, 90%, or 95% identical to KLH-CTEELRVRLASHLRK-CONH2 (SEQ ID NO: 54) or KLH-CTEELRVSLASHLRK-CONH2 (SEQ ID NO: 55), optionally with one or more substitutions or deletions, e.g., of up to 20% of the residues. For example, the methods can include immunizing the animal with a peptide comprising a sequence that is at least 80% identical to at least 10 consecutive amino acids from: the heparin-binding domain of APOE, e.g., a peptide comprising TEELRVRLASHLRK (SEQ ID NO: 3) or TEELRVSLASHLRK (SEQ ID NO: 2). Such immunizations are repeated as necessary at intervals of up to several weeks to obtain a sufficient titer of antibodies. Following the last antigen boost, the animals are sacrificed, and spleen cells removed.

Fusion with mammalian myeloma cells or other fusion partners capable of replicating indefinitely in cell culture is effected by known techniques, for example, using polyethylene glycol ("PEG") or other fusing agents (See Milstein and Kohler, *Eur. J. Immunol.* 6:511 (1976), which is hereby incorporated by reference). This immortal cell line, which is preferably murine, but can also be derived from cells of other mammalian species, including but not limited to rats and humans, is selected to be deficient in enzymes necessary for the utilization of certain nutrients, to be capable of rapid growth, and to have good fusion capability. Many such cell lines are known to those skilled in the art, and others are regularly described.

Procedures for raising polyclonal antibodies are also known. Typically, such antibodies can be raised by administering the protein or polypeptide of the present invention subcutaneously to New Zealand white rabbits that have first been bled to obtain pre-immune serum. The antigens can be injected, e.g., at a total volume of 100 µl per site at six different sites. Each injected material will contain synthetic surfactant adjuvant pluronic polyols, or pulverized acrylamide gel containing the protein or polypeptide after SDS-polyacrylamide gel electrophoresis. The rabbits are then bled two weeks after the first injection and periodically boosted with the same antigen three times every six weeks. A sample of serum is then collected 10 days after each boost. Polyclonal antibodies are then recovered from the serum by affinity chromatography using the corresponding antigen to capture the antibody. Ultimately, the rabbits are euthanized, e.g., with pentobarbital 150 mg/Kg IV. This and other procedures for raising polyclonal antibodies are disclosed in E. Harlow, et. al., editors, *Antibodies: A Laboratory Manual* (1988).

The method described herein comprises any one of the step(s) of producing a chimeric antibody, humanized anti-

body, single-chain antibody, Fab-fragment, bi-specific antibody, fusion antibody, labeled antibody or an analog of any one of those. Corresponding methods are known to the person skilled in the art and are described, e.g., in Harlow and Lane "Antibodies, A Laboratory Manual", CSH Press, Cold Spring Harbor (1988). When derivatives of said antibodies are obtained by the phage display technique, surface plasmon resonance as employed in the BIACore system can be used to increase the efficiency of phage antibodies which bind to the same epitope as that of any one of the antibodies described herein (Schier, Human Antibodies Hybridomas 7 (1996), 97-105; Malmborg, J. Immunol. Methods 183 (1995), 7-13). The production of chimeric antibodies is described, for example, in international application WO89/09622. Methods for the production of humanized antibodies are described in, e.g., European application EP-A1 0 239 400 and international application WO90/07861. A further source of antibodies to be utilized in accordance with the present invention are so-called xenogeneic antibodies. The general principle for the production of xenogeneic antibodies such as human-like antibodies in mice is described in, e.g., international applications WO91/10741, WO94/02602, WO96/34096 and WO 96/33735. As discussed above, the antibody described herein may exist in a variety of forms besides complete antibodies; including, for example, Fv, Fab and F (ab) 2, as well as in single chains; see e.g. international application WO88/09344.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, 2nd ed. (1988); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* Elsevier, N.Y., 563-681 (1981), said references incorporated by reference in their entireties. The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Thus, the term "monoclonal antibody" is not limited to antibodies produced through hybridoma technology.

In the known hybridoma process (Kohler et al., *Nature* 256 (1975), 495) the relatively short-lived, or mortal, lymphocytes from a mammal, e.g., B cells derived from a murine subject as described herein, are fused with an immortal tumor cell line (e.g., a myeloma cell line), thus, producing hybrid cells or "hybridomas" which are both immortal and capable of producing the genetically coded antibody of the B cell. The resulting hybrids are segregated into single genetic strains by selection, dilution, and re-growth with each individual strain comprising specific genes for the formation of a single antibody. They produce antibodies, which are homogeneous against a desired antigen and, in reference to their pure genetic parentage, are termed "monoclonal".

Hybridoma cells thus prepared are seeded and grown in a suitable culture medium that contain one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. Those skilled in the art will appreciate that reagents, cell lines and media for the formation, selection and growth of hybridomas are commercially available from a number of sources and standardized protocols are well established. Generally, culture medium in which the

hybridoma cells are growing is assayed for production of monoclonal antibodies against the desired antigen. The binding specificity of the monoclonal antibodies produced by hybridoma cells is determined by in vitro assays such as immunoprecipitation, radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA) as described herein. After hybridoma cells are identified that produce antibodies of the desired specificity, affinity and/or activity, the clones may be subcloned by limiting dilution procedures and grown 10 by standard methods; see, e.g., Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, pp 59-103 (1986). It will further be appreciated that the monoclonal antibodies secreted by the subclones may be separated from culture medium, ascites fluid or serum by conventional 15 purification procedures such as, for example, protein-A, hydroxylapatite chromatography, gel electrophoresis, dialysis or affinity chromatography.

In another embodiment, lymphocytes can be selected by micromanipulation and the variable genes isolated. For 20 example, peripheral blood mononuclear cells can be isolated from an immunized or naturally immune mammal, e.g., a human, and cultured for about 7 days in vitro. The cultures can be screened for specific immunoglobulins that meet the screening criteria. Cells from positive wells can be isolated. 25 Individual Ig-producing B cells can be isolated by FACS or by identifying them in a complement-mediated hemolytic plaque assay. Ig-producing B cells can be micromanipulated into a tube and the VH and VL genes can be amplified using, e.g., RT-PCR. The VH and VL genes can be cloned into an antibody expression vector and transfected into cells (e.g., eukaryotic or prokaryotic cells) for expression.

Alternatively, antibody-producing cell lines may be selected and cultured using techniques well known to the skilled artisan. Such techniques are described in a variety of 30 laboratory manuals and primary publications. In this respect, techniques suitable for use in the invention as described below are described in *Current Protocols in Immunology*, Coligan et al., Eds., Green Publishing Associates and Wiley-Interscience, John Wiley and Sons, New York (1991) which 35 is herein incorporated by reference in its entirety, including supplements.

Antibodies, such as those described above, can be made, for example, by preparing and expressing synthetic genes that encode the recited amino acid sequences. Methods of 40 generating variants (e.g., comprising amino acid substitutions) of any of the anti-ApoE antibodies are well known in the art. These methods include, but are not limited to, preparation by site-directed (or oligonucleotide-mediated) mutagenesis, PCR mutagenesis, and cassette mutagenesis of 45 a prepared DNA molecule encoding the antibody or any portion thereof (e.g., a framework region, a CDR, a constant region). Site-directed mutagenesis is well known in the art (see, e.g., Carter et al., *Nucl. Acids Res.*, 13:4431-4443 (1985) and Kunkel et al., *Proc. Natl. Acad. Sci. USA*, 82:488 50 (1987)). PCR mutagenesis is also suitable for making amino acid sequence variants of the starting polypeptide. See Higuchi, in *PCR Protocols*, pp. 177-183 (Academic Press, 1990); and Vallette et al., *Nucl. Acids Res.* 17:723-733 (1989). Another method for preparing sequence variants, 55 cassette mutagenesis, is based on the technique described by Wells et al., *Gene*, 34:315-323 (1985).

Antibodies can be produced in bacterial or eukaryotic cells. Some antibodies, e.g., Fab's, can be produced in bacterial cells, e.g., *E. coli* cells. Antibodies can also be 60 produced in eukaryotic cells such as transformed cell lines (e.g., CHO, 293E, COS, Hela). In addition, antibodies (e.g., scFv's) can be expressed in a yeast cell such as *Pichia* (see,

e.g., Powers et al., *J Immunol Methods*. 251:123-35 (2001), *Hanseula*, or *Saccharomyces*. To produce the antibody or antigen binding fragments thereof of interest, a polynucleotide encoding the antibody is constructed, introduced into an expression vector, and then expressed in suitable host cells. Standard molecular biology techniques are used to prepare the recombinant expression vector, transfet the host cells, select for transformants, culture the host cells and recover the antibody.

If the antibody is to be expressed in bacterial cells (e.g., *E. coli*), the expression vector should have characteristics that permit amplification of the vector in the bacterial cells. Additionally, when *E. coli* such as JM109, DH5 $\alpha$ , HB101, or XL1-Blue is used as a host, the vector must have a promoter, for example, a lacZ promoter (Ward et al., 341: 544-546 (1989)), araB promoter (Better et al., *Science*, 240:1041-1043 (1988)), or T7 promoter that can allow efficient expression in *E. coli*. Examples of such vectors include, for example, M13-series vectors, pUC-series vectors, pBR322, pBluescript, pCR-Script, pGEX-5X-1 (Pharmacia), "QIAexpress system" (QIAGEN), pEGFP, and pET (when this expression vector is used, the host is preferably BL21 expressing T7 RNA polymerase). The expression vector may contain a signal sequence for antibody secretion. For production into the periplasm of *E. coli*, the pelB signal sequence (Lei et al., *J. Bacteriol.*, 169:4379 (1987)) may be used as the signal sequence for antibody secretion. For bacterial expression, calcium chloride methods or electroporation methods may be used to introduce the expression vector into the bacterial cell.

If the antibody is to be expressed in animal cells such as CHO, COS, and NIH3T3 cells, the expression vector includes a promoter necessary for expression in these cells, for example, an SV40 promoter (Mulligan et al., *Nature*, 277:108 (1979)), MMLV-LTR promoter, EF1 $\alpha$  promoter (Mizushima et al., *Nucleic Acids Res.*, 18:5322 (1990)), or CMV promoter. In addition to the nucleic acid sequence encoding the immunoglobulin or domain thereof, the recombinant expression vectors may carry additional sequences, such as sequences that regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see e.g., U.S. Pat. Nos. 4,399,216, 4,634,665 and 5,179,017). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin, or methotrexate, on a host cell into which the vector has been introduced. Examples of vectors with selectable markers include pMAM, pDR2, pBK-RSV, pBK-CMV, pOPRSV, and pOP13.

In one embodiment, antibodies are produced in mammalian cells. Exemplary mammalian host cells for expressing an antibody include Chinese Hamster Ovary (CHO cells) (including dhfr $^{-}$  CHO cells, described in Urlaub and Chasin (1980) *Proc. Natl. Acad. Sci. USA* 77:4216-4220, used with a DHFR selectable marker, e.g., as described in Kaufman and Sharp (1982) *Mol. Biol.* 159:601-621), human embryonic kidney 293 cells (e.g., 293, 293E, 293T), COS cells, NIH3T3 cells, lymphocytic cell lines, e.g., NSO myeloma cells and SP2 cells, and a cell from a transgenic animal, e.g., a transgenic mammal.

The antibodies of the present disclosure can be isolated from inside or outside (such as medium) of the host cell and purified as substantially pure and homogenous antibodies. Methods for isolation and purification commonly used for antibody purification may be used for the isolation and purification of antibodies, and are not limited to any par-

ticular method. Antibodies may be isolated and purified by appropriately selecting and combining, for example, column chromatography, filtration, ultrafiltration, salting out, solvent precipitation, solvent extraction, distillation, immunoprecipitation, SDS-polyacrylamide gel electrophoresis, isoelectric focusing, dialysis, and recrystallization. Chromatography includes, for example, affinity chromatography, ion exchange chromatography, hydrophobic chromatography, gel filtration, reverse-phase chromatography, and adsorption chromatography (Strategies for Protein Purification and Characterization: A Laboratory Course Manual. Ed Daniel R. Marshak et al., Cold Spring Harbor Laboratory Press, 1996). Chromatography can be carried out using liquid phase chromatography such as HPLC and FPLC. Columns used for affinity chromatography include protein A column and protein G column. Examples of columns using protein A column include Hyper D, POROS, and Sepharose FF (GE Healthcare Biosciences). The present disclosure also includes antibodies that are highly purified using these purification methods.

#### Characterization of the Antibodies

The ApoE-binding properties of the antibodies described herein may be measured by any standard method, e.g., one or more of the following methods: OCTET®, Surface Plasmon Resonance (SPR), BIACORE™ analysis, Enzyme Linked Immunosorbent Assay (ELISA), EIA (enzyme immunoassay), RIA (radioimmunoassay), and Fluorescence Resonance Energy Transfer (FRET).

Methods for using SPR are described, for example, in U.S. Pat. No. 5,641,640; Raether (1988) *Surface Plasmons* Springer Verlag; Sjolander and Urbaniczky (1991) *Anal. Chem.* 63:2338-2345; Szabo et al. (1995) *Curr. Opin. Struct. Biol.* 5:699-705 and on-line resources provide by BIACore International AB (Uppsala, Sweden). Information from SPR can be used to provide an accurate and quantitative measure of the equilibrium dissociation constant ( $K_d$ ), and kinetic parameters, including  $K_{on}$  and  $K_{off}$  for the binding of a biomolecule to a target.

Epitopes can also be directly mapped by assessing the ability of different antibodies to compete with each other for binding to wild type ApoE or mutant ApoE (e.g. ApoEch) using BIACORE chromatographic techniques (Pharmacia BIATEchnology Handbook, "Epitope Mapping", Section 6.3.2, (May 1994); see also Johne et al. (1993) *J. Immunol. Methods*, 160:191-198).

When employing an enzyme immunoassay, a sample containing an antibody, for example, a culture supernatant of antibody-producing cells or a purified antibody is added to an antigen-coated plate. A secondary antibody labeled with an enzyme such as alkaline phosphatase is added, the plate is incubated, and after washing, an enzyme substrate such as p-nitrophenylphosphate is added, and the absorbance is measured to evaluate the antigen binding activity.

Additional general guidance for evaluating antibodies, e.g., Western blots and immunoprecipitation assays, can be found in *Antibodies: A Laboratory Manual*, ed. by Harlow and Lane, Cold Spring Harbor press (1988)).

#### Mutant ApoE Proteins, Peptides and Fusion Proteins Thereof

The present disclosure provides mutant ApoE proteins or fragments thereof containing amino acid substitutions at one or more positions in the HSPG-binding domain as compared to a wild type ApoE protein. In some embodiments, the mutant ApoE protein or fragments thereof includes an amino acid other than Arginine at position 136. In some embodiments, the mutant ApoE protein or fragments thereof contains Serine, Histidine, or Cysteine at position 136. Also

provided are nucleic acid (e.g., DNA or RNA) sequences encoding the mutant ApoE proteins or fragments thereof, and vectors containing the nucleic acid sequences. The mutant ApoE proteins or fragments thereof, nucleic acids encoding such proteins or fragments, and vectors containing the nucleic acid sequences are useful for treating or preventing disorders associated with dementia or mild cognitive impairment (MCI) (e.g. Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, or Huntington's disease), neurodegenerative diseases, cerebrovascular diseases, brain injury, retinal degeneration, or retinal injury.

In some embodiments, the mutant ApoE protein is an ApoEch protein (e.g. ApoE2ch, ApoE3ch, or ApoE4ch protein). Fragments of the ApoEch protein that includes the amino acid position 136 are also contemplated here. Exemplary sequence of a full-length ApoE3ch protein is shown below. The mutation from arginine to serine is bolded and double underlined.

(SEQ ID NO: 45)  
 MKVLWAALLVTPLAGCQAKVEQAVETEPEPELRRQTEWQSGQRWELALG  
 RFWDYLRLWVQTLSEQVQEELLSSQVTQELRALMDETMKELKAYKSELEEQ  
 LTPVAEETRARLSKELQAAQARLGADMEDVCGRLLVQYRGEVQAMLQOST  
 EELRVS**S**LASHLRKLRKRLRDADDLQKRLAVYQAGAREGAERGLSAIRER  
 LGPLVHQGRVRAATVGSLAGQPLQERAQAWGERLRARMEEMGSRTDRRLD  
 EVKEQVAEVRAKLEEQAQQIRLQAEAFQARLKSWFEPVLVEDMQRWAGL  
 VEKVQAAVGTSAAPVPSDNH

In some embodiments, the methods disclosed herein allows the mutant ApoE protein or fragments thereof to cross the blood-brain barrier. The mutant ApoE protein or fragments thereof may be delivered using nanocarriers, including but not limited to, polymeric nanoparticles, lipid based nanoparticles, liposome, micelle, dendrimer, a human cell expressing the protein, and nanotube (See, Dominguez et al. J Nanosci nanotechnol. 14(1):766-79, 2014). In some embodiments, the mutant ApoE protein or fragments thereof is delivered intranasally, via intracarotid or transmucosal delivery (e.g. intracarotid infusion of hypertonic solutions (arabinose or mannitol); see, Sanchez-Covarrubias et al., Curr Pharm Des. 20(10): 1422-49, 2014 and Miyake et al., World J Otorhinolaryngol Head Neck Surg. 1(1):11-16, 2015), or via the use of chlorotoxin (See, McCall et al., Tissue Barriers 2(4):e944449, 2014). Hypothermia techniques, receptor-mediated transport, cell-penetrating peptides, and cell-mediated delivery can also be used to facilitate the ApoE3ch protein to cross the blood brain barrier (See, Pandey et al., Tissue Barriers 4(1): e1129476, 2016). For example, immunocytes and stem cells (e.g., neural stem cells, induced pluripotent cells, and mesenchymal stem cells) can be used to carry therapeutic payloads across the BBB. Nanoparticle-loaded mesenchymal stem cells can be used for this purpose (See e.g., Roger et al. Biomaterials 31:8393-401, 2010). Genetically modified stem cells (e.g. genetically modified mesenchymal stem cells) can also be used (See e.g., Ebrahimi and Lalvand Hygeia. J. D. Med. vol. 5 (1): 90-104, 2013). Chemical drug delivery systems (CDDS), such as those described in He et al., Cells, 7(4):24, 2018, can also be used. Additional methods of transporting proteins across the blood-brain barrier are known in the art.

Nucleic acids (e.g., DNA or mRNA) encoding the mutant ApoE protein (e.g., any of the mutant ApoE proteins

described herein, e.g. ApoEch) or fragments thereof are contemplated herein. In some embodiments, mRNA encoding the ApoEch protein may be modified to increase stability (such as those described in Zangi et al., Nat Biotechnol. 31(10):898-907, 2013 and developed by Moderna, Inc.; and those described in Alberer et al., Lancet 390(10101):1511-1520, 2017 and developed by Curevac and BioNTech).

Viral vectors containing DNA sequences encoding the mutant ApoE or fragments thereof are contemplated herein. An exemplary cDNA sequence encoding the full-length ApoE3ch protein (including the signal peptide region) is shown below. The mutation from Cytosine to Adenine is bolded and double underlined.

15

(SEQ ID NO: 56)  
 ATGAAGGTTCTGTGGCTGCCTGGTACATTCTGGCAGGATGCCA  
 GGCAAGGTGGACAAGCGGTGGAGACAGAGCCGGAGCCGAGCTGCC  
 AGCAGACCGAGTGGCAGAGCGGCCAGCGCTGGAACTGGACTGGTC  
 GCGCTGGGATTACCTGGCTGGGTGCAGACACTGTCTGAGCAGGTG  
 CAGGA  
 GGAGCTGCTCAGCTCCAGGTACCCAGGAACGTGAGGGCCTGATGGAC  
 AGACCATGAAGGAGTTGAAGGCTACAAATCGGAACCTGGAGGAACACTG  
 ACCCGGTGGCGGAGGAGACGCGGGCACGGCTGTCCAAGGAGCTGCAGGC  
 GGCAGGCCGGCTGGCGCGGACATGGAGGACGTGTGCGCCGCGCTGG  
 TGCACTACCGCGCCAGGTGCAGGCCATGCTGGCCAGAGCACCGAGGAG  
 CTGGGGTG**A**GCTCGCCTCCACCTCGCAGCAGCTGCGTAAGCGGCTCCT  
 CGCGATGCCGATGACCTGCAGAACGCCCTGGCAGTGTACCAAGGCCGGG  
 CCCGCGAGGGCGCCAGCGCGGCCCTAGCGCCATCCCGAGGCCCTGGG  
 CCCCTGGTGAACAGGGCCGCGTGCAGGCCACTGTGGCTCCCTGGC  
 CGGCCAGCCGCTACAGGAGCGGGCCCAGGCCCTGGGGCGAGCGGCTGCC  
 CGCGGATGGAGGAGATGGCAGCCGGACCCCGCAGCCCTGGACGAGGTG  
 AAGGAGCAGGTGGCGGAGGTGCGCGCCAAGCTGGAGGAGCAGGCCAGCA  
 GATACTGCAGGCCAGGCCTCCAGGCCCTCAAGAGCTGGTTCG  
 AGCCCCCTGGTGAAGACATGCAGGCCAGTGGGCCGGCTGGTGGAGAAG  
 GTGCAGGCTGCCGTGGCACCAGCGCCGCCCTGTGCCAGCGACAATCA  
 CTGA

Suitable vectors are known in the art. In some embodiments, the viral vector is an AAV vector (such as those described in Rosenberg et al., Hum Gene Ther Clin Dev 29 (1): 24-47, 2018). cDNA sequences encoding an ApoE protein containing a mutation at the R136 position other than R136S are also included. In some embodiments, the mutation is R136H or R136C.

Peptides and Fusion Proteins

In some embodiments, provided herein are peptides that comprise or consist of the HSPG/heparin-binding domain of a wild type or mutant ApoE (e.g., any of the mutant ApoE proteins described herein). In some instances, the amino acid sequence of the peptides provided herein comprise or consist of the sequences selected from the group consisting of

(SEQ ID NO: 57)  
STEELRVRLASHLRKLRKRLLRDADDLQK,

(SEQ ID NO: 58)  
STEELRVSLASHLRKLRKRLLRDADDLQK,

(SEQ ID NO: 59)  
RLVQYRGEVQAMLGQSTEELRVRLASHLRKL,  
and

(SEQ ID NO: 60) 10 RLVQYRGEVQAMLGQSTEELRVSLASHLRKL.

Variants having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater sequence identity with these sequences can also be used. Also disclosed are fusion proteins comprising the peptides provided above. In some embodiments, the fusion proteins further include an Fc region of a human antibody (e.g., human IgG1, IgG2, IgG3, or IgG4). In some instances, the fusion protein comprises an Fc region of a human antibody at the C-terminal of the HSPG/heparin-binding domain of a wild type or mutant ApoE. In some instances, the fusion protein comprises an Fc region of a human antibody at the N-terminal of the HSPG/heparin-binding domain of a wild type or mutant ApoE.

In some instances, the peptides and fusion proteins provided herein competes with a wild type ApoE protein for binding to HSPG/heparin. In some instances, the peptides and fusion proteins provided herein reduce or modulate the binding between a wild type ApoE protein and HSPG/heparin. In certain embodiments, the peptides and fusion proteins provided herein inhibits and/or reduces HSPG/heparin-binding of a wild type ApoE protein, and reduces the severity of symptoms when administered to human patients having one or more of, or animal models of: disorders associated with dementia or mild cognitive impairment (MCI) (e.g. Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, Huntington's disease), neurodegenerative diseases, cerebrovascular diseases, brain injury, retinal degeneration, or retinal injury. These features of the peptides and fusion proteins provided herein can be measured according to methods known in the art.

Also provided herein are anti-ApoE vaccines, which can be used to elicit a protective immune response against ApoE. In some embodiments, the anti-ApoE vaccines include one or more of the ApoE peptides provided herein (e.g., and a pharmaceutically acceptable adjuvant. Pharmaceutically acceptable adjuvants are known in the art.

#### Pharmaceutical Compositions and Methods of Administration

The methods described herein include the use of pharmaceutical compositions comprising any of the antibodies, peptides or fusion proteins described herein as an active ingredient.

Pharmaceutical compositions typically include a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" includes saline, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration.

Pharmaceutical compositions are typically formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intracranial, intranasal, intra-carotid, intravenous, intra-dermal, subcutaneous, oral (e.g., inhalation), and transmucosal.

Methods of formulating suitable pharmaceutical compositions are known in the art, see, e.g., Remington: *The Science and Practice of Pharmacy*, 21st ed., 2005; and the books in the series *Drugs and the Pharmaceutical Sciences: a Series of Textbooks and Monographs* (Dekker, NY). For example, solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

20 Pharmaceutical compositions suitable for injectable use can include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and 25 must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethyleneglycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the 30 action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, 35 sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients 45 from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying, which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or 50 capsules, e.g., gelatin capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash. Pharmaceutically compatible binding agents, and/or adju-

vant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds can be delivered in the form of an aerosol spray from a pressured container or dispenser that contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer. Such methods include those described in U.S. Pat. No. 6,468,798.

Systemic administration of a therapeutic compound as described herein can also be by transmucosal. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories or injection.

In one embodiment, the therapeutic compounds are prepared with carriers that will protect the therapeutic compounds against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Such formulations can be prepared using standard techniques, or obtained commercially, e.g., from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to selected cells with monoclonal antibodies to cellular antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

#### CRISPR/Cas9-Mediated Gene Editing of APOE

Included herein are methods for treating or preventing disorders associated with dementia and/or mild cognitive impairment (MCI) (e.g. Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, or Huntington's disease), neurodegenerative diseases, cerebrovascular diseases, brain injury, retinal degeneration, or retinal injury, by editing the APOE gene using a genome editing system. Generally, the methods include administering a therapeutically effective amount of a genome editing system as described herein, to a subject who is in need of, or who has been determined to be in need of, such treatment. The term "genome editing system" refers to any system having RNA-guided DNA editing activity. Genome editing systems of the present disclosure include at least two components adapted from naturally occurring CRISPR systems: a gRNA and an RNA-guided nuclease. These two components form a complex that is capable of associating with a specific nucleic acid sequence in a cell and editing the DNA in or around that nucleic acid sequence, for example by making one or more of a single-strand break (an SSB or nick), a double-strand break (a DSB) and/or a base substitution. See, e.g., WO2018/026976 for a full description of genome editing systems. In certain aspects, the present disclosure provides AAV vectors encoding

CRISPR/Cas9 genome editing systems, and on the use of such vectors to treat or prevent disorders as described herein. RNA-Guided Nucleases/Cas9

Various RNA-guided nucleases can be used in the present methods, e.g., as described in WO 2018/026976. In some embodiments, the RNA-guided nuclease used in the present methods and compositions is a *S. aureus* Cas9 or a *S. pyogenes* cas9. Exemplary Cas9 proteins of the disclosure may be isolated or derived from any species, including, but not limited to, a bacteria or an archaea. In some embodiments of this disclosure a Cas9 sequence is modified to include two nuclear localization sequences (NLSS) (e.g., PKKKRKV (SEQ ID NO:61) at the C- and N-termini of the Cas9 protein, and a mini-polyadenylation signal (or Poly-A sequence). An exemplary NLS is SV40 large T antigen NLS (PKKKRKY (SEQ ID NO:62)) and nucleoplasmin NLS (KRPAATKKAGQAKKKK (SEQ ID NO:63)). Other NLSS are known in the art; see, e.g., Cokol et al., EMBO Rep. 2000 Nov. 15; 1(5):411-415; Freitas and Cunha, Curr Genomics. 2009 December; 10(8): 550-557. An exemplary polyadenylation signal is TAGCAATAAAGGATCGTTT-ATTTTCATTGGAAAGCGTGTGTTGGTTTTGATCA GGC CGC (SEQ ID NO:64). In some embodiments, the RNA-guided nuclease is a nuclease-dead Cas protein (e.g., dCas9).

#### Guide RNAs

Provided herein are guide RNAs (gRNAs) designed to target one or more sites in the HSPG binding domain of a wild type ApoE. In some embodiments, the gRNAs are designed to introduce a mutation in the wild type ApoE that results in a mutation at amino acid position 136. In some embodiments, the guide RNAs provided herein are designed to introduce an R136S mutation in a wild type APOE gene (e.g. APOE2, APOE3, or APOE4), where exemplary guide RNAs can be found in Table 7. In some embodiments, also provided are templates for repairing the double stranded break and introducing an R136S mutation. An exemplary template sequence is as follows:

(SEQ ID NO: 65)  
 CGCCTGGTGCAGTACCGCGGCCAGGTGCAGGCCATGCTCGGCCAGAGCAC  
aGAGGAGCTcCG**c**GT**G**a**G**t**C**TC**G**C**a**q**t**CCACCTGCGCAAGCTGCGTAAG  
 CGGCTCCCTCCGCGATGCCGATGACCTGC

where silent mutations to abolish PAM motifs are double underlined, the codon corresponding to the R136S mutation is bolded, and silent mutation to generate SacI site for cleaving PCR products from clones that received the template is italicized.

In some embodiments, the guide RNAs provided herein are designed to target exon 3 (amino acids 1-61) of a wild type APOE gene, or of a variant present in a subject (the methods can thus include determining the sequence of the APOE gene in a subject, and using that sequence to determine the sequence of a suitable guideRNA for targeting exon 3 in that subject). In some embodiments, a double stranded break repair through non-homologous end joining (NHEJ) results in short insertions or deletions leading to ApoE knockout. Exemplary guide RNA sequences for ApoE knockout are shown in Table 8.

#### Base Editing

In some embodiments, the APOE gene is edited using the base editing technique (e.g. those described in Rees and Liu, Nature Reviews Genetics 19, 770-788, 2018; Komor et al., Nature 533, 420-424). In some embodiments, guide RNAs

are designed to introduce an R136H mutation in a wild type APOE gene (e.g. APOE2, APOE3, or APOE4) using base editing, where exemplary guide RNAs can be found in Table 6. Base editors that convert C/G to A/T and adenine base editors that convert A/T to G/C can be used to introduce point mutations. Exemplary base editors include those described in Komor et al., *Nature* 533, 420-424 and Gaudelli et al., *Nature* 551, 464-471).

#### AAV Delivery Systems

The methods include delivery of a CRISPR/Cas9 genome editing system, including a Cas9 nuclease and one or two guide RNAs, to a subject in need thereof. The delivery methods can include, e.g., viral delivery, e.g., preferably using an adeno-associated virus (AAV) vector that comprises sequences encoding the Cas9 and guide RNA(s). Adeno-associated virus is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka et al., *Curr. Topics in Micro and Immunol.* 158:97-129 (1992)). AAV vectors efficiently transduce various cell types and can produce long-term expression of transgenes *in vivo*. AAV vectors have been extensively used for gene augmentation or replacement and have shown therapeutic efficacy in a range of animal models as well as in the clinic; see, e.g., Migozzi and High, *Nature Reviews Genetics* 12, 341-355 (2011); Deyle and Russell, *Curr Opin Mol Ther.* 2009 August; 11(4): 442-447; Asokan et al., *Mol Ther.* 2012 April; 20(4): 699-708. AAV vectors containing as little as 300 base pairs of AAV can be packaged and can produce recombinant protein expression. For example, AAV2, AAV5, AAV2/5, AAV2/8 and AAV2/7 vectors have been used to introduce DNA into photoreceptor cells (see, e.g., Pang et al., *Vision Research* 2008, 48 (3): 377-385; Khani et al., *Invest Ophthalmol Vis Sci.* 2007 September; 48(9):3954-61; Allocca et al., *J. Virol.* 2007 81(20):11372-11380). In some embodiments, the AAV vector can include (or include a sequence encoding) an AAV capsid polypeptide described in PCT/US2014/060163; for example, a virus particle comprising an AAV capsid polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, and 17 of PCT/US2014/060163, and a Cas9 sequence and guide RNA sequence as described herein. In some embodiments, the AAV capsid polypeptide is an Anc80 polypeptide, e.g., Anc80L27; Anc80L59; Anc80L60; Anc80L62; Anc80L65; Anc80L33; Anc80L36; or Anc80L44. In some embodiments, the AAV incorporates inverted terminal repeats (ITRs) derived from the AAV2 serotype. Exemplary left and right ITRs are presented in Table 6 of WO 2018/026976. It should be noted, however, that numerous modified versions of the AAV2 ITRs are used in the field, and the ITR sequences shown below are exemplary and are not intended to be limiting. Modifications of these sequences are known in the art, or will be evident to skilled artisans, and are thus included in the scope of this disclosure.

Cas9 expression is driven by a promoter known in the art. In some embodiments, expression is driven by one of three promoters: cytomegalovirus (CMV), elongation factor-1 (EFS), or human g-protein receptor coupled kinase-1 (hGRK1), which is specifically expressed in retinal photoreceptor cells. Nucleotide sequences for each of these promoters are provided in Table 5 of WO 2018/026976. Modifications of these sequences may be possible or desirable in certain applications, and such modifications are within the scope of this disclosure.

Expression of the gRNAs in the AAV vector is driven by a promoter known in the art. In some embodiments, a

polymerase III promoter, such as a human U6 promoter. An exemplary U6 promoter sequence is presented below:

(SEQ ID NO: 66)  
 5 AAGGTGGGGCAGGAAGAGGGCCTATTCGGCATGATTCTTCATATTGCA  
 TATACGATACAAGGCTGTTAGAGAGATAATTAGAATTATGACTGTAAC  
 ACACAAAAGATATTAGTACAAAAATACGTGACGTAGAAAGTAATAATTCTT  
 10 GGGTAGTTGCAGTTAAAATTATGTTAAAATGGACTATCATATGCT  
 TACCGTAACCTGAAAGTATTCGATTCTGGCTTATATATCTTGTGGA  
 AAGGACGAAACACC.

In some embodiments, the nucleic acid or AAV vector shares at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater sequence identity with one of the nucleic acids or AAV vectors recited above.

The AAV genomes described above can be packaged into AAV capsids (for example, AAV5 capsids), which capsids can be included in compositions (such as pharmaceutical compositions) and/or administered to subjects. An exemplary pharmaceutical composition comprising an AAV capsid according to this disclosure can include a pharmaceutically acceptable carrier such as balanced saline solution (BSS) and one or more surfactants (e.g., Tween 20) and/or a thermosensitive or reverse-thermosensitive polymer (e.g., pluronic). Other pharmaceutical formulation elements known in the art may also be suitable for use in the compositions described here.

Compositions comprising AAV vectors according to this disclosure can be administered to subjects by any suitable means, including without limitation injection (e.g., intracranial injection) and intranasal delivery. The concentration of AAV vector within the composition is selected to ensure, among other things, that a sufficient AAV dose is administered to the brain of the subject, taking account of dead volume within the injection apparatus and the relatively limited volume that can be safely administered. Suitable doses may include, for example,  $1 \times 10^{11}$  viral genomes (vg)/mL,  $2 \times 10^{11}$  viral genomes (vg)/mL,  $3 \times 10^{11}$  viral genomes (vg)/mL,  $4 \times 10^{11}$  viral genomes (vg)/mL,  $5 \times 10^{11}$  viral genomes (vg)/mL,  $6 \times 10^{11}$  viral genomes (vg)/mL,  $7 \times 10^{11}$  viral genomes (vg)/mL,  $8 \times 10^{11}$  viral genomes (vg)/mL,  $9 \times 10^{11}$  viral genomes (vg)/mL,  $1 \times 10^{12}$  vg/mL,  $2 \times 10^{12}$  viral genomes (vg)/mL,  $3 \times 10^{12}$  viral genomes (vg)/mL,  $4 \times 10^{12}$  viral genomes (vg)/mL,  $5 \times 10^{12}$  viral genomes (vg)/mL,  $7 \times 10^{12}$  viral genomes (vg)/mL,  $9 \times 10^{12}$  viral genomes (vg)/mL,  $1 \times 10^{13}$  vg/mL,  $2 \times 10^{13}$  viral genomes (vg)/mL,  $3 \times 10^{13}$  viral genomes (vg)/mL,  $4 \times 10^{13}$  viral genomes (vg)/mL,  $5 \times 10^{13}$  viral genomes (vg)/mL,  $6 \times 10^{13}$  viral genomes (vg)/mL,  $7 \times 10^{13}$  viral genomes (vg)/mL,  $8 \times 10^{13}$  viral genomes (vg)/mL, or  $9 \times 10^{13}$  viral genomes (vg)/mL. Any suitable volume of the composition may be delivered to the subretinal or cochlear space. In some instances, the volume is selected to form a bleb in the subretinal space, for example 1 microliter, 10 microliters, 50 microliters, 100 microliters, 150 microliters, 200 microliters, 250 microliters, 300 microliters, etc.

Explants are particularly useful for studying the expression of gRNAs and/or Cas9 following viral transduction, and for studying genome editing over comparatively short intervals. These models also permit higher throughput than may be possible in animal models, and can be predictive of expression and genome editing in animal models and sub-

jects. Small (mouse, rat) and large animal models (such as rabbit, pig, nonhuman primate) can be used for pharmacological and/or toxicological studies and for testing the systems, nucleotides, vectors and compositions of this disclosure under conditions and at volumes that approximate those that will be used in clinic. Because model systems are selected to recapitulate relevant aspects of human anatomy and/or physiology, the data obtained in these systems will generally (though not necessarily) be predictive of the behavior of AAV vectors and compositions according to this disclosure in human and animal subjects.

#### Methods of Screening (Test Compounds)

Included herein are methods for screening test compounds, e.g., polypeptides, polynucleotides, inorganic or organic large or small molecule test compounds, to identify agents useful in the treatment or prevention of disorders associated with dementia and/or mild cognitive impairment (e.g., Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, or Huntington's disease), neurodegenerative diseases, cerebrovascular diseases, brain injury, retinal degeneration, or retinal injury. In some embodiments, the test compounds modulate the HSPG/heparin-binding properties of an ApoE protein (e.g. a wild type ApoE protein). In some embodiments, the test compounds reduce the HSPG/heparin-binding properties of an ApoE protein (e.g. a wild type ApoE protein).

As used herein, "small molecules" refers to small organic or inorganic molecules of molecular weight below about 3,000 Daltons. In general, small molecules useful for the invention have a molecular weight of less than 3,000 Daltons (Da). The small molecules can be, e.g., from at least about 100 Da to about 3,000 Da (e.g., between about 100 to about 3,000 Da, about 100 to about 2500 Da, about 100 to about 2,000 Da, about 100 to about 1,750 Da, about 100 to about 1,500 Da, about 100 to about 1,250 Da, about 100 to about 1,000 Da, about 100 to about 750 Da, about 100 to about 500 Da, about 200 to about 1500, about 500 to about 1000, about 300 to about 1000 Da, or about 100 to about 250 Da).

The test compounds can be, e.g., natural products or members of a combinatorial chemistry library. A set of diverse molecules should be used to cover a variety of functions such as charge, aromaticity, hydrogen bonding, flexibility, size, length of side chain, hydrophobicity, and rigidity. Combinatorial techniques suitable for synthesizing small molecules are known in the art, e.g., as exemplified by Obrecht and Villalgoro, *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, Pergamon-Elsevier Science Limited (1998), and include those such as the "split and pool" or "parallel" synthesis techniques, solid-phase and solution-phase techniques, and encoding techniques (see, for example, Czarnik, *Curr. Opin. Chem. Bio.* 1:60-6 (1997)). In addition, a number of small molecule libraries are commercially available. A number of suitable small molecule test compounds are listed in U.S. Pat. No. 6,503,713, incorporated herein by reference in its entirety.

Libraries screened using the methods of the present invention can comprise a variety of types of test compounds. A given library can comprise a set of structurally related or unrelated test compounds. In some embodiments, the test compounds are peptide or peptidomimetic molecules. In some embodiments, the test compounds are nucleic acids.

In some embodiments, the test compounds and libraries thereof can be obtained by systematically altering the structure of a first test compound, e.g., a first test compound that

is structurally similar to a known natural binding partner of the target polypeptide, or a first small molecule identified as capable of binding the target polypeptide, e.g., using methods known in the art or the methods described herein, and correlating that structure to a resulting biological activity, e.g., a structure-activity relationship study. As one of skill in the art will appreciate, there are a variety of standard methods for creating such a structure-activity relationship. Thus, in some instances, the work may be largely empirical, and in others, the three-dimensional structure of an endogenous polypeptide or portion thereof can be used as a starting point for the rational design of a small molecule compound or compounds. For example, in one embodiment, a general library of small molecules is screened, e.g., using the methods described herein.

In some embodiments, a test compound is applied to a test sample, e.g., a sample containing one or more ApoE protein(s), and one or more effects of the test compound (e.g. HSPG/heparin binding affinity of the ApoE protein(s)) is evaluated. The ability of test compounds to modify the HSPG/heparin binding affinity of the ApoE protein(s) can be evaluated, e.g. using heparin sepharose columns, or antibodies that specifically recognize the HSPG-binding domain of ApoE as described herein. In some embodiments, methods for screening test compounds as described herein include evaluating the ability of a test compound to modify (e.g. inhibit or reduce) binding of antibodies as described herein that bind to one or more HSPG-binding sites or one or more sites of allosteric modulation of HSPG binding of a wild type or mutant ApoE. In some embodiments, a test compound competes with the antibodies as described herein for ApoE binding.

In some embodiments, the test sample is, or is derived from (e.g., a sample taken from) an in vivo model of a disorder as described herein. For example, an animal model, e.g., a rodent such as a rat, can be used.

A test compound that has been screened by a method described herein and determined to reduce or modify ApoE and HSPG/heparin binding, can be considered a candidate compound. A candidate compound that has been screened, e.g., in an in vivo model of a disorder, e.g., dementia and/or mild cognitive impairment (such as those associated with Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease or Huntington's disease), neurodegenerative diseases, cerebrovascular diseases, brain injury, retinal degeneration, or retinal injury, and determined to have a desirable effect on the disorder, e.g., on one or more symptoms of the disorder, can be considered a candidate therapeutic agent. Candidate therapeutic agents, once screened in a clinical setting, are therapeutic agents. Candidate compounds, candidate therapeutic agents, and therapeutic agents can be optionally optimized and/or derivatized, and formulated with physiologically acceptable excipients to form pharmaceutical compositions.

Thus, test compounds identified as "hits" (e.g., test compounds that have a desirable effect on the disorder) in a first screen can be selected and systematically altered, e.g., using rational design, to optimize binding affinity, avidity, specificity, or other parameter. Such optimization can also be screened for using the methods described herein. Thus, in one embodiment, the invention includes screening a first library of compounds using a method known in the art and/or described herein, identifying one or more hits in that library, subjecting those hits to systematic structural altera-

tion to create a second library of compounds structurally related to the hit, and screening the second library using the methods described herein.

Test compounds identified as hits can be considered candidate therapeutic compounds, useful in treating, preventing, or delaying of development or progression of disorders associated with dementia and/or mild cognitive impairment, as described herein, e.g., Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease or Huntington's disease, and useful in treating, preventing, or delaying of development or progression of neurodegenerative diseases, cerebrovascular diseases, brain injury, retinal degeneration, or retinal injury. A variety of techniques useful for determining the structures of "hits" can be used in the methods described herein, e.g., NMR, mass spectrometry, gas chromatography equipped with electron capture detectors, fluorescence and absorption spectroscopy. Thus, the invention also includes compounds identified as "hits" by the methods described herein, and methods for their administration and use in the treatment, prevention, or delay of development or progression of a disorder described herein.

Test compounds identified as candidate therapeutic compounds can be further screened by administration to an animal model of a disorder associated with any of the disorders as described herein. The animal can be monitored for a change in the disorder, e.g., for an improvement in a parameter of the disorder, e.g., a parameter related to clinical outcome.

#### Methods of Treatment

The methods described herein include methods for the treatment, prevention, or delay of development or progression of disorders associated with dementia and/or mild cognitive impairments, neurodegenerative diseases, cerebrovascular diseases, brain injury, retinal degeneration, or retinal injury. In some embodiments, the disorder associated with dementia and/or mild cognitive impairments is Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, or Huntington's disease. Additional non-limiting examples of neurodegenerative diseases include prion disease, motor neuron disease, and amyotrophic lateral sclerosis (ALS). Non-limiting examples of cerebrovascular diseases include stroke, carotid stenosis, vertebral stenosis, and aneurysms. Non-limiting examples of brain injuries include traumatic brain injury and acquired brain injury. Retinal degeneration such as glaucoma, age-related macular degeneration, may involve amyloid-beta and neurofibrillary tangle toxicity, establishing a link between retinal degeneration and neurodegeneration (e.g., Alzheimer's disease) (See, e.g. Mckinnon, *Frontiers in Bioscience* 8, s1140-1156, 2003; Johnson et al. *PNAS* 99 (18) 11830-11835, 2002; and Sivak, *Investigative Ophthalmology & Visual Science*, 54 (1) 871-880, 2013). Accordingly, treatments for neurodegeneration can be used to treat retinal or optic nerve degeneration.

The methods include administering a therapeutically effective amount of any of the antibodies, peptides, fusion proteins, or genome editing system as described herein, to a subject who is in need of, or who has been determined to be in need of, such treatment.

The methods described herein are also useful for subjects at risk for developing any of the disorders described herein. Subjects at risk for developing Alzheimer's disease may include those that are homozygous or heterozygous for the APOE4 allele, carriers of autosomal dominant Alzheimer's disease-causing mutations (e.g. mutations in the amyloid beta precursor (APP) gene, PSEN1 gene, or PSEN2 gene),

trisomy 21 (e.g. subjects whose cognitive impairment is developmental only). Subjects at risk for developing Alzheimer's disease may also include those that have polygenic risk scores associated with increased risk of developing the disease, and those with brain imaging or other biomarker (e.g. biomarker in the body fluids) evidence of Alzheimer's disease. The methods for preventing or delaying the development of disorders described herein may also be useful for subjects that are not at risk for developing the above disorders, such as any subjects over the age of 50 (e.g. over the age of 55, 60, 65, 70, 75, 80, 85, 90, or 95).

As used in this context, to "treat" means to ameliorate at least one symptom of the disorder associated with the disorders as described herein. Often, Alzheimer's disease results in fibril formation, amyloid aggregation, and reduced cognitive performance; thus, a treatment can result in a reduction in fibril formation and/or amyloid aggregation in the brain, reduced tau formation of tangles, improved brain metabolism, improved neurocognitive functions and/or cognitive performance.

#### EXAMPLES

The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art can develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

##### Example 1: Identification of the APOE3 Christchurch R136S Mutation in a PSEN1 Mutation Carrier

#### Materials and Methods:

Clinical assessments: Institutional review boards from the University of Antioquia, Massachusetts General Hospital, and the Schepens Eye Research Institute of Massachusetts Eye and Ear approved this study. Like all of the research participants, the proband case provided her written informed consent. Clinical ratings and neuropsychological tests were performed as noted in Table 1. PSEN1 E280A genotyping was conducted as previously described.<sup>1</sup>

All clinical measures were undertaken at the University of Antioquia (Medellín, Colombia) and were conducted in Spanish by physicians and psychologists trained in assessment. Neurocognitive testing included a comprehensive multi-domain assessment. Some of the test administered were the Spanish versions of the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating (CDR), and the Consortium to Establish a Registry for Alzheimer's disease battery, which have been adapted to this Colombian population.<sup>2</sup> Additional testing consisted of the Yesavage Geriatric Depression Scale<sup>3</sup> and the Functional Assessment Staging test<sup>4</sup>, which were done within six months of brain imaging.

A detailed ophthalmic evaluation was performed. It included visual acuity assessment, slit-lamp and indirect ophthalmoscopy examination. Ultra-widefield fundus and fundus autofluorescence images using Optos Panoramic 200Tx imaging system (Optos PLC, Dunfermline, Scotland, UK) were obtained. Additionally, Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) and OCT angiography with Cirrus HD-OCT with AngioPlex (Carl Zeiss Meditec, Dublin, CA) were also done.

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Additional studies were conducted after the PSEN1 E280A mutation carrier was discovered to have two copies of the APOE3ch variant. A fasting serum lipid panel was performed to explore the possibility of hyperliproteinemia type III, a condition found in 5-10% of persons homozygous for the relatively AD protective APOE2 allele and in most but not all APOE3ch carriers.<sup>5</sup>

Finally, an analysis of data from clinically and neuropathologically verified AD cases and controls from the AD Genetics Consortium was used to clarify whether homozygosity for the APOE2 allele was associated with an exceptionally low risk of late-onset AD dementia.

**Whole exome sequencing:** Whole-exome capture and sequencing were performed using Illumina chemistry for variant discovery; rare variants with less than 1% frequency in genes previously associated with AD were considered in the search for candidate risk modifiers. Specifically, rare DNA variants (minor allele frequency <1%) within exonic regions and splice-site junctions (5 bp into introns) of genes were identified using bioinformatics tools. Whole exome libraries were constructed and sequenced on an Illumina HiSeq 4000 sequencer with the use of 151 bp paired-end reads. Library construction was performed using a previously described protocol<sup>6</sup> modified as follows. Genomic DNA input was reduced from 3 µg to 50 ng in 10 µL of solution and enzymatically sheared. Dual-indexed Illumina paired end adapters were replaced with palindromic forked adapters with unique 8 base index sequences embedded within the adapter and added to each end for adapter ligation. In-solution hybrid selection was performed using the Illumina Rapid Capture Exome enrichment kit with 38 Mb target territory (29 Mb baited). The targeted region included 98.3% of the intervals in the Refseq exome database. Dual-indexed libraries were pooled into groups of up to 96 samples prior to hybridization. The enriched library pools were quantified via PicoGreen after elution from streptavidin beads and then normalized. For cluster amplification and sequencing, the libraries prepared using forked, indexed adapters were quantified using quantitative PCR (KAPA biosystems), normalized to 2 nM using Hamilton Starlet Liquid Handling system, and pooled with equal volume using the Hamilton Starlet Liquid Handling system. Pools were then denatured in 0.1 N NaOH. Denatured samples were diluted into strip tubes using the Hamilton Starlet Liquid Handling system. Cluster amplification of the templates was performed according to the manufacturer's protocol (Illumina) using the Illumina cBot. Flowcells were sequenced on HiSeq 4000 Sequencing-by-Synthesis Kits, then analyzed using RTA2.7.3.

Exome sequencing data was processed and analyzed with the bioinformatics pipeline of the Center's Clinical Exome Sequencing of the Center for Personalized Medicine (CPM) Clinical Genomics Laboratory and the Translational Genomics Research Institute. Briefly, Edico Genome's Dragen Genome Pipeline with default parameters was used to perform sequence alignment and variant calling. The open source software samtools and bcftools (samtools.github.io/) were used along with a set of custom scripts to perform coverage determination and initial variant filtering based on ExAC (Exome Aggregation Consortium, exac.broadinstitute.org/) allele frequencies.<sup>7</sup> Sequence alignment was done against the Human hs37d5 decoy genome.<sup>8</sup> To identify the potential modifier variants, a primary gene list of 15 genes was generated based on two HPO terms: HP: 0002511, Alzheimer disease; HP: 0003584, Late onset. These genes were AAGAB, ABCC8, AKT2, APOE, APP, BEAN1, GATA1, GCK, HMGA1, HNF1B, HNF4A, LDB3, PAX4,

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PSEN1, and PSEN2.<sup>9</sup> Rare DNA variants (minor allele frequency <1%) within exonic regions and splice-site junctions (5 bp into introns) of these genes were further annotated and analyzed using a commercial tool (Cartagenia v5.0). Sequence alterations were reported according to the Human Genome Variation Society (HGVS v2.0) nomenclature guidelines.<sup>5</sup>

**Whole genome sequencing:** Whole-genome sequencing (WGS) and a Genomizer analysis (v 10.1.0) were used to 10 conduct a comprehensive and unbiased ranking of other potential genetic risk modifiers, including those associated with a lower risk of Alzheimer's dementia, helping to exclude other potentially protective genetic factors.<sup>10</sup> For processing the WGS data, the same dragen pipeline 15 described above was used. The data was aligned to the GRCh37 decoy genome (hs37d5). Variants that were called at a depth of <10x were filtered out and then were annotated using Ensembl's Variant Effect Predictor (VEP) tool. The version of VEP using was v93. The filtered and annotated set 20 of variants was then compiled for Genomizer analysis.

**APOE structure display:** Image was obtained and modified from the RCSB PDB (rcsb.org) of PDB 2L7B a previously published structure<sup>11</sup> using NGL Viewer<sup>12</sup>.

**APOE Genotyping by Sanger sequencing:** Reaction mixture for the amplification process was performed in a 50 µL volume that included the following components: 1×PfuUltra II Hostart Master Mix, 1 µL of each primer (10 µmol/L) (Forward primer: 5'-AGCCCTTCTCCCCGCCTCC-CACTGT-3' (SEQ ID NO: 67) and Reverse primer: 30 5'-CTCCGCCACCTGCTCCTCACCTCG-3' (SEQ ID NO: 68)), 5% DMSO and 1 µL of genomic DNA (100 ng/µL).<sup>13</sup> PCR cycling was run with initial denaturation at 95° C. for 2 min followed by 35 cycles with denaturation at 95° C. for 20 seconds, annealing at 60° C. for 30 seconds, 35 extension at 72° C. for 40 seconds, and a final extension at 72° C. for 5 min. PCR products were purified using QIAquick Gel Extraction kit from Qiagen and sequenced by MGH CCIB DNA core using the 3730xl sequencer from Applied Biosystems.

**MRI and PET imaging:** Pittsburgh Compound B (PiB), flortaucipir (FTP) positron emission tomography (PET) and structural magnetic resonance imaging (MRI) measurements were acquired at Massachusetts General Hospital and analyzed at Massachusetts General Hospital and Banner 45 Alzheimer's Institute as previously described.<sup>14</sup> Fluorodeoxyglucose PET images were acquired at the University of Antioquia, Colombia, and analyzed as previously described<sup>15</sup>. Imaging data from the case were compared to those from younger PSEN1 E280A mutation carriers who developed MCI at the kindred's expected age at clinical onset, and from mutation carriers who were cognitively unimpaired.

MRI was performed on a 3T Tim Trio (Siemens) and included a magnetization-prepared rapid gradient-echo (55 MPRAGE) processed with Freesurfer (FS) to identify grey white and pial surfaces to permit regions of interest (ROI) parcellation as follows: cerebellar grey, hippocampus, and the following Braak Stage related cortices: entorhinal, parahippocampal, inferior temporal, fusiform, posterior cingulate, as described previously<sup>16-19</sup>.

18F-Flortaucipir (FTP) was prepared at MGH with a radiochemical yield of 14±3% and specific activity of 216±60 GBq/µmol at the end of synthesis (60 min), and validated for human use (Shoup et al., 2013). 11C-Pittsburgh 60 Compound B was prepared and PET images were acquired as previously described.<sup>16</sup> All PET images were acquired using a Siemens/CTI (Knoxville, TN) ECAT HR+ scanner

(3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution and 2.4 mm slice interval. <sup>11</sup>C PiB PET was acquired with a 8.5 to 15 mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12×15 seconds, 57×60 seconds)). <sup>18</sup>F FTP was acquired from 80-100 minutes after a 9.0 to 11.0 mCi bolus injection in 4×5-minute frames. PET images were reconstructed and attenuation-corrected, and each frame was evaluated to verify adequate count statistics and absence of head motion.

<sup>18</sup>F FTP specific binding was expressed in FS ROIs as the standardized uptake value ratio (SUV<sub>R</sub>) to cerebellum, similar to a previous report<sup>19</sup>, using the FS cerebellar grey ROI as reference. For voxelwise analyses, each subject's MPRAGE was registered to the template MR in SPM8 (SPM), and the spatially transformed SUV<sub>R</sub> PET data was smoothed with a 8 mm Gaussian kernel to account for individual anatomic differences<sup>20</sup>. To account for possible <sup>18</sup>F FTP off-target binding in choroid plexus, which may confound hippocampal signal, we used a linear regression to regress the choroid plexus, as previously reported<sup>21</sup>.

<sup>11</sup>C PiB PET data were expressed as the distribution volume ratio (DVR) with cerebellar grey as reference tissue; regional time-activity curves were used to compute regional DVRs for each ROI using the Logan graphical method applied to data from 40 to 60 minutes after injection<sup>16,22</sup>. <sup>11</sup>C PiB retention was assessed using a large cortical ROI aggregate that included frontal, lateral temporal and retrosplenial cortices (FLR) as described previously<sup>23,24</sup>.

<sup>18</sup>F-fludeoxyglucose PET was performed on a 64-section PET/computed tomography imaging system (Biograph mCT; Siemens) using intravenous administration of 5 mCi (185 million Bq) of <sup>18</sup>F-fludeoxyglucose after a 30-minute radiotracer uptake period when resting in a darkened room, followed by a 30-minute dynamic emission scan (six 5-minute frames). Images were reconstructed with computed tomographic attenuation correction. Precuneus to whole-brain cerebral metabolic rate for glucose (CMR<sub>gl</sub>) ratios were characterized from a bilateral region of interest (ROI) in each participant's <sup>18</sup>F-fludeoxyglucose PET image using an automated brain mapping algorithm (SPM8; filion.ucl.ac.uk/spm/software/spm8). Hippocampal to total intracranial volume ratios were characterized from bilateral ROIs in each participant's T1-weighted MR image using Free-Surfer (surfer.nmr.mgh.harvard.edu). All images were visually inspected to verify ROI characterization.

Amyloid aggregation studies: Human ApoE3 protein fragments (including the carboxyl-terminus domain plus a histidine tag) with and without the Christchurch variant were synthesized in bacteria, purified (Innovagen), and used to assess the differential effects of these proteins on A $\beta$ <sub>42</sub> aggregation in vitro using Thioflavin T (SensoLyte® ThT  $\beta$ -Amyloid (1-42) Aggregation kit, cat. #AS-72214). For this assay, 55  $\mu$ M of A $\beta$ <sub>42</sub> was added to solutions of either 10  $\mu$ M Wild Type apoE3 protein or Mutant 136 Arg $\rightarrow$ Ser ApoE3 protein in a transparent, no-binding 96-well plate. Samples were then mixed with 2 mM Thioflavin T dye and fluorescence was read at Ex/Em=440/484 at intermittent time intervals over 2 hours. The plate was kept at 37° C. with 15 seconds shaking between reads.

Full-length ApoE3 proteins with and without the Christchurch mutation were also expressed in Flp-In™ T-REX™ 293 (Thermo Fisher Scientific) mammalian cells via transient transfection to confirm the impact of these proteins on A $\beta$ 42 aggregation using a previously published split-luciferase complementation assay.<sup>26</sup> The latter analysis were conducted using the human APOE3 expression from

Addgene (Plasmid #8708627) as the WT or APOE3 with the Christchurch variant introduced via site-directed mutagenesis. Reagents for luciferase assay were purchased from Promega.

## 5 Results

About 1,200 Colombian Presenilin 1 (PSEN1) E280A mutation carriers and 4,600 non-carriers were identified, who together compose the world's largest known kindred with autosomal dominant Alzheimer's disease (ADAD).<sup>28,29</sup> The mutation carriers usually develop mild cognitive impairment (MCI) and dementia at the respective median ages of 44 (95% CI, 43-45) and 49 (95% CI, 49-50) years.<sup>30,31</sup> Studying autosomal dominant AD (ADAD) mutation carriers who remain cognitively unimpaired until older ages could help in the discovery of risk-reducing gene variants.<sup>32</sup> Characterizing AD biomarkers in these individuals could help inform the potentially targetable mechanisms by which these genes exert their relative protective effects. We identified a PSEN1 E280A mutation carrier who did not develop MCI until her seventies, nearly three decades after the median age at onset.

This study was conducted with the participant's written informed consent following Institutional Review Board guidelines (her exact age and other identifying information are omitted to protect her anonymity and confidentiality). The participant was confirmed to carry the amyloid- $\beta$ <sub>42</sub> (A $\beta$ <sub>42</sub>)-overproducing PSEN1 E280A mutation, confirmed by report of family informants to be cognitively unimpaired until her seventies, and subsequently met criteria for MCI<sup>33</sup> during a 24-month period of annual assessments. She remained fully independent for basic and instrumental activities of daily living, without evident signs of worsening of her abilities to perform these activities. At intake assessment, her memory deficits were limited to recent events and her neurological exams were normal. Her age and education-adjusted neuropsychological test scores indicated a preferential impairment in recall memory, relatively preserved recognition memory, initial learning, naming, visuospatial abilities and verbal fluency skills, and relatively stable cognitive performance during the 24-month assessment period (Table 1).

TABLE 1

Cognitive Test Scores and Percentiles				
	Cognitive Tests	Raw Scores (Percentiles**)	Mean (SD)**	
50	MMSE/30*	18 (1 <sup>st</sup> )	16 (<1 <sup>st</sup> )	22 (1.7)
	Naming/15	9 (7 <sup>th</sup> )	9 (7 <sup>th</sup> )	12.03 (2.1)
	CERAD Word List	10 (5 <sup>th</sup> )	6 (<1 <sup>st</sup> )	15.64 (3.44)
55	CERAD Learning/30	0 (<1 <sup>st</sup> )	0 (<1 <sup>st</sup> )	5.77 (1.98)
	CERAD Word List Delayed Recall/10	9 (27 <sup>th</sup> )	8 (5 <sup>th</sup> )	9.58 (0.98)
60	CERAD Word List Recognition/10	8 (18 <sup>th</sup> )	9 (39 <sup>th</sup> )	9.42 (1.57)
	CERAD Praxis-Copy/11	0 (<1 <sup>st</sup> )	2 (3 <sup>rd</sup> )	7.52 (2.84)
65	CERAD Praxis-Recall/11	12 (13 <sup>th</sup> )	12 (13 <sup>th</sup> )	16.97 (4.3)
	Semantic Fluency (Animals)	10 (13 <sup>th</sup> )	11(14 <sup>th</sup> )	23.75 (11.89)
	Phonemic Fluency ("F" Words)	10 (13 <sup>th</sup> )	10 (13 <sup>th</sup> )	

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TABLE 1-continued

Cognitive Tests	Raw Scores (Percentiles**)			Mean (SD)**
Raven's Matrices Test, Form A/12	7 (27 <sup>th</sup> )	7 (27 <sup>th</sup> )	8 (47 <sup>th</sup> )	8.21 (2.13)
GDS/15	9	2	9	
EDG/7	3	3	4	

MMSE: Mini-Mental State Examination

CERAD: Consortium to Establish a Registry for Alzheimer's Disease Test Battery.

GDS: Geriatric Depression Scale

EDG: Global Deterioration Scale

\*MMSE subtests that require reading and writing skills were not administered due to her limited literacy skills. Her maximum possible score was 23 (instead of 30).

\*\*Percentiles were calculated using norms for this Colombian population.

Percentiles between 25 and 75 place her performance in the average range for her age and education.

Percentiles between 9 and 25 classify her performance as below average. Percentiles between 2 and 8 classify her performance as low. Percentiles below 1 classify her performance as extremely low.

#Brain imaging described in this report was acquired three months after the initial cognitive testing.

Whole exome sequencing corroborated her PSEN1 E280A mutation and discovered that she also had two copies of the rare APOE3 Christchurch R136S (APOEch) mutation. Sanger sequencing confirmed the latter finding. Whole genome sequencing and a Genomizer analysis were used to comprehensively identify and rank all potentially significant rare and common variants.<sup>34</sup> Using this approach, the PSEN1 E280A mutation was confirmed to be the participant's primary risk factor and APOE3ch homozygosity was confirmed to be her primary resistance factor.

APOE, the major susceptibility gene for late-onset AD, has three common alleles (APOE2, 3, and 4). Compared to the most common APOE3/3 genotype, APOE2 is associated with a lower AD risk and older age at dementia onset,<sup>35</sup> and each additional copy of APOE4 is associated with a higher risk and younger age at onset.<sup>36,37</sup> The APOEch variant, an arginine-to-serine substitution at amino acid 136 (136Arg→Ser), corresponding to codon 154,<sup>38</sup> can reside on any of the common APOE alleles,<sup>39</sup> including this participant's two APOE3 alleles. FIG. 1 shows a model of the structure of the wild type ApoE3 protein. N-terminal (residues 1-191) and C-terminal (residues 201-299) domains are highlighted. The amino acid positions for APOE4 (C112R), APOE3ch (R136S) and APOE2 (R158C) variants are shown.

The APOE3ch variant was absent from AlzAD or ExAC databases reporting on about 180,000 exomes. The R136S was previously identified in APOE2 individuals with HLP III but its potential effect in the progression of AD has not been previously reported.<sup>40</sup> We sequenced DNA samples from two other PSEN1 E280A carriers with delayed age-at-onset (age at onset 62 and 70 years) via whole genome sequencing. None of these individuals had the APOE3 R136S variant nor APOE2; the latter was previously shown to delay disease onset in this kindred.<sup>41</sup>

To confirm a potential association between the APOE3 R136S mutation and delayed age at onset of AD, we conducted whole genome sequencing, neurological, and neuropsychological testing in the four descendants of the proband case, which were all older than fifty years, and expected to carry the APOE3 R136S. FIG. 2 shows representative Sanger sequencing results of APOE from control, proband and descendant's samples. Upper row: C112 homozygous sequences are shown in all cases. Middle row: R136 homozygous sequence is shown in left panel from a

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control individual. Middle panel shows homozygous change resulting in R136S mutation. Right panel shows a R136S heterozygous mutation example of a descendant of the proband. Low row: R158 homozygous sequences are shown in all cases. FIG. 3 shows the proband's genealogy, with circles representing females, squares representing males, diamonds representing individuals whose gender has been masked for privacy, arrowhead depicts proband individual with MCI, and shading indicates individual with history of dementia. Deceased individuals are marked with a crossed bar. The individual APOE and PSEN1 genotypes are indicated as appropriate to preserve anonymity. Although other unknown genetic or epigenetic factors may have contributed to late age at onset of cognitive impairment in these two related PSEN1 E280A carriers, we suggest that the APOE3 R136S variant modifies the AD phenotype by buffering the effects of amyloid-β accumulation in the brain and subsequently delaying the emergence of tau pathology, neurodegeneration (i.e. brain atrophy), and symptoms onset.

Carriers of APOEch and other rare mutations in APOE's low density lipoprotein receptor (LDLR) binding region commonly have hyperlipoproteinemia type III (HLP-III), similar to that observed in 5-10% of APOE2 homozygotes.<sup>43,44</sup> The participant in this report was confirmed to have HLP-III, including APOEch and elevated triglyceride and total cholesterol levels (See, Table 2).

TABLE 2

Dyslipidemia workup			
Lipid panel	Test	Subject	Normal range*
Triglycerides (mg/dl)	691.88	<250	
Total Cholesterol (mg/dl)	511.76	150-199	
VLDL-C (mg/dl)	(-)	<30	
LDL-C (mg/dl)	(-)	≤130	
Direct LDL-C (mg/dl)	147	≤130	
HDL-C (mg/dl)	55.74	≥40	
Cholesterol/HDL ratio	9.18	<5	
Apolipoprotein A-I (mg/dl)	177	F: 98-210	
Apolipoprotein B (mg/dl)	217	F: 44-148	
Apo B/Apo-I ratio	1.23	F: 0.35-1.15	
Lipoprotein A (mg/dl)	86.6	≤30	

HDL-C: High-density lipoprotein cholesterol,

VLDL-C: Very low-density lipoprotein cholesterol,

LDL-C: Low-density lipoprotein cholesterol.

\*Normal range according to Merck Manual and Laboratory values.

Detailed laboratory workup showed abnormal lipid profile in our proband individual and three of the four descendants carrying the APOE3 R136S (Table 3). These four subjects had high level of total cholesterol and triglycerides. Very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) were higher in two of the descendants and not measurable in the proband individual and one of the descendants, which had triglyceride levels higher 400 mg/dL (the threshold for accuracy of the indirect method of lipid profiling) (Table 3). Further analyses using direct enzymatic tests showed higher than normal LDL in these two individuals. One of the descendants had a lipid profile within normal limits despite carrying the APOE3 R136S and the APOE4. Incomplete penetrance of HLP III has been previously reported for APOE2 and for R136S mutation carriers.<sup>45</sup> We ruled out secondary causes of lipid disorders as diabetes, obesity, alcoholism, renal disorders or thyroid diseases in these subjects. None of the mutation carrier individuals had xanthomas, which are diagnostic of HLP III, or cardiovascular diseases. The combination of the abnormal lipid profile

and APOE3 R136S mutation in these subjects is consistent with a diagnosis of familial HLP III.

the \* in FIG. 4F) with a small defect in the external limiting membrane and ellipsoid layer (arrow in FIG. 4F).

TABLE 3

Test	Dementia and dyslipidemia workup in study population					Normal range*
	1 (F-75)	2 (F-51)	3 (F-53)	4 (M-49)	5 (M-54)	
<b>CBC</b>						
RBC count ( $\times 10^6$ mm $^3$ )	4.7	4.73	4.47	5.26	5.37	4.2-5.9
Hemoglobin (g/dl)	13	14.1	12.9	15.1	15.1	M: 14-17 F: 12-16
Hematocrit (%)	38.5	42.3	39.2	46.3	45.7	M: 41-51 F: 36-47
MCV (fL)	81.9	89.4	87.8	88.1	85	80-100
MCH (pg)	27.6	29.8	28.8	28.6	28.1	28-32
MCHC (g/dl)	33.7	33.4	32.8	32.5	33	32-36
RDW (%)	13.7	12.5	13	13.3	13.5	11.5-14.5
WBC count ( $\times 10^3$ mm $^3$ )	5.51	10.45	9.61	12.78	20.18	4.5-11
Platelets ( $\times 10^3$ mm $^3$ )	264	289	334	256	295	150-350
MPV (fL)	7	8.2	8.8	8.3	7.8	6.5-13.5
ESR (mm/h)	30	20	51	18	2	M: 0-15 F: 0-20
BMP						
Glucose (mg/dl)	107.1	128.28	107.82	112.15	131.19	70-105
BUN (mg/dl)	11.98	13.03	9.71	15.65	14.39	8-20
Creatinine (mg/dl)	0.57	0.59	0.67	1.04	0.95	0.7-1.3
Sodium (mmol/l)	139.3	141.4	140	137.3	136.6	136-145
Potassium (mmol/l)	3.79	4.03	4.92	4.76	4.29	3.5-5
Chloride (mmol/l)	102	106.5	108.3	106.6	107.1	98-106
LPP						
Total Cholesterol (mg/dl)	511.76	192.6	434.25	336.21	323.2	150-199
HDL-C (mg/dl)	55.74	60.52	60.56	53.76	33.78	$\geq 40$
Cholesterol/HDL ratio	9.18	3.18	7.17	6.25	9.57	<5
Triglycerides (mg/dl)	691.88	50.32	321.3	282.49	437.92	<250
VLDL-C (mg/dl)	(—)	10.06	64.26	56.5	(—)	<30
LDL-C (mg/dl)	(—)	122.02	309.43	225.95	(—)	$\leq 130$
<b>Additional tests</b>						
Apolipoprotein A-I (mg/dl)	177	106	150	126	133	M: 88-180 F: 98-210
Apolipoprotein B (mg/dl)	217	75	179	173	160	M: 55-151 F: 44-148
Apo B/Apo-I ratio	1.23	0.71	1.19	1.37	1.2	M: 0.45-1.25 F: 0.35-1.15
Hemolytic Complement 50% (U/ml)	50.8	58	58.6	56.1	68.8	31.6-57.6
Plasmatic homocysteine ( $\mu$ mol/l)	9.54	6.47	7.48	15.34	13.55	M: 4-16 F: 3-14
Lipoprotein A (mg/dl)	86.6	6	86.1	6.5	62	$\leq 30$
Serum complement C3 (mg/dl)	130.1	1202.6	1314.5	1281.9	1292.6	55-120
Serum complement C4 (mg/dl)	20.6	177.9	131.7	146.5	245.5	20-59
Complement Clq (mg/dl)	24	23	28	28	33	10-25
Free thyroxine (ng/dl)	1.38	1.13	1.12	1.26	1.09	0.9-2.4
TSH ( $\mu$ IU/ml)	4.5	0.78	4.08	3.56	3.72	0.50-5.0
Vitamin B12 (pg/ml)	517	382	294	263	352	200-800
Folate (ng/ml)	16.14	7.52	8.38	2.14	6.6	2.5-20

A detailed ophthalmic evaluation of the PSEN1 E280A mutation carrier with two APOE3ch alleles was performed. This carrier had a vision of 20/70 in the right eye and 20/40 in the left eye. The anterior segment exam was notable for a posterior chamber intraocular lens in the right eye with a dense posterior capsular opacification. Anterior segment of the left eye was notable for a nuclear sclerotic cataract (FIGS. 4A and 4B). The posterior segment examination of both eyes was normal, with a clear vitreous cavity, normal appearing optic nerve, macula, and peripheral retina. Further testing via optical coherence tomography (OCT) of the right eye was normal except for a small area of hyper-reflectivity overlying the fovea (FIG. 4D). FIG. 4C shows an infrared image of the right eye that depicts the cross section of the retina (line) seen in FIG. 4D. Further, OCT imaging of the left eye revealed a degenerative lamellar hole (denoted by

While several mechanisms have been proposed to account for the impact of APOE variants on AD risk, most studies have focused on their differential effects (APOE2<3<4) on  $\text{A}\beta_{42}$  aggregation and plaque burden.<sup>47</sup> In the present study, neuroimaging measurements were used to clarify whether the participant's resistance to the clinical onset of AD was associated with a) relatively little  $\text{A}\beta$  plaque burden despite more than seventy years of  $\text{A}\beta_{42}$  overproduction or with b) relatively high  $\text{A}\beta$  plaque burden but limited downstream measurements of paired helical filament (PHF) tau (neurofibrillary tangle burden) and neurodegeneration.

The participant's neuroimaging findings are shown in FIG. 5. The positron emission tomography (PET) images are superimposed onto the medial and lateral surfaces of the left hemisphere. The top row shows PET measurements of amyloid plaque burden (PiB DVRs). The bottom row shows

PET measurements of paired helical filament (PHF) tau (i.e., neurofibrillary tangle) burden. The person with late-onset of MCI is in her seventies, and the person with the typical age at MCI onset is 44 years old.

As shown in FIG. 5, the person with late onset of MCI had unusually high PET measurements of A $\beta$  plaque burden, as indicated by a higher mean cortical-to-cerebellar Pittsburgh Compound B (PiB) distribution volume ratio (DVR=1.96) than in PSEN1 E280A carriers who developed MCI in their forties (DVRs of 1.49-1.60). Despite her high A $\beta$  plaque burden, the magnitude and/or spatial extent of her PHF tau burden and neurodegeneration were relatively limited: Her flortaucipir (tau) PET measurements were restricted to medial temporal and less commonly affected occipital regions with relative sparing of other regions that are characteristically affected in the clinical stages of AD (FIG. 5). Her fluorodeoxyglucose PET measurements of the cerebral metabolic rate for glucose were preserved in brain regions that are known to be preferentially affected by AD, including higher precuneus-to-whole brain measurements than in PSEN1 E280A mutation carriers who developed MCI at younger ages and many younger, cognitively unimpaired mutation carriers.

FIG. 6 shows measurements of mean cortical amyloid plaque burden, entorhinal cortex PHF tau burden, hippocampal volume, and precuneus glucose metabolism. These measurements were based on brain imaging results obtain from the PSEN1 E280A mutation carrier with two APOE3ch alleles and exceptionally late-onset of MCI (red dots), PSEN1 E280A mutation carriers with MCI at the kindred's typical, younger age at MCI onset (black dots), and PSEN1 E280A mutation carriers who have not yet developed MCI (gray dots). Amyloid plaque burden is expressed as mean cortical-to-cerebellar distribution volume ratios (DVRs). Paired helical filament (PHF) tau burden is expressed as entorhinal cortex-to-cerebellar flortaucipir (FTP) standard uptake value ratios (SUVRs). Hippocampal volumes, which may be reduced by hippocampal atrophy, are expressed as hippocampal-to-whole brain volume ratios. Cerebral glucose metabolism, which is reduced in AD-affected brain regions with synaptic dysfunction and loss, is reflected as precuneus-to-whole brain cerebral metabolic rate for glucose (CMRg) ratios. As shown FIG. 6, while the PSEN1 E280A mutation carrier with two APOE3ch alleles had by far the highest amyloid plaque burden, she did not have comparably severe PHF tau burden or hippocampal atrophy, and she had no evidence of precuneus glucose hypometabolism. Her MRI-based hippocampal-to-whole brain volume, a hippocampal atrophy measurement that can be affected by AD and/or normal aging, was within the range of mutation carriers who developed MCI in their forties. Without wishing to be bound by theory, these results suggest that this APOE3ch homozygote's resistance to the clinical onset of AD is mediated through a mechanism that limits tau pathology and neurodegeneration even in the face of high A $\beta$  plaque burden.

To study functional consequences of the APOE3ch variant, A $\beta$ <sub>42</sub> aggregation in vitro in the presence of the bacteria-derived wild type human ApoE3 protein, presence of the mutant ApoE3ch protein, or in the absence of any ApoE protein were compared. The rate of A $\beta$ 42 fibril formation was detected by Thioflavin T fluorescence. A $\beta$ <sub>42</sub> aggregation was highest in the presence of wild type human ApoE3 protein (C-terminus domain), lower in the presence of human ApoE3ch (similar to that observed in the presence of ApoE<sup>48</sup>), and lowest in the absence of any ApoE (FIG. 7).

This finding was confirmed using a sensitive split-luciferase complementation assay in which luciferase signal is reconstituted once amyloid forms oligomers,<sup>48</sup> some of the most toxic amyloid species.<sup>49</sup> Full-length ApoE3ch expression in mammalian cells triggered significantly less oligomerization of A $\beta$ <sub>42</sub> compared to wild type ApoE3, as luciferase luminescence by oligomer formation was significantly reduced in ApoE3ch compared to wild type ApoE3 (FIG. 8). These results provide validation of the genetic analysis and suggest that the protective effects of the ApoEch protein may result, at least in part, from its limited ability to promote A $\beta$ <sub>42</sub> aggregation. It remains possible that the research participant may have had even greater A $\beta$  plaque deposition had she survived to her seventies without the APOE3ch genotype and that the ApoE3ch protein altered the morphology of A $\beta$  aggregates in ways that limited downstream neuroinflammation, tau pathology, neurodegeneration and cognitive decline.

A small percentage of Colombian kindred members were found to carry one copy of the APOE3ch mutation,<sup>50</sup> including four PSEN1 E280A mutation carriers who progressed to MCI at the median age of 45. For this reason, it was postulated that APOE3ch homozygosity may be required to dramatically lower the risk and postpone the clinical onset of autosomal dominant AD. Because the sample size was small, it remains possible that APOEch heterozygote individuals may have partial protection against autosomal dominant AD-related cognitive decline and substantial protection against sporadic late onset AD and/or neurodegeneration.

These results suggest that APOE variants differ in the extent of their pathogenic functions (APOEch and APOE2<3<4) and APOE3ch/3ch and APOE2/2 are associated with greatest functional loss. Interventions that safely and sufficiently edit APOE, lower its expression, or inhibit its pathogenic functions could have a profound impact on the treatment and prevention of AD. Interestingly, suppression of APOE expression in brain using an anti-sense oligonucleotide in A $\beta$ -overproducing mice led to altered A $\beta$  plaque morphology and fewer dystrophic neurites.<sup>51</sup> This approach may be feasible because absence of APOE expression was tolerated in a middle-aged man who was homozygous for a frame-shift variant<sup>52</sup> and availability of statins to treat HPL-III support the potential tolerability of ApoE-lowering treatments. See, e.g. Reiman et al. Nat Commun 11(1): 667, 2020.

Without wishing to be bound by theory, these results further suggest that homozygosity for APOE3ch—and APOE2—is associated with a profound resistance to the clinical onset of AD; that these genotypes exert their beneficial effects by directly or indirectly limiting downstream tau pathology and neurodegeneration; and that these effects are not based solely on the magnitude of A $\beta$  plaque burden despite relative reductions in ApoE-mediated A $\beta$  aggregation. These findings have implications for APOE's roles in the understanding, treatment, and prevention of AD, and may galvanize interest in developing APOE-modifying genetic and drug therapies for this disorder.

#### Example 2: Heparin Binding Properties of the APOE3ch Mutant Protein

##### Materials and Methods

Heparin column protocol: The heparin binding affinity of ApoE2, ApoE3, ApoE3ch and ApoE4 protein isoforms were compared using 1 ml Heparin Columns (BioVision-6554-1). The columns were acclimatized to room temperature for 1 hour prior to use. The columns were washed with 5 mL of

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20 mM TRIS-HCL (pH7.5). 1 mL sample containing 50 µg/mL of APOE recombinant protein in 20 mM TRIS-HCL (pH7.5) was then recycled through the column 5 times. The column was then washed through 5 times with 20 mM TRIS-HCL (pH7.5). An increasing NaCl gradient (0.025-1M) in 20 mM TRIS-HCL was passed through the column and 1 mL fractions were collected and subsequently prepared for western blotting.

**Western blotting:** Western Blotting confirmed the elution of ApoE isoforms within fractions collected from the heparin binding columns. Fractions were diluted in 10 µl RIPA buffer (Cell Signaling Technology), 4 µl DTT (1M) and 10 µl Laemmli buffer to a final volume of 40 µl. Samples were separated on a 4-20% Mini-PROTEAN® TGXTM Precast Protein Gels (Bio-Rad), transferred to nitrocellulose membranes (VWR; 27376-991), blocked with Odyssey Blocking Buffer (LI-COR Biosciences, Lincoln, NE), and probed with mouse anti-his tag (Novus biologicals), and IRDye 800CW donkey anti-rabbit (LI-COR Biosciences) antibodies. Immunoreactive bands were visualized using the Odyssey Infrared Imaging System and visualized on the Image Studio version 2.1 (LI-COR Biosciences). Individual gels were stitched together to generate FIG. 10.

**Heparin plate ELISA protocol:** An ELISA was carried out using heparin microplates (Bioworld; 50-197-531). These were blocked for one hour using sample preparation reagent (DY008). Heparin plates were incubated with 0.1 µg/well of each of the recombinant ApoE protein isoforms (ApoE2, ApoE3, ApoE3ch and ApoE4) for 2 hours, the plate was then washed five times in PBS containing a gradient of NaCl (0-0.5M) and then washed three times in the Wash Buffer (DY008). Anti-His tag antibody was incubated overnight at 1:10,000 (Novus biologicals; NBP2-61482). The plate was then washed five times to ensure removal of unbound primary antibody, incubated with donkey anti-rabbit-HRP (1:10000) for 45 minutes, and then washed five times to ensure removal of secondary antibody. Sulfuric acid from the ELISA reagent kit (DY008) was warmed to 37° C. prior to addition of 100 µl of tetramethylbenzidine (Millipore) initiating the detection phase of the reaction. After a 5-mins incubation, sulfuric acid was added to terminate the reaction. The plate was then read using a SPECTRAmax plus 384 (Molecular Devices). The wavelength of the read was 450 nm. For calculating the amount of antigen present in the samples, a standard curve was plotted using Prism 6 (GraphPad Software) based on the serial diluted recombinant Notch3 protein.

#### Results

Heparin sulfate proteoglycans (HSPG) moieties are a type of glycosaminoglycans present in hundreds of proteins located in the plasma membrane and in the extracellular matrix. Protein-protein interactions mediated via HSPG play a critical role in a multitude of processes relevant to Alzheimer's pathology including amyloid and tau pathology and neurodegeneration. The ability of various ApoE isoforms, including ApoEch, to bind to heparin, a glycosaminoglycan commonly used to model HSPG-protein interactions, was investigated. Briefly, fractions containing ApoE isoforms ApoE2 and ApoE4 eluted from heparin columns under an increasing NaCl gradient (0-0.65M) were analyzed using ELISA. As shown in FIG. 9, the ApoE variant associated with higher risk of Alzheimer's disease, ApoE4, has higher affinity for heparin compared to the variant ApoE2, which is known to be protective. Next, fractions that contain His-tagged ApoE2, ApoE3, ApoE4 and ApoE3ch which were eluted from heparin columns under an increasing NaCl gradient (0-0.65M) were analyzed using western blot. As

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shown in FIG. 10, ApoE3ch had impaired heparin binding, which is much lower than that of ApoE2. The affinity of the ApoE isoforms for heparin were also analyzed using the heparin plate ELISA protocol as described in Materials and Methods. As shown in FIGS. 11A-11B, ApoE3ch showed remarkably low level of heparin binding, as ApoE3ch was released from the heparin column at much lower concentrations of NaCl compared to those required for ApoE4 release.

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#### Example 3: Generation of Antibodies Against Wild Type ApoE and ApoEch Mutant Protein

#### Materials and Methods

**Antibody competition assay:** Antibodies were incubated with an ApoE3 recombinant protein (50 µg/ml in 20 mM Tris-HCL) at a 1:10 ratio and incubated for 3 hours at room temperature. A negative control containing the media only, and a positive control containing the recombinant protein ApoE3 only were used. The antibody/ApoE3 recombinant protein solution and controls were passed through heparin columns and exposed to an increasing NaCl gradient (as described in Example 2 above). Fractions were collected and assessed by ELISA and western blotting.

**BCA Assay:** Fractions collected from the heparin columns were first screened using the bicinchoninic acid assay (BCA assay) (Pierce BCA Protein Assay Kit). The assay was preformed using 200 µl of Reagent A and B Mix and 25 µl of each fraction. The 96 well plate was incubated for 30 minutes at 37° C., and read at 562 nm. The plate was read using Synergy 2 microplate reader (BioTek Instrument. Inc) and the Gen5 version 1.11 software).

**Western Blotting:** Western Blotting confirmed the elution of ApoE3 recombinant protein within fractions collected from the heparin binding columns. Fractions were diluted in 10 µl using RIPA buffer (Cell Signaling Technology), 10× (DTT 1M) and 4× Laemmli buffer for a final volume of 40 µl. Samples were separated on a 4-20% Mini-PROTEAN® TGXTM Precast Protein Gels (Bio-Rad), transferred to nitrocellulose membranes (VWR; 27376-991), blocked with Odyssey Blocking Buffer (LI-COR Biosciences, Lincoln, NE), and probed with mouse anti-his tag (Novus biologicals) and IRDye 800CW donkey anti-rabbit (LI-COR Biosciences) antibodies. Immunoreactive bands were visualized using the Odyssey Infrared Imaging System and visualized on the Image Studio version 2.1 (LI-COR Biosciences).

**ELISA:** Antibodies designed against the heparin-binding domain of ApoE were tested for their affinity to ApoE3 and ApoEch mutant recombinant proteins using ELISA. The Ni-NTA HisSorb Plates (Qiagen) were washed 3 times with wash buffer 1 (DY008). The ApoE recombinant proteins were suspended in buffer (DY008) to give a final concentration of 0.5 µg/ml. The plates were incubated with 200 µl of ApoE recombinant proteins for 2 hours, and washed 5 times with 1× wash buffer (DY008). The plates were then incubated with antibodies at a serial dilution of from 1:1,000 to 1:32,000 for overnight at 4° C. The plate was then washed 5 times in 1× wash buffer (DY008), and incubated with anti-mouse HRP (Abcam; ab97046, 1:10,000) for 45 minutes, followed by 5 washes in 1× wash buffer to ensure complete removal of unbound secondary antibody. The sulfuric acid from the ELISA reagent kit (DY008) was warmed to 37° C. 100 µl of tetramethylbenzidine (Millipore) was added to initiate the detection phase of the reaction. After a 5-min incubation, sulfuric acid was added to termi-

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nate the reaction. The plate was then read using Synergy 2 microplate reader (BioTek Instrument, Inc) and the Gen5 version1.11 software).

#### Results

A monoclonal antibody against amino acids 130 to 143 of ApoE was generated and tested for its effect on the binding between full-length ApoE3 protein and heparin. Briefly, full-length wild type ApoE3 protein or those pre-incubated with the monoclonal antibody was passed through a heparin column and recycled five times to ensure maximal ApoE3 binding. The column was then washed five times with 20 mM Tris-HCl (pH=7.5) and exposed to an increasing gradient of NaCl (0 to 1M) in 20 mM Tris-HCl (pH=7.5). The elution from the Tris-HCl washes and from various NaCl concentrations were collected (FIGS. 12A-12C).

The fractions collected from the column were first screened by the bicinchoninic acid (BCA) assay. As shown in FIG. 13A, protein signal was detected for wild type ApoE3 in fractions to the right of the curve, indicating strong binding of ApoE3 to heparin. In contrast, strong signal was observed in early fractions with low ionic strength when ApoE3 was pre-incubated with the monoclonal antibody (FIG. 13B). To verify the results, western blotting was used to analyze the column washes and NaCl gradient fractions collected from the heparin column. As shown in FIG. 14, pre-incubation of wild type ApoE3 with the monoclonal antibody (A3Ab) (this antibody was named 1343 in Arboleda-Velasquez et al., *Nature Medicine*, 25, pages 1680-1683 (2019)) reduced its ability to bind to heparin, to a level similar to that of an ApoE3ch mutant protein. Individual gels were stitched together to generate FIG. 14. These results suggest that an antibody may be used to modify the binding properties of ApoE to heparin, thereby preventing or treating Alzheimer's disease or related dementias or neurodegeneration.

To generate monoclonal antibodies against the heparin-binding domain of ApoE, mice were immunized using the wild type ApoE peptide: KLH-CTEELRVRLASHLRK-CONH2 (SEQ ID NO:54), and the ApoEch peptide: KLH-CTEELRVSLASHLRK-CONH2 (SEQ ID NO:55). A cysteine residue was added at the N-terminus to facilitate conjugation of the peptides. Cell fusions were obtained from positive clones and cell supernatants tested for activity against the wild type and mutant peptides and proteins. Seven antibodies generated were analyzed by ELISA as examples, as described in the materials and methods section. The 19G10-2 antibody serum displayed specificity towards both the full-length and C-terminal of the APOE3ch mutant protein and some interaction with the wild type APOE3 protein (FIG. 15A). The 23B2 antibody displayed reactivity to both the wild type ApoE3 and ApoE3ch mutant C-terminal and full-length recombinant proteins (FIG. 15B). The 2H79-1 antibody displayed non-specific binding to bovine serum albumin (BSA) and showed no affinity for either wild type ApoE3 or ApoE3ch mutant (FIG. 15C). Both the 30E1-2 and 16H8 antibodies showed reactivity to the full-length and C-terminal ApoE3ch mutant proteins and the C-terminal form of wild type ApoE3, but did not react with the full-length wild type APOE3 protein (FIGS. 15D and 15E). The 25F1-2 antibody serum showed high affinity for the full-length and C-terminal ApoE3ch mutant proteins, and appeared to have variable binding to the C-terminus of the wild type ApoE3 protein and some interaction with the full-length wild type ApoE3 protein (FIG. 15F). The 29G10-2 antibody showed high affinity for both the full-length and C-terminal of the ApoE3ch mutant proteins, and also showed reactivity to the C-terminal wild type ApoE3

and BSA. Lastly, the 29G10-2 antibody did not interact with the full-length wild type ApoE3 protein (FIG. 15G).

The variable heavy chain (VH), variable light chain (VL) and complementarity determining region (CDR) sequences of 25F1-2 and 19G10-2 are described herein.

Further, the following parental clones with specificity for wild type ApoE were generated, and the specificity for the wild type ApoE peptide (WT peptide), the wild type ApoE protein (WT protein), the mutant ApoE peptide (ApoEch; Mut peptide) and the mutant ApoE3ch protein (Mut protein) were tested as shown in Table 6. The values indicate levels of absorbance as detected by ELISA. The bolded clones showed specificity for the wild type ApoE peptide (KLH-CTEELRVRLASHLRK-CONH2 (SEQ ID NO:54) and the wild type ApoE protein).

TABLE 6

	WT peptide	WT protein	Mut peptide	Mut protein
1D5	1.742	1.086	0.060	0.062
1H4	2.578	2.113	0.070	0.056
3A6	2.412	0.733	0.059	0.056
7C3	1.698	1.245	0.064	0.051
7C4	2.097	0.586	0.057	0.056
7C11	1.282	0.689	0.058	0.055
16G6	0.739	0.449	0.076	0.067
Pos. ctrl	1.980	1.171	0.254	0.144
Neg. ctrl	0.068	0.051	0.056	0.048

#### Example 4: Generation of Fusion Proteins

##### Containing the Heparin-Binding Domain of APOE

#### Materials and Methods

**Peptide Competition Assay:** Wild type ApoE3 and ApoE3ch mutant peptides (50 µg/ml) were incubated with ApoE3 recombinant protein (50 µg/ml prepared in 20 mM Tris-HCl) for 3 hours at room temperature. The peptide/ApoE3 recombinant protein solution were then passed through heparin columns and exposed to an increasing NaCl gradient (as described in Example 2 and 3 above). Fractions were collected and assessed by western blotting.

**Western Blotting:** Western blotting confirmed the elution of ApoE3 within fractions collected from the heparin binding columns. Fractions were diluted in 10 µl RIPA buffer (Cell Signaling Technology), 10x (DTT 1M) and 4x Laemmli buffer to a final volume of 40 µl. Samples were separated on a 4-20% Mini-PROTEAN® TGXTM Precast Protein Gels (Bio-Rad), transferred to nitrocellulose membranes (VWR; 27376-991), blocked with Odyssey Blocking Buffer (LI-COR Biosciences, Lincoln, NE), and probed with mouse anti-his tag (Novus biologicals) and IRDye 800CW donkey anti-rabbit (LI-COR Biosciences) antibodies. Immunoreactive bands were visualized using the Odyssey Infrared Imaging System and visualized on the Image Studio version 2.1 (LI-COR Biosciences).

#### Results

Peptides containing amino acids 130-143 of the wild type ApoE protein and ApoEch mutant protein, respectively, were generated. To examine the effect of these peptides on the binding between wild type ApoE3 recombinant protein and heparin sepharose, a peptide competition assay was carried out as described in materials and methods. As shown in FIG. 16, the wild type ApoE peptide resulted in a one-fraction shift of wild type ApoE3 recombinant protein binding, suggesting that this peptide can compete with wild type full-length ApoE3 for binding to heparin. These results suggest that ApoE fragments containing amino acids 130-

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143 of the wild type ApoE protein may be used to change the binding properties of ApoE to heparin, thereby preventing or treating Alzheimer's disease or related dementias or neurodegeneration.

To increase protein stability of the peptides, C-terminal and N-terminal fusion proteins containing the heparin-binding domain of human ApoE (wild type and the R136S mutant version) or a site of allosteric modulation of the heparin-binding domain were generated using the backbone Fc IgG2 constructs pfuse-hfc1 and pfcn-hg2 (Invivogen). The human ApoE fragments excluded the sites for APOE2 and APOE4 variants. Administration of ApoE fragments with an R at position 136 may compete with endogenous ApoE for interaction with binding partners including HSPG leading to protection against neurodegeneration. Administration of ApoE fragments with an S at position 136 may bind molecules that do not bind to the wild type ApoE, leading to protection against neurodegeneration. The amino acid sequences for the fragments from the wild type and the R136S mutant ApoE used to generate the fusion proteins are shown below (the R136 position is bolded and double underlined).

## Downstream of R136 Fragment

WT (SEQ ID NO: 57)  
STEELRVRLASHLRKLRKRLLRDADDLQK

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-continued

## Mutant

(SEQ ID NO: 58)

STEELRVSLASHLRKLRKRLLRDADDLOK

## Upstream of R136 Fragment

WT

(SEQ ID NO: 59)

RLVQYRGEVQAMLGQSTEELRVRLASHLRKL

## Mutant

(SEQ ID NO: 60)

RLVOYRGEVOAMLGOSTEELRVSLASHLRKL

15 FIGS. 17A-17D show models of the interaction of ApoE fragments with heparin. FIG. 17A shows a model of the wild type ApoE fragment (downstream of R136 fragment, helix) interacting with heparin. FIG. 17B shows a model of the fragment of ApoE R136S (downstream of R136 fragment, helix) interacting with heparin. FIG. 17C shows a model of the wild type ApoE fragment (upstream of R136 fragment, helix) interacting with heparin. FIG. 17D shows a model of the fragment of ApoE R136S (upstream of R136 fragment, helix) interacting with heparin.

<sup>25</sup> The nucleic acid and amino acid sequences for exemplary fusion protein constructs containing either the downstream of R136 fragment or the upstream of R136 fragment are shown below.

184Q pfcbn-hg2 ApoE 114-144  
Nucleic acid sequence  
(SEQ ID NO: 81)  
1 GGATCTGCGA TCGCTCCGGT GCCCGTCAGT GGGCAGAGCG CACATCGCCC ACAGTCCCCG  
61 AGAAGTTGGG GGGGGGGTC GGCAATTGAA CGGGTGCCTA GAGAAGGTGG CGGGGGGTAA  
121 ACTGGAAAG TGATGTCGTG TACTGGCTCC GCCTTTTCC CGAGGGTGGG GGAGAACCGT  
181 ATATAAGTGC AGTAGTCGCC GTGAACGTTC TTTTCGCAA CGGGTTTGCC GCCAGAACAC  
241 AGCTGAAGCT TCGAGGGCT CGCATCTCTC CTTCACGCGC CCGCGGCCCT ACCTGAGGCC  
301 GCCATCCACG CCGGTTGAGT CGCGTTCTGC CGCCTCCCGC CTGTGGTGCC TCCTGAACCT  
361 CGTCGCCCGT CTAGGTAAGT TAAAGCTCA GGTGAGACCC GGGCCTTGT CGCGCCTCGC  
421 CTTGGAGCCT ACCTAGACTC AGCCGGCTCT CCACGCTTTG CCTGACCCtg cttgctcaac  
481 tctacgtCTT TGTTCGTT TCTGTTCTGC GCCGTTACAG ATCCAAGCTG TGACCGGGCGC  
541 CTACCTGAGA TCACCGGCGA AGGAGGGCA CCATGTACAG GATGCAACTC CTGCTCTGCA  
601 TTGCACTAAG TCTTGCACCT GTCACGAATT CGGCACCTCT CGAGCGAAA TCTAGTGTGCG  
661 AGTGCCACC GTGCCAGCA CCACCTGTGG CAGGACCGTC AGTCTTCCTC TTCCCCCCAA  
721 AACCCAAGGA CACCCCTATG ATCTCCCGGA CCCCTGAGGT CACGTGCGTG GTGGTGGACG  
781 TGAGCCACGA AGACCCCGAG GTCCAGTTCA ACTGGTACGT GGACGGCGTG GAGGTGCAATA  
841 ATGCCAACAG AAAGCCACGG GAGGAGCAGT TCAACAGCAC GTTCCGTGTG GTCAAGCGTCC  
901 TCACCGTTGT GCACCAGGAC TGGCTGAACG GCAAGGAGTA CAAGTGCAAG GTCTCCAACAA  
961 AAGGCCCTCC AGCCCCCATC GAGAAAAACCA TCTCCAAAAC CAAAGGGCAG CCCCAGAAC  
1021 CACAGGTGA CACCCCTGCC CCATCCCGGG AGGAGATGAC CAAGAACCGAG GTCAGCGTCA  
1081 CCTGCTGGT CAAAGGCTTC TACCCCCAGCG ACATGCCCGT GGAGTGGGAG AGCAATGGGCG  
1141 AGCCGGAGAA CAACTACAAG ACCACGCCCTC CCATGCTGGA CTCCGACGGC TCCTTCTTCC  
1201 TCTACAGCAA GCTCACCGTG GACAAGAGCA GGTGGCAGCA GGGGAACGTC TTCTCATGCT

-Continued

1261 CCGTGATGCA TGAGGCTCTG CACAAACACT ACACGCAGAA GAGCCTCTCC CTGTCTCCGG  
 1321 GTGCACGTAC GCGCCTGGTG CAGTACCGCG GCGAGGTGCA GCCCATGCTC GGCCAGAGCA  
 1381 CCGAGGAGCT CGGGGTGCGC CTCGCCTCCC ACCTGCGCAA GCTGTgaTAT CTCGAGCTAG  
 1441 CTGGCCAGAC ATGATAAGAT ACATTGATGA GTTTGGACAA ACCACAACTA GAATGCAGTG  
 1501 AAAAAAATGC TTTATTTGTG AAATTGTGA TGCTATTGCT TTATTTGTAA CCATTATAAG  
 1561 CTGCAATAAA CAAGTTAACCA ACAACAATTG CATTCACTTT ATGTTTCAGG TTCAGGGGA  
 1621 GGTGTGGGAG GTTTTTAAA GCAAGTAAA CCTCTACAAA TGTGGTATGG AATTAATTCT  
 1681 AAAATACAGC ATAGCAAAAC TTTAACCTCC AAATCAAGCC TCTACTTGAA TCCTTTCTG  
 1741 AGGGATGAAT AAGGCATAGG CATCAGGGC TGTTGCCAAT GTGCATTAGC TGTTGCAGC  
 1801 CTCACCTTCT TTCACTGGAGT TTAAGATATA GTGTATTTC CCAAGGTTG AACTAGCTCT  
 1861 TCATTTCTT ATGTTTTAAA TGCACTGACC TCCCACATTC CCTTTTAGT AAAATATTCA  
 1921 GAAATAATT AAATACATCA TTGCAATGAA AATAATGTT TTTTATTAGG CAGAATCCAG  
 1981 ATGCTCAAGG CCCTTCATAA TATCCCCAG TTTAGTAGTT GGACTTAGGG AACAAAGGAA  
 2041 CCTTTAATAG AAATTGGACA GCAAGAAAGC GAGCTTCTAG CTTATCCTCA GTCTGCTCC  
 2101 TCTGCCACAA AGTGCACGCA GTTGCAGGCC GGGTCGCGCA GGGCGAACTC CCGCCCCCAC  
 2161 GGCTGCTCGC CGATCTCGGT CATGCCCGGC CCGGAGGCGT CCGGAAGTT CGTGGACACG  
 2221 ACCTCCGACC ACTCGCGTA CAGCTCGTCC AGGCCGCGCA CCCACACCCA GGCCAGGGTG  
 2281 TTGTCCGGCA CCACCTGGTC CTGGACCGCG CTGATGAACA GGGTCACGTC GTCCGGACC  
 2341 ACACCGCGCA AGTCGTCTC CACGAAGTCC CGGGAGAACCC CGAGCCGGTC GGTCCAGAAC  
 2401 TCGACCGCTC CGGCGACGTC GCGCGCGGTG AGCACCGGAA CGGCACACTGGT CAACTGGCC  
 2461 ATGATGGCTC CTcctgtcag gagaggaaag agaagaaggt tagtacaatt gCTATAGTGA  
 2521 GTTGTATTAT ACTATGCAGA TATACTATGC CAATGATTAA TTGTCAAACCT AGGGCTGCAg  
 2581 ggtcatagt gccacttttc ctgcactgcc ccatctctg cccacccttt cccaggcata  
 2641 gacagtcaacttacCAA ACTCACAGGA GGGAGAACGG AGAACGTTGA GACAGACCCG  
 2701 CGGGACCGCC GAACTGCGAG GGGACGTGGC TAGGGCGGCT TCTTTATGG TGCGCCGGCC  
 2761 CTCGGAGGCA GGGCGCTCGG GGAGGCCTAG CGGCCAATCT GCGGTGGCAG GAGGCAGGGC  
 2821 CGAAGGGCGT GCCTGACCAA TCCGGAGCAC ATAGGAGTCT CAGCCCCCG CCCCCAAAGCA  
 2881 AGGGGAAGTC ACGCGCTGT AGCGCCAGCG TGTTGTGAA TGGGGGCTTG GGGGGTTGG  
 2941 GGCCTGACT AGTCAAAACA AACTCCCATT GACGTCAATG GGGTGGAGAC TTGGAATCC  
 3001 CCGTGAGTCA AACCGCTATC CACGCCATT GATGTACTGC CAAACCGCA TCATCATGGT  
 3061 AATAGCGATG ACTAATACGT AGATGTACTG CCAAGTAGGA AAGTCCCAT AAGTCATGTA  
 3121 CTGGGCATAA TGCCAGGCCG GCCATTACG GTCATTGACG TCAATAGGGG GCGTACTTGG  
 3181 CATATGATAC ACTTGATGTA CTGCCAAGTG GGCAGTTAC CGTAAATACT CCACCCATTG  
 3241 ACGTCAATGG AAAGTCCCTA TTGGCGTTAC TATGGAAACA TACGTCAATTA TTGACGTCAA  
 3301 TGGCGGGGGG TCGTTGGCG GTCAGCCAGG CGGGCCATT ACCGTAAGTT ATGTAACGCC  
 3361 TGCAGGTTAA TTAAGAACAT GTGAGCAAA GGCCAGCAAA AGGCCAGGAA CCGTAAAAG  
 3421 GCCGCGTTGC TGGCGTTTT CCATAGGCTC CGCCCCCTG ACGAGCATCA CAAAATCGA  
 3481 CGCTCAAGTC AGAGGTGGCG AAACCCGACA GGACTATAAA GATACCAGGC GTTCCCCCT  
 3541 GGAAGCTCCC TCGTGCCTC TCCTGTTCCG ACCCTGCCGC TTACCGGATA CCTGTCCGCC  
 3601 TTCTCCCTT CGGGAAAGCGT GGCGCTTTCT CATAAGCTCAC GCTGTAGGTA TCTCAGTTCG  
 3661 GTGTAGGTCG TTCGCTCCAA GCTGGCTGT GTGCACGAAC CCCCCGTTCA GCGCGACCGC

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**59****60**

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3721 TGCAGCTTAT CCGGTAACCA TCGTCTTGAG TCCAACCCGG TAAGACACGA CTTATGCCA  
 3781 CTGGCAGCAG CCACTGGTAA CAGGATTAGC AGAGCGAGGT ATGTAGGCAG TGCTACAGAG  
 3841 TTCTTGAAAGT GGTGGCTAA CTACGGCTAC ACTAGAAGAA CAGTATTGG TATCTGCCT  
 3901 CTGCTGAAGC CAGTTACCTT CGGAAAAAGA GTTGGTAGCT CTTGATCCGG CAAACAAACC  
 3961 ACCGCTGGTA CGGGTGGTTT TTTGTTTGC AAGCAGCAGA TTACGCCAG AAAAAGGA  
 4021 TCTCAAGAACG ATCCTTGAT CTTTCTACG GGGCTGACG CTCAGTGGAA CGAAAACCTCA  
 4081 CGTTAAGGGA TTTGGTCAT GGCTAGTTAA TTAACATTAA AATCAGCGGC CGCAATAAAA  
 4141 TATCTTTATT TTCATTACAT CTGTTGTTG GTTTTTGTG TGAATCGTAA CTAACATACG  
 4201 CTCTCCATCA AAACAAAACG AAACAAAACA AACTAGCAAATAGGCTGTC CCCAGTGCAA  
 4261 GTGCAGGTGC CAGAACATTT CTCTATCGAA

Amino acid sequence

(SEQ ID NO: 82)

MYRMQLLSCIALSLALVTNSAPLERKSSVECPVAPPVAGPSVFLFPP  
 KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVEINAUTKPREEQF  
 NSTFRVSVLTVHWDWLNGKEYKCKVSNKGLPAPIEKTISKTKQPREPQV  
 YTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMILDS  
 DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHTQKSLSLSPGARTRL  
 VQYRGEVQAMLQSTEELRVRLASHLRKL

184R pfccn-hg2 ApoE 114-144 R1365

Nucleic acid sequence

(SEQ ID NO: 83)

1 GGATCTGCGA TCGCTCCGGT GCCCGTCAGT GGGCAGAGCG CACATGCCACAGTCCCCG  
 61 AGAACAGTTGGG GGGAGGGGTC GGCAATTGAA CGGGTGCCTA GAGAACAGTGG CGCGGGGTAA  
 121 ACTGGGAAAG TGATGTCGTG TACTGGCTCC GCCTTTTCC CGAGGGTGGG GGAGAACCGT  
 181 ATATAAGTGC AGTAGTCGCC GTAACGTTTC TTTTCGCAA CGGGTTTGCC GCCAGAACAC  
 241 AGCTGAAGCT TCGAGGGGCT CGCATCTCTC CTTCACGCC CGCCGCCCT ACCTGAGGCC  
 301 GCCATCCACG CGGGTTGAGT CGCGTCTGC CGCCCTCCCGC CTGTGGTGCC TCCTGAACGT  
 361 CGTCCGCCGT CTAGGTAAGT TTAAAGCTCA GGTCGAGACC GGGCCTTGT CGGGCGCTCC  
 421 CTTGGAGCCT ACCTAGACTC AGCCGCTCT CCACGCTTG CCTGACCCtg ctgtgtcaac  
 481 tctacgTCTT TGTTCTGTT TCTGTTCTGC GCCGTTACAG ATCCAAGCTG TGACCGGCGC  
 541 CTACCTGAGA TCACCGCGA AGGAGGGCCA CCATGTACAG GATGCAACTC CTGTCTTGCA  
 601 TTGCACTAAG TCTTGACTT GTCACGAATT CGGCACCTCT CGAGCGAAA TCTAGTGTG  
 661 AGTGCCCACC GTGCCAGCA CCACCTGTGG CAGGACCGTC AGTCTTCTC TTCCCCCAA  
 721 AACCCAAAGGA CACCCCTCATG ATCTCCCGA CCCCTGAGGT CACGTGGCGTG GTGGTGGACG  
 781 TGAGGCCAGCA AGACCCCGAG GTCCAGTTCA ACTGGTACGT GGACGGCGTG GAGGTGCATA  
 841 ATGCCAAGAC AAAGCCACGG GAGGAGCAGT TCAACAGCAC GTTCCGTGTG GTCAGCGTCC  
 901 TCACCGTTGT GCACCAAGGAC TGGCTGAACG GCAAGGGAGTA CAAGTGCAAG GTCTCCAACA  
 961 AAGGCCTCCC AGCCCCATC GAGAAAACCA TCTCCAAAC CAAAGGGCAG CGCCGAGAAC  
 1021 CACAGGTGTA CACCCCTGCC CCATCCGGG AGGAGATGAC CAAGAACCGAG GTCAGCCTGA  
 1081 CCTGCCTGGT CAAAGGCTTC TACCCAGCG ACATGCCGT GGAGTGGGAG AGCAATGGC  
 1141 AGCCGGAGAA CAACTACAAG ACCACGCCCTC CCATGCTGGA CTCCGACGGC TCCTTCTTCC  
 1201 TCTACAGCAA GCTCACCGTG GACAAGAGCA GGTGGCAGCA GGGGAACGTC TTCTCATGCT  
 1261 CCGTGATGCA TGAGGCTCTG CACAACCACT ACACGCAGAA GAGCCTCTCC CTGTCTCCGG

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1321 GTGCACGTAC GCGCCTGGTG CAGTACCGCG GCGAGGTGCA GGCCATGCTC GGCCAGAGCA  
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 1441 CTGGCCAGAC ATGATAAGAT ACATTGATGA GTTTGGACAA ACCACAACTA GAATGCAGTG  
 1501 AAAAAAATGC TTTATTGTG AAATTGTGA TGCTATTGCT TTATTTGTAAC CATTATAAG  
 1561 CTGCAATAAA CAAGTTAACCA ACAACAATTG CATTCACTTT ATGTTTCAGG TTCAGGGGA  
 1621 GGTGTGGGAG GTTTTTAAA GCAAGTAAAA CCTCTACAAA TGTTGATGG AATTAATTCT  
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 1741 AGGGATGAAT AAGGCATAGG CATCAGGGGC TGTTGCCAAT GTGCATTAGC TGTTGCAGC  
 1801 CTCACCTCTC TTCATGGAGT TTAAGATATA GTGTATTTC CCAAGGTTG AACTAGCTCT  
 1861 TCATTTCTT ATGTTTTAAA TGCACTGACC TCCCCACATTC CCTTTTAGT AAAATATTCA  
 1921 GAAATAATT AAATACATCA TTGCAATGAA AATAATGTT TTTTATTAGG CAGAATCCAG  
 1981 ATGCTCAAGG CCCTTCATAA TATCCCCAG TTTAGTAGTT GGACTTAGGG AACAAAGGAA  
 2041 CCTTTAATAG AAATTGGACA GCAAGAAAGC GAGCTCTAG CTTATCCTCA GTCCGTCTCC  
 2101 TCTGCCACAA AGTGCGCAGCA GTTGCAGGCC GGGTCGCGCA GGGCGAACTC CGGCCACAC  
 2161 GGCTGCTCGC CGATCTCGGT CATGGCCGGC CGGGAGGC GT CCCGAAGTT CGTGGACACG  
 2221 ACCTCCGACC ACTCGCGTA CAGCTCGTCC AGGCCGCGCA CCCACACCCA GGCCAGGGTG  
 2281 TTGTCCGGCA CCACCTGGTC CTGGACCGCG CTGATGAACA GGGTCACGTC GTCCGGGACC  
 2341 ACACCGCGCA AGTCGTCCTC CACGAAGTCC CGGGAGAAC CGAGCCGGTC GGTCCAGAAC  
 2401 TCGACCGTC CGGCGACGTC GCGCGCGGT AGCACCGAA CGGCACTGGT CAACTGGCC  
 2461 ATGATGGCTC CTCCtgcag gagagaaaa agaagaagg tagtacaatt gCTATAGTGA  
 2521 GTGTATTTAT ACTATGCAGA TATACTATGC CAATGATTAA TTGTCAAAC AGGGCTGCAg  
 2581 ggttcatagt gccacttttc ctgactgcc ccaccccttc cccaggcata  
 2641 gacagtcagt gacttacCAA ACTCACAGGA GGGAGAAGGC AGAAGCTTGA GACAGACCCG  
 2701 CGGGACCGCC GAACTGCGAG GGGACGTGGC TAGGGCGGT TCTTTATGG TGCGCCGGCC  
 2761 CTCGGAGGCA GGGCGCTCGG GGAGGCCTAG CGGCCAATCT GCGGTGGCAG GAGGCGGGC  
 2821 CGAAGGGCGT GCCTGACCAA TCCGGAGCAC ATAGGAGTCT CAGCCCCCG CCCAAAGCA  
 2881 AGGGGAAGTC ACGGCCCTGT AGCGCCAGCG TGTTGTAAA TGGGGCTTG GGGGGTTGG  
 2941 GGCCCTGACT AGTCAAAACA AACTCCCATT GACGTCAATG GGGTGGAGAC TTGGAAATCC  
 3001 CGGTGAGTCA AACCGCTATC CACGCCATT GATGACTGC CAAACCGCA TCATCATGGT  
 3061 AATAGCGATG ACTAATACGT AGATGACTG CCAAGTAGGA AAGTCCCATA AGGTCAATGTA  
 3121 CTGGGCATAA TGCCAGGC GGCCATTAC GTCATTGACG TCAATAGGG GCGTACTTGG  
 3181 CATATGATAC ACTTGATGTA CTGCCAAGTG GGCAGTTAC CGTAAATACT CCACCCATTG  
 3241 ACGTCAATGG AAAGTCCCTA TTGGCGTTAC TATGGGAACA TACGTCAATTA TTGACGTCAA  
 3301 TGGCGGGGG TCGTTGGCG GTCAGCCAGG CGGGCCATT ACCGTAAGTT ATGTAACGCC  
 3361 TGCAGGTTAA TTAAGAACAT GTGAGCAAA GGCCAGCAA AGGCCAGGAA CCGTAAAAG  
 3421 GCCGCCTGTC TGGCGTTTT CCATAGGCTC CGCCCCCTG ACGAGCATCA CAAAATCGA  
 3481 CGCTCAAGTC AGAGGTGGCG AAACCGACA GGACTATAAA GATACCAGGC GTTTCCCCCT  
 3541 GGAAGCTCCC TCGTGCCTC TCCTGTTCCG ACCCTGCCGC TTACCGGATA CCTGTCCGCC  
 3601 TTTCTCCCTT CGGGAGCGT GGCGCTTCT CATAGCTCAC GCTGTAGGTA TCTCAGTTCG  
 3661 GTGTAGGTCG TTGCGCTCAA GCTGGCTGT GTGCACGAAC CCCCCGTTCA GCCCGACCGC

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3721 TGCGCCTTAT CCGGTAAC TA CGCTTGAG TCCAACCCGG TAAGACACGA CTTATCGCCA  
 3781 CTGGCAGCAG CCACTGGTAA CAGGATTAGC AGAGCGAGGT ATGTTAGGCAG TGCTACAGAG  
 3841 TTCTTGAAAGT GGTGGCTAA CTACGGCTAC ACTAGAAGAA CAGTATTGG TATCTGCCT  
 3901 CTGCTGAAGC CAGTTACCTT CGGAAAAAGA GTTGGTAGCT CTTGATCCGG CAAACAAACC  
 3961 ACCGCTGGTA GCGGTGGTTT TTTTGTTC AAGCAGCAGA TTACGCGCAG AAAAAAAGGA  
 4021 TCTCAAGAAC ATCCTTGAT CTTCCTACG GGGCTGACG CTCAGTGGAA CGAAAACCTCA  
 4081 CGTTAAGGGA TTTTGGTCAT GGCTAGTTAA TTAACATTTA AATCAGCGGC CGCAATAAAA  
 4141 TATCTTTATT TTCATTACAT CTGTGTGTTG GTTTTTGTG TGAATCGTAA CTAACATACG  
 4201 CTCTCCATCA AAACAAAACG AAACAAAACA AACTAGCAAAT ATAGGCTGTC CCCAGTGCAA  
 4261 GTGCAGGTGC CAGAACATTT CTCTATCGAA

Amino acid sequence

(SEQ ID NO: 84)

MYRMQLLSCIALSLALVTNSAPLERKSSVECPGPAPPVAGPSVFLFPP

PKPDTLMSIRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVEINAKTKPREEQF

NSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKQPREPQV

YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQOPENNYKTPPMQLDS

DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGARTRL

VQYRGEVQAMLGQSTEELRVSLASHLRKL

197F pfuse hfc2 ApoE 114-144  
Nucleic acid sequence

(SEQ ID NO: 85)

1 GGATCTCGA TCGCTCCGGT GCCCGTCAGT GGGCAGAGCG CACATGCCAC ACAGTCCCCG  
 61 AGAAGTTGGG GGGAGGGGTC GGCAATTGAA CGGGTGCCTA GAGAAGGTGG CGCGGGGTAA  
 121 ACTGGAAAG TGATCTCGTG TACTGGCTCC GCCTTTTCC CGAGGGTGGG GGAGAACCGT  
 181 ATATAAGTGC AGTAGTCGCC GTGAACGTTG TTTTCGCAA CGGGTTTGCC GCCAGAACAC  
 241 AGCTGAAGCT TCGAGGGGCT CGCATCTCTC CTTCACGCGC CCGCCGCCCT ACCTGAGGCC  
 301 GCCATCCACG CGGGTTGAGT CGCGTTCTGC CGCCTCCCGC CTGTGGTGCC TCCTGAACCTG  
 361 CGTCCGCCGT CTAGGTAAGT TTAAAGCTCA GGTCGAGACC GGGCCTTGT CGGGCGCTCC  
 421 CTTGGAGCCT ACCTAGACTC AGCCGGCTCT CCACGCTTGT CCTGACCCCTG CTTGCTCAAC  
 481 TCTACGTCTT TGTTCTGTT TCTGTTCTGC GCCGTTACAG ATCCAAGCTG TGACCGGCC  
 541 CTACCTGAGA TCACggcGA AGGAGGGCCA CCATGTACAG GATGCAACTC CTGTCTTGCA  
 601 TTGCACTAAG TCTTGACTT GTCACTGATT CGATACGCCT GGTGCACTAC CGCGCGAGG  
 661 TGCAGGCCAT GCTCGGCCAG AGtActGAGG AGCTGCGGGT GCGCCTCGCC TCCCACCTGC  
 721 GCAAGCTGat ATCGGCCATG GTTGTACAG TGAGTGCCCC ACCTTGCCCC GAACCACCTG  
 781 TGGCAGGACC TTCAGCTTC CTCTTCCCC CAAAACCCAA GGACACCCCTG ATGATCTCCA  
 841 GAACCCCTGA GGTCACTGTC GTGGTGGTGG ACGTGAGCCA CGAAGACCCC GAGGTCCAGT  
 901 TCAACTGGTA CGTGGACGGC ATGGAGGTGC ATAATGCCA GACAAAGCCA CGGGAGGAGC  
 961 AGTTCAACAG CACGTTCCGT GTGGTCAGCG TCCTCACCGT CGTGCACCGAG GACTGGCTGA  
 1021 ACGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAAGGCCT CCCAGCCCC ATCGAGAAAA  
 1081 CCATCTCCAA AACCAAAGGG CAGCCCCGAG AACCAACAGGT GTACACCCCTG CCCCCATCCCC  
 1141 GGGAGGAGAT GACCAAGAAC CAGGTCAAGCC TGACCTGCCT GGTCAAAGGC TTCTACCCCA  
 1201 GCGACATCGC CGTGGAGTGG GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACAC  
 1261 CTCCCATGCT GGACTCCGAC GGCTCCTCTC TCCTCTACAG CAAGCTCACC GTGGACAAGA

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1321 GCAGGGTGGCA GCAGGGGAAC GTCTTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC  
 1381 ACTACACACA GAAGAGCCTC TCCCTGTCTC CGGGTAAATG AgtgcacgG CTAGCTGGCC  
 1441 AGACATGATA AGATAACATTG ATGAGTTGG ACAAACACACA ACTAGAATGC AGTGAAAAAA  
 1501 ATGCTTTATT TGTGAAATTT GTGATGCTAT TGCTTTATTG TAACCATTAA TAAGCTGCAA  
 1561 TAAACAAAGTT AACAAACAACA ATTGCATTCA TTTTATGTTT CAGGTTCAAGG GGGAGGTGTG  
 1621 GGAGGTTTTT TAAAGCAAGT AAAACCTCTA CAAATGTGGT ATGGAATTAA TTCTAAAATA  
 1681 CAGCATAGCA AAACCTTAAC CTCCAAATCA AGCCTCTACT TGAATCCTTT TCTGAGGGAT  
 1741 GAATAAGGCA TAGGCATCAG GGGCTGTTGC CAATGTGCAT TAGCTGTTG CAGCCTCACC  
 1801 TTCTTCATG GAGTTAAGA TATAGTGTAT TTTCCAAGG TTTGAACCTAG CTCTCATT  
 1861 CTTTATGTTT TAAATGCACT GACCTCCCAC ATTCCCTTT TAGTAAAATA TTCAGAAATA  
 1921 ATTTAAATAC ATCATTGCAA TGAAAATAAA TGTTTTTAT TAGGCAGAAT CCAGATGCTC  
 1981 AAGGCCCTTC ATAATATCCC CCAGTTAGT AGTTGGACTT AGGGAAACAAA GGAACCTTTA  
 2041 ATAGAAATTG GACAGCAAGA AAGCGAGCTT CTAGCTTATC CTCAGTCCTG CTCCCTGCCC  
 2101 ACAAAGTGCA CGCAGTTGCC GGCGGGTGC CGCAGGGCGA ACTCCCGCCCC CCACGGCTGC  
 2161 TCGCCGATCT CGGTATGGC CGGCCGGAG GCGTCCCGGA AGTCGTGGA CACGACCTCC  
 2221 GACCACCTGG CGTACAGCTC GTCCAGGCC CGCACCCACA CCCAGGCCAG GGTGTTGTCC  
 2281 GGCACCAACTT GGTCCTGGAC CGCGCTGATG AACAGGGTCA CGTCGTCCCG GACCACACCG  
 2341 GCGAAGTCGT CCTCCACGAA GTCCCGGGAG AACCCGAGCC GGTCGGTCCA GAACTCGACC  
 2401 GCTCCGGCGA CGTCGCGCAG GGTGAGCACC GGAACGGCAC TGGTCAACTT GGCCATGATG  
 2461 GCTCCTCctg tcaggagagg aaagagaaga aggttagtac aattgCTATA GTGAGTTGTA  
 2521 TTATACTATG CAGATATACT ATGCCAATGA TTAATTGTC AACTAGGGCT GCAgggttca  
 2581 tagtgccact tttcctgcac tgccccatct cctgcccacc ctttcccagg catagacagt  
 2641 cagtgaactta cAAACTCAC AGGAGGGAGA AGGCAGAACG TTGAGACAGA CCCGCGGGAC  
 2701 CGCCGAACTG CGAGGGGACG TGGCTAGGGC GGCTTCTTTT ATGGTGGCCC GCCCCTCGGA  
 2761 GGCAGGGCGC TCAGGGGAGGC CTAGCGGCCA ATCTGCGGTG GCAGGGAGGCG GGGCCGAAGG  
 2821 CCGTGCTGA CCAATCCGA GCACATAGGA GTCTCAGCCC CCCGCCCAA AGCAAGGGGA  
 2881 AGTCACCGCGC CTGTAGCGCC AGCGTGTGT GAAATGGGGG CTGGGGGGG TTGGGGCCCT  
 2941 GACTAGTC AACAACCTCC CATTGACGTC AATGGGGTGG AGACTTGAA ATCCCCGTGA  
 3001 GTCAAACCGC TATCCACGCC CATTGATGTA CTGCCAAAC CGCATCATCA TGGTAATAGC  
 3061 GATGACTAAT ACGTAGATGT ACTGCCAAGT AGGAAAGTCC CATAAGGTCA TGTACTGGC  
 3121 ATAATGCCAG CGGGGCCATT TACCGTCATT GACGTCATA GGGGGCGTAC TTGGCATATG  
 3181 ATACACTGTA TGTACTGCCA AGTGGGCAGT TTACCGTAA TACTCCACCC ATTGACGTCA  
 3241 ATGGAAAGTC CCTATTGGCG TTACTATGGG AACATACGTC ATTATTGACG TCAATGGCG  
 3301 GGGGTCGTTG GGCAGTCAGC CAGGGGGGCC ATTTACCGTA AGTTATGTA CGCCTGCAGG  
 3361 TTAATTAAGA ACATGTGAGC AAAAGGCCAG CAAAGGCCA GGAACCGTAA AAAGGCCGCG  
 3421 TTGCTGGCGT TTTCCATAG GCTCCGCCCT CCTGACGAGC ATCACAAAAA TCGACGCTCA  
 3481 AGTCAGAGGT GGCAGAACCC GACAGGACTA TAAAGATACC AGGCAGTTCC CCCTGGAAGC  
 3541 TCCCTCGTGC GCTCTCCTGT TCCGACCCCTG CCGCTTACCG GATACTGTC CGCCTTCTC  
 3601 CCTTCGGGAA GCGTGGCGCT TTCTCATAGC TCACGCTGTA GGTATCTCAG TTGGTGTAG  
 3661 GTCGTTCGCT CCAAGCTGGG CTGTGTGCAC GAAACCCCCCG TTCAGCCCGA CGCCTGCGCC  
 3721 TTATCCGTA ACTATCGTCT TGAGTCCAAC CCGGTAAGAC ACGACTTATC GCCACTGGCA

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3781 GCAGCCACTG GTAACAGGAT TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG  
 3841 AAGTGGTGGC CTAACTACGG CTACACTAGA AGAACAGTAT TTGGTATCTG CGCTCTGCTG  
 3901 AAGCCAGTTA CCTTCGGAAA AAGAGTTGGT AGCTCTTGAT CCGGCAAACA AACCAACCGCT  
 3961 GGTAGCGGTG GTTTTTTGT TTGCAAGCAG CAGATTACGC GCAGAAAAAA AGGATCTCAA  
 4021 GAAGATCCTT TGATCTTTTC TACGGGGTCT GACGCTCAGT GGAACGAAAAA CTCACGTTAA  
 4081 GGGATTTGG TCATGGCTAG TTAATTAACA TTTAAATCAG CGGCCGCAAT AAAATATCCT  
 4141 TATTTTCATT ACATCTGTGT GTTGGTTTT TGTGTGAATC GTAACTAACA TACGCTCTCC  
 4201 ATCAAAACAA AACGAAACAA AACAAACTAG CAAAATAGGC TGTCcccAGT GCAAGTGCAG  
 4261 GTGCCAGAAC ATTTCTCTAT CGAA

## Amino acid sequence

(SEQ ID NO: 86)

MYRMQLLSCIALSLALVTSIRLVQYRGEVQAMLGQSTEELRVRLAS

HLRKLIAMVRSVECPCPAPPVAGPSVFLFPPKPKDLMISRTPEVTCVVVVDV

SHEDPEVQFNWVYDGMEVEINAKTKPREEQFNSTFRVVSVLTVVHQDWLNG

KEYKCKVSNKGLPAPIEKTSKKGQPREPVYTLPPSREEMTKNQVSLTCLV

KGFYP PSDIAVEWESNGQPENNYKTPPMULDSDGSFFLYSKLTVDKSRWQQGN

VFSCSVMHEALHNHYTQKSLSLSPGK

197G pfuse-hfc2 ApoE 114-144 R136S  
Nucleic acid sequence

(SEQ ID NO: 87)

1 GGATCTCGCA TCGCTCGGT GCCCGTCAGT GGGCAGAGCG CACATCGCCC ACAGTCCCCG  
 61 AGAAGTTGGG GGGAGGGGTC GGCAATTGAA CGGGTGCCTA GAGAAGGTGG CGCGGGGTAA  
 121 ACTGGGAAAG TGATGTCGTG TACTGGCTCC GCCTTTTCC CGAGGGTGGG GGAGAACCGT  
 181 ATATAAGTGC AGTAGTCGCC GTGAACGTTC TTTTCGCAA CGGGTTTGCC GCCAGAACAC  
 241 AGCTGAAGCT TCGAGGGCT CGCATCTCTC CTTCACGCGC CGCCCGCCCT ACCTGAGGCC  
 301 GCCATCCACG CCCGTTGAGT CCCGTTCTGC CGCCTCCCGC CTGTGGTGCC TCCTGAACGT  
 361 CGTCCGGCGT CTAGGTAAGT TTAAAGCTCA GGTGAGACCC GGGCCTTTGT CGCGCGCTCC  
 421 CTTGGAGCCT ACCTAGACTC AGCCGGCTCT CCACGCTTTG CCTGACCCCTG CTTGCTCAAC  
 481 TCTACGTCTT TGTTCTGTT TCTGTTCTGC GCCGTTACAG ATCCAAGCTG TGACCGGCCG  
 541 CTACCTGAGA TCAccggcGA AGGAGGGCCA CCATGTACAG GATGCAACTC CTGTCTTGCA  
 601 TTGCACTAAG TCTTGACTT GTCACGAATT CGataCGCT GGTGCAAGTAC CGCGGGGAGG  
 661 TGCAGGCCAT GCTCGGCCAG AGtActGAGG AGCTGCGGGT GaGCCCGCC TCCCACCTGC  
 721 GCAAGCTGat ATCGGCCATG GTTAGATCTG TGGAGTGCCT ACCTTGCCCA GCACCACCTG  
 781 TGGCAGGACC TTCAGTCTTC CTCTTCCCCC CAAAACCCAA GGACACCCCTG ATGATCTCCA  
 841 GAACCCCTGA GGTACAGTGC GTGGTGGTGG ACGTGAGCCA CGAAGACCCC GAGGTCCAGT  
 901 TCAACTGGTA CGTGGACGGC ATGGAGGTGC ATAATGCCA GACAAAGCCA CGGGAGGAGC  
 961 AGTTCAACAG CACGTTCCGT GTGGTCAGCG TCCTCACCGT CGTGCACCAAG GACTGGCTGA  
 1021 ACGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAAGGCT CCCAGCCCCC ATCGAGAAAA  
 1081 CCATCTCCAA AACCAAAGGG CAGCCCCGAG ACCACACAGGT GTACACCCCTG CCCCCATCCC  
 1141 GGGAGGAGAT GACCAAGAAC CAGGTCAAGCC TGACCTGCCT GGTCAAAGGC TTCTACCCCA  
 1201 GCGACATCGC CGTGGAGTGG GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACAC  
 1261 CTCCCATGCT GGACTCCGAC GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA  
 1321 GCAGGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC

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1381 ACTACACACA GAAGAGCCTC TCCCTGTCTC CGGGTAAATG AgtgcacgG CTAGCTGGCC  
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 1561 TAAACAAAGT AACAAACA ATTGCATTCA TTTTATGTTT CAGGTTCAAGG GGGAGGTGTG  
 1621 GGAGGTTTT TAAAGCAAGT AAAACCTCTA CAAATGTGGT ATGGAATTAA TTCTAAAATA  
 1681 CAGCATGCA AAACCTAAC CTCCAAATCA AGCCTCTACT TGAATCCTT TCTGAGGGAT  
 1741 GAATAAGGCA TAGGCATCAG GGGCTGTTGC CAATGTGCAT TAGCTGTTG CAGCCTCACC  
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 1861 CTTTATGTT TAAATGCACT GACCTCCCAC ATTCCCTTT TAGTAAAATA TTCAGAAATA  
 1921 ATTTAAATAC ATCATTGCAA TGAAAATAAA TGTGTTTTAT TAGGCAGAAT CCAGATGCTC  
 1981 AAGGCCCTTC ATAATATCCC CCAGTTAGT AGTTGGACTT AGGGAAACAAA GGAACCTTTA  
 2041 ATAGAAATTG GACAGCAAGA AAGCGAGCTT CTAGCTTATC CTCAGCCTG CTCCCTGCCC  
 2101 ACAAAGTGCA CGCAGTTGCC GGCGGGGTGCG CGCAGGGCGA ACTCCCGCCCC CCACGGCTGC  
 2161 TCGCCGATCT CGGTCACTGGC CGGCCGGAG GCGTCCCGGA AGTCGTGGA CACGACCTCC  
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 2341 GCGAAGTCGT CCTCCACGAA GTCCCGGGAG AACCCGAGCC GGTCGGTCCA GAACTCGACC  
 2401 GCTCCGGCGA CGTCGCGCGC GGTGAGCACC GGAACGGCAC TGGTCAACTT GGCCATGATG  
 2461 GCTCCTCctg tcaggagagg aaagagaaga aggttagtac aatttgCTATA GTGAGTTGTA  
 2521 TTATACTATG CAGATATAC ATGCCAATGA TTAATTGTCA AACTAGGGCT GCAGgggtca  
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 2641 cagtgcactt cAAACTCAC AGGAGGGAGA AGGCAGAACG TTGAGACAGA CCCGCGGGAC  
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 2761 GGCAGGGCGC CTGGGGAGGC CTAGCGGCCA ATCTGCGGTG CGAGGAGGCG GGGCGAAGG  
 2821 CCGTGCTGA CCAATCCGGA GCACATAGGA GTCTCAGCCC CCCGCCCAA AGCAAGGGGA  
 2881 AGTCACCGCGC CTGTAGCGCC AGCGTGTGTTG GAAATGGGGG CTTGGGGGGG TTGGGGCCCT  
 2941 GACTAGTCAA AACAAACTCC CATTGACGTC AATGGGGTGG AGACTTGGAA ATCCCCGTGA  
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 3241 ATGGAAAGTC CCTATTGGCG TTACTATGGG AACATACGTC ATTATTGACG TCAATGGCG  
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3781 GCAGCCACTG GTAACAGGAT TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG  
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 3961 GGTAGCGGTG GTTTTTTGT TTGCAAGCAG CAGATTACGC GCAGAAAAAA AGGATCTCAA  
 4021 GAAGATCCTT TGATCTTTTACACGGGTCT GACGCTCAGT GGAACGAAAAA CTCACGTTAA  
 4081 GGGATTTGG TCATGGCTAG TTAATTAACA TTTAAATCAG CGGCCGCAAT AAAATATCTT  
 4141 TATTTCATT ACATCTGTGT GTGGTTTTT TGTGTGAATC GTAACAAACA TACGCTCTCC  
 4201 ATCAAAACAA AACGAAACAA AACAAACTAG CAAAATAGGC TGTCAGGTAGT GCAAGTGCAG  
 4261 GTGCCAGAAC ATTTCTCTAT CGAA

Amino acid sequence

(SEQ ID NO: 88)

MYRMQLLSCIALSLALVNTSIRLVQYRGEVQAMLGQSTEELRVSLASH  
 LRKLISAMVRSVECPAPPVAGPSVFLFPPKPKDLMISRTPETCVVVDS  
 HEDPEVQFNWYVDGMEVEINAKTPREEQFNSTFRVSVLTVEIQDWLNKG  
 EYKCKVSNKGLPAPIEKTIKKGQPREPVYTLPPSREEMTKNQVSLTCLVK  
 GFYPSDIAVEWESNGQPENNYKTTPPMLSDGSFFLYSKLTVDKSRQQQNV  
 FSCSVMHEALHNHYTQKSLSLSPKG

184U pfcn hg2 ApoE 129-157  
 Nucleic acid sequence

(SEQ ID NO: 89)

1 GGATCTCGCA TCGCTCCGGT GCCCGTCAGT GGGCAGAGCG CACATCGCCC ACAGTCCCCG  
 61 AGAAGTTGGG GGGAGGGGTC GGCAATTGAA CGGGTGCCTA GAGAAGGTGG CGCGGGGTAA  
 121 ACTGGGAAAG TGATGTCGTG TACTGGCTCC GCCTTTTCC CGAGGGTGGG GGAGAACCGT  
 181 ATATAAGTGC AGTACTCGCC GTGAACGTT TTTTCGAA CGGGTTGCC GCCAGAACAC  
 241 AGCTGAAGCT TCGAGGGGCT CGCACCTCTC CTTCACCGCC CCGCCGCCCT ACCTGAGGCC  
 301 GCCATCCACG CCGGTTGAGT CGCGTTCTGC CGCCTCCGC CTGTGGTGCC TCCTGAACCTG  
 361 CGTCCGGCGT CTAGGTAAGT TTAAAGCTCA GGTGAGACCC GGGCCTTGCT CCAGGCGCTCC  
 421 CTTGGAGCCT ACCTAGACTC AGCCGGCTCT CCACGCTTG CCTGACCCtg ctgtctcaac  
 481 tctacgtCTT TGTTTCTGTT TCTGTTCTGC GCGTTACAG ATCCAAGCTG TGACCGGGC  
 541 CTACCTGAGA TCACCGCGA AGGAGGGCCA CCATGTACAG GATGCAACTC CTGTCTTGCA  
 601 TTGCACTAAG TCTTGCACCTT GTCACGAATT CGGCACCTCT CGAGCGAAA TCTAGTGTG  
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 1081 CCTGCCTGGT CAAAGGCTTC TACCCAGCG ACATCGCCGT GGAGTGGGAG AGCAATGGG  
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 1921 ATTTAAATAC ATCATTGCAA TGAAAATAAA TGTTTTTAT TAGGCAGAAT CCAGATGCTC  
 1981 AAGGCCCTTC ATAATATCCC CCAGTTAGT AGTTGGACTT AGGGAAACAAA GGAACCTTTA  
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 2701 CGCCGAACCTG CGAGGGGACG TGGCTAGGGC GGCTTCTTTT ATGGTGCAGCC GGCCCTCGGA  
 2761 GGCAGGGCCG TCGGGGAGGC CTAGCCGCCA ATCTGGGTG GCAGGAGGGC GGGCCGAAGG  
 2821 CGGTGCGCTGA CCAATCGGA GCACATAGGA GTCTCAGCCC CCCGCCCAA AGCAAGGGGA  
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3841 AAGTGGTGGC CTAACTACGG CTACACTAGA AGAACAGTAT TTGGTATCTG CGCTCTGCTG  
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 4021 GAAGATCCTT TGATCTTTC TACGGGTCT GACGCTCAGT GGAAACGAAAAA CTCACGTTAA  
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 4141 TATTTTCATT ACATCTGTG TTGTTTTTGT TGTGTGAATC GTAACAAACA TACGCTCTCC  
 4201 ATCAAAACAA AACGAAACAA AACAAACTAG CAAAATAGGC TGCCCCAGT GCAAGTGCAG  
 4261 GTGCCAGAAC ATTTCTCTAT CGAA

## Amino acid sequence

(SEQ ID NO: 90)

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 NSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKKGQPREPQV  
 YTLPPSREEMTKNQVSLTCLVKFYPNSDIAVEWESNGQOPENNYKTPPMQLDS  
 DGSFFLYSKLTVDKSRWQQGNVFCSVHEALHNHTQKSLSLSPGARTSTE  
 ELRVRLASHLRKLKRLLRDADDLQK

184V pfccn hg2 129-157 R136S  
 Nucleic acid sequence

(SEQ ID NO: 91)

1 GGATCTCGGA TCGCTCCGGT GCCCGTCAGT GGGCAGAGCG CACATCGCCC ACAGTCCCCG  
 61 AGAAGTTGGG GGGAGGGTC GGCAATTGAA CGGGTGCATA GAGAAGGTGG CGCGGGGTAA  
 121 ACTGGGAAAG TGATGTCGTG TACTGGCTCC GCCTTTTCC CGAGGGTGGG GGAGAACCGT  
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 241 AGCTGAAGCT TCGAGGGCT CGCATCTCTC CTTCACGCGC CGCCGCCCT ACCTGAGGCC  
 301 GCCATCCACG CGGGTTGAGT CGCGTTCTGC CGCCCTCCCGC CTGTGGTGCC TCCTGAACGT  
 361 CGTCCGCCGT CTAGGTAAGT TAAAGCTCA GGTCGAGACC GGGCCTTGT CGGGCGCTCC  
 421 CTTGGAGCCT ACCTAGACTC AGCCGGCTCT CCACGCTTG CCTGACCCtg ctgtcaac  
 481 tctacgTCTT TGTTCTGTT TCTGTTCTGC GCCGTTACAG ATCCAAGCTG TGACCGGCC  
 541 CTACCTGAGA TCACCGCGA AGGAGGGCCA CCATGTACAG GATGCAACTC CTGCTTGCA  
 601 TTGCACTAAG TCTTGACTT GTCACGAATT CGGCACCTCT CGAGCGAAA TCTAGTGTG  
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 1861 CTTTATGTTT TAAATGCACT GACCTCCCAC ATTCCCTTT TAGTAAAATA TTCAGAAATA  
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 4201 ATCAAAACAA AACGAAACAA AACAAACTAG CAAAATAGC TGTCAGGAGT GCAAGTGCAG  
 4261 GTGCCAGAAC ATTTCTCTAT CGAA

Amino acid sequence

(SEQ ID NO: 92)

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 YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMILDS  
 DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHTQKSLSLSPGARTSTE  
 ELRVSLASHLRKLRKRLRDADDLQK

197H pfuse hfc2 ApoE 129-157  
 Nucleic acid sequence

(SEQ ID NO: 93)

1 GGATCTCGA TCGCTCCGGT GCCCGTCAGT GGGCAGAGCG CACATCGCCC ACAGTCCCCG  
 61 AGAAGTTGGG GGGAGGGGTC GGCAATTGAA CGGGTGCCTA GAGAAGGTGG CGCGGGGTAA  
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 241 AGCTGAAGCT TCGAGGGCT CGCATCTCTC CTTCACGCG CCGCCGCCCT ACCTGAGGCC  
 301 GCCATCCACG CCGGTTGAGT CGCGTTCTGC CGCCTCCCGC CTGTGGTGCC TCCTGAACTG  
 361 CGTCCGCCGT CTAGGTAAGT TTAAAGCTCA GGTCGAGACC GGGCCTTGT CGGGCGCTCC  
 421 CTTGGAGCCT ACCTAGACTC AGCGGGCTCT CCACGCTTG CCTGACCCtgc ctgtcaac  
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 541 CTACCTGAGA TCAccggcGA AGGAGGGCCA CCATGTACAG GATGCAACTC CTGTCTTGCA  
 601 TTGCACTAAG TCTTGACTT GTCACGAATT CGATAAGCAC CGAGGAGCTG CGGGTGCGCC  
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 1801 CATGGAGTTT AAGATATAGT GTATTTCCC AAGGTTGAA CTAGCTCTTC ATTTCTTTAT  
 1861 GTTTAAATG CACTGACCTC CCACATTCCC TTTTAGTAA AATATTAGA AATAATTAA  
 1921 ATACATCATT GCAATGAAAA TAAATGTTT TTATTAGGCA GAATCCAGAT GCTCAAGGCC  
 1981 CTTCATAATA TCCCCCAGTT TAGTAGTTGG ACTTAGGGAA CAAAGGAACC TTTAATAGAA  
 2041 ATTGGACAGC AAGAAAGCGA GCTTCAGT TATCCTCAGT CCTGCTCCTC TGCCACAAAG  
 2101 TGCACGCACT TGCGGCCGG GTGCGCAGG GCGAACTCCC GCCCCCACGG CTGCTGCCG  
 2161 ATCTCGGTCA TGGCGGCCGG GGAGGCGTCC CGGAAGTTCG TGGACACGAC CTCCGACCAC  
 2221 TCGGCGTACA GCTCGTCCAG GCCGCGCACC CACACCCAGG CCAGGGTGT GTCCGGCACC  
 2281 ACCTGGTCT GGACCGCGCT GATGAACAGG GTCACTCGT CCGGGACCAC ACCGGCGAAG  
 2341 TCGTCTCCA CGAAGTCCCAG GGAGAACCCAG AGCCGGTCGG TCCAGAACTC GACCGCTCG  
 2401 GCGACGTCGC CGCGCGGTGAG CACCGGAACG GCACTGGTCA ACTTGGCCAT GATGGCTCCT  
 2461 Cctgtcagga gaggaaagag aagaaggta gtacaattgC TATAGTGAGT TGTATTATAC  
 2521 TATGCAGATA TACTATGCCA ATGATTAATT GTCAAACACTAG GGCTGCAggg ttcatagtgc  
 2581 cactttctt gcactgcccc atctctgcc cacccttcc caggcataga cagtcagtga  
 2641 cttacCAAAC TCACAGGAGG GAGAAGGCAG AAGCTTGAGA CAGACCCGCG GGACCGCCGA  
 2701 ACTGCGAGGG GACGTGGCTA GGGCGGCTTC TTTTATGGTG CGCCGGCCCT CGGAGGCAGG  
 2761 GCGCTCGGGG AGGCCTAGCG GCCAATCTGC GGTGGCAGGA GGCAGGGCCCG AAGGCGTGC  
 2821 CTGACCAATC CGGAGCACAT AGGAGTCTCA GCCCCCCCCC CCAAAGCAAG GGGAAAGTCAC  
 2881 GGCCTGTAG CGCCAGCGTG TTGTGAAATG GGGGCTTGGG GGGGTTGGG CCCTGACTAG  
 2941 TCAAAACAAA CTCCCATTGA CGTCAATGGG GTGGAGACTT GGAAATCCCC GTGAGTCAAA  
 3001 CCGCTATCCA CGCCATTGA TGTACTGCCA AAACCGCATC ATCATGGTAA TAGCGATGAC  
 3061 TAATACGTAG ATGTACTGCC AAGTAGGAAA GTCCCATAAG GTCATGTACT GGGCATAATG  
 3121 CCAGGCGGGC CATTACCGT CATTGACGTC AATAGGGGGC GTACTGGCA TATGATACAC  
 3181 TTGATGTACT GCCAAGTGGG CAGTTACCG TAAATACTCC ACCCATTGAC GTCAATGGAA  
 3241 AGTCCCTATT GGCCTTACTA TGGGAAACATA CGTCATTATT GACGTCAATG GGCAGGGGTC  
 3301 GTTGGGGGGT CAGCCAGGGC GGCCTTTAC CGTAAGTTAT GTAACGCCG CAGGTTAATT  
 3361 AAGAACATGT GAGCAAAAGG CCAGCAAAAG GCCAGGAACG GTAAAAAGGC CGCGTTGCTG  
 3421 GCGTTTTCC ATAGGCTCCG CCCCCCTGAC GAGCATCACA AAAATCGACG CTCAAGTCAG  
 3481 AGGTGGGAA ACCCGACAGG ACTATAAAGA TACCAAGCGT TTCCCCCTGG AAGCTCCCTC  
 3541 GTGCGCTCTC CTGTTCCGAC CCTGCCGCTT ACCGGATACC TGTCGCCCTT TCTCCCTCG  
 3601 GGAAGCGTGG CGCTTTCTCA TAGCTCACGC TGTTAGGTATC TCAGTTGGT GTAGGTGTT  
 3661 CGCTCCAAGC TGGGCTGTGT GCACGAACCC CCCGTTCAAGC CCGACCGCTG CGCCTTATCC  
 3721 GGTAACATACG GTCTTGAGTC CAACCCGGTA AGACACGACT TATCGCCACT GGCAGCAGCC  
 3781 ACTGGTAACA GGATTAGCAG AGCGAGGTAT GTAGGCGGTG CTACAGAGTT CTTGAAGTGG  
 3841 TGGCCTAACT ACGGCTACAC TAGAAGAACAA GTATTTGGTA TCTGCGCTCT GCTGAAGCCA

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3901 GTTACCTTCG GAAAAAGAGT TGGTAGCTCT TGATCCGGCA AACAAACCAC CGCTGGTAGC  
 3961 GGTGGTTTT TTGTTGCAA GCAGCAGATT ACGCGCAGAA AAAAAGGATC TCAAGAAGAT  
 4021 CCTTGATCT TTTCTACGGG GTCTGACGCT CAGTGGAACG AAAACTCACG TTAAGGGATT  
 4081 TTGGTCATGG CTAGTTAATT AACATTTAAA TCAGCGGCCG CAATAAAATA TCTTTATTTT  
 4141 CATTACATCT GTGTGTTGGT TTTTGTGTG AATCGTAAC AACATACGCT CTCCATCAAA  
 4201 ACAAAACGAA ACAAAACAAA CTAGCAAAT AGGCTGTCCC CAGTGCAAGT GCAGGTGCCA  
 4261 GAACATTTCT CTATCGAA

## Amino acid sequence

(SEQ ID NO: 94)

MYRMQLLSCIALSLALVTSISTEELRVRLASHLRKLRKRLRADDL

QKISAMVRSPCAPPVAGPSVFLFPPPKDLMISRPEVTCVVVDVSHE

DPEVQFNWYVDGMEVHNNAKTKPREEQFNSTFRVSVLTVEIQDWLNKEY

KCKVSNKGLPAPIEKTSKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF

YPSDIAVEWESNGQPENNYKTPPMULDGSFFLYSKLTVDKSRWQQGNVFS

CSVMHEALHNHYTQKSLSLSPKG

1971 pfuse hfc2 ApoE 129-157 R136S

## Nucleic acid sequence

(SEQ ID NO: 95)

1 GGATCTCGGA TCGCTCGGT GCCCGTCAGT GGGCAGAGCG CACATCGCCC ACAGTCCCCG  
 61 AGAAGTTGGG GGGAGGGGTC GGCAATTGAA CGGGTGCCTA GAGAAGGTGG CGCGGGGTAA  
 121 ACTGGGAAAG TGATGTCGTG TACTGGCTCC GCCTTTTCC CGAGGGTGGG GGAGAACCGT  
 181 ATATAAGTGC AGTAGTCGCC GTGAACGTTC TTTTCGCAA CGGGTTGCC GCCAGAACAC  
 241 AGCTGAAGCT TCGAGGGCT CGCATCTCTC CTTCACGCGC CGCCGCCCT ACCTGAGGCC  
 301 GCCATCCACG CGGGTTGAGT CGCGTTCTGC CGCCTCCCGC CTGTGGTGCC TCCTGAACGT  
 361 CGTCCGCGT CTAGGTAAGT TTAAAGCTCA GGTCGAGACC GGGCCTTGT CGCGCCTCC  
 421 CTTGGAGGCT ACCTAGACTC AGCCGGCTCT CCACGCTTTG CCTGACCCtg ctgtctcaac  
 481 tctacgTCTT TGTTCTGTT TCTGTTCTGC GCGTTACAG ATCCAAGCTG TGACCGGCC  
 541 CTACCTGAGA TCAccggcGA AGGAGGGCCA CCATGTACAG GATGCAACTC CTGTCTTGCA  
 601 TTGCACTAAG TCTTGACTT GTCACGAATT CGATAAGCAC CGAGGGACTG CGGGTGaGCC  
 661 TCGCCTCCCA CCTGCGCAAG CTGCGTAAGC GGCTCCTCCG CGATGCCGAT GACCTGCAGA  
 721 AGatatacgGC CATGGTTAGA TCTGTTGGAGT GCCCACCTTG CCCAGCACCA CCTGTGGCAG  
 781 GACCTTCAGT CTTCTCTTC CCCCCAAAC CCAAGGACAC CCTGATGATC TCCAGAACCC  
 841 CTGAGGTAC GTGCGTGGTG GTGGACGTGA GCCACGAAGA CCCCCGAGGTC CAGTTCAACT  
 901 GGTACGTGGA CGGCATGGAG GTGCCATAATG CCAAGACAAA GCCACGGGAG GAGCAGTTCA  
 961 ACAGCACGTT CCGTGTGGTC AGCGTCTCA CGCGTGTGCA CCAGGACTGG CTGAACGGCA  
 1021 AGGAGTACAA GTGCAAGGTC TCCAACAAAG GCCTCCCAGC CCCCCATCGAG AAAACCATCT  
 1081 CCAAAACCAA AGGGCAGCCC CGAGAACAC AGGTGTACAC CCTGCCCCCA TCCCGGGAGG  
 1141 AGATGACCAA GAACCAGGTC AGCCTGACCT GCCTGGTCAA AGGCTTCTAC CCCAGCGACA  
 1201 TCGCCGTGGA GTGGGAGAGC AATGGGCAGC CGGAGAACAA CTACAAGACC ACACCTCCCA  
 1261 TGCTGGACTC CGACGGCTCC TTCTTCTCT ACAGCAAGCT CACCGTGGAC AAGAGCAGGT  
 1321 GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCTGA GGCTCTGCAC AACCACTACA  
 1381 CACAGAAGAG CCTCTCCCTG TCTCCGGTA AATGAgtgcc acggctagct GGCCAGACAT  
 1441 GATAAGATAC ATTGATGAGT TTGGACAAAC CACAACCTAGA ATGCAGTGAA AAAATGCTT

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1501 TATTTGTGAA ATTTGTGATG CTATTGCTT ATTGTAACC ATTATAAGCT GCAATAAAC  
 1561 AGTTAACAC ACAATTGCA TTCATTTAT GTTCAGGTT CAGGGGGAGG TGTGGGAGGT  
 1621 TTTTAAAGC AAGTAAAACC TCTACAAATG TGGTATGGAA TTAATTCTAA AATACAGCAT  
 1681 AGCAAACCT TAACCTCAA ATCAAGCCTC TACTTGAATC CTTTCTGAG GGATGAATAA  
 1741 GGCATAGGCA TCAGGGCTG TTGCCAATGT GCATTAGCTG TTTGCAGCCT CACCTCTTT  
 1801 CATGGAGTTT AAGATATAGT GTATTTCCC AAGGTTGAA CTAGCTCTC ATTTCTTAT  
 1861 GTTTAAATG CACTGACCTC CCACATTCCC TTTTAGTAA AATATTCAGA AATAATTAA  
 1921 ATACATCATT GCAATGAAAA TAAATGTTT TTATTAGGCA GAATCCAGAT GCTCAAGGCC  
 1981 CTTCATAATA TCCCCCAGTT TAGTAGTTGG ACTTAGGGAA CAAAGGAACC TTTAATAGAA  
 2041 ATTGGACAGC AAGAAAGCGA GCTCTAGCT TATCCTCAGT CCTGCTCCTC TGCCACAAAG  
 2101 TGCACGCAGT TGCCGGCCGG GTGCCGCAGG GCGAAGCTCCC GCCCCCACGG CTGCTCGCCG  
 2161 ATCTCGGTC A TGGCCGGCCC GGAGGCGTCC CGGAAGTTCG TGGACACGAC CTCCGACCAC  
 2221 TCGCGTACA GCTCGTCCAG GCCCGGCACC CACACCCAGG CCAGGGTGT GTCCGGCACC  
 2281 ACCTGGTCT GGACCGCGCT GATGAACAGG GTCACTGCTG CCCGGACCAC ACCGGCGAAG  
 2341 TCGTCCTCCA CGAAGTCCCG GGAGAACCCG AGCCGGTCGG TCCAGAACTC GACCGCTCCG  
 2401 GCGACGTCGC GCGCGGTGAG CACCGGAACG GCACTGGTCA ACTTGCCAT GATGGCTCCT  
 2461 Cctgtcagga gaggaaagag aagaaggta gtacaattgc TATAGTGAGT TGTATTATAC  
 2521 TATGCAGATA TACTATGCCA ATGATTAATT GTCAAACACTAG GGCTGCAggg ttcatagtgc  
 2581 cactttcct gcactgcccc atctcctgcc cacccttcc cagggataga cagtcaatgc  
 2641 cttacAAAC TCACAGGAGG GAGAAGGCAG AAGCTTGAGA CAGACCCGCG GGACCGCCGA  
 2701 ACTGCGAGGG GACGTGGCTA GGGCGGCTTC TTTTATGGTG CGCCGGCCCT CGGAGGCAGG  
 2761 GCGCTCGGGG AGGCCTAGCG GCCAATCTGC GGTGGCAGGA GGCGGGCCCG AAGGCGGTGC  
 2821 CTGACCAATC CGGAGCACAT AGGAGTCTCA GCCCCCGCC CAAAGCAAG GGGAAAGTCAC  
 2881 GCGCCTGTAG CGCCAGCGTG TTGTGAAATG GGGGCTTGGG GGGGTTGGGG CCCTGACTAG  
 2941 TCAAAACAAA CTCCCATGTA CGTCAATGGG GTGGAGACTT GGAAATCCCC GTGAGTCAAA  
 3001 CCGCTATCCA CGCCCCATTGA TGTACTGCCA AAACCGCATC ATCATGGTAA TAGCGATGAC  
 3061 TAATACGTAG ATGTACTGCC AAGTAGGAAA GTCCCATAAG GTCATGTACT GGGCATAATG  
 3121 CCAGGCGGGC CATTACCGT CATTGACGTC AATAGGGGGC GTACTGGCA TATGATACAC  
 3181 TTGATGTACT GCCAAGTGGG CAGTTACCG TAAATACTCC ACCCATTGAC GTCAATGGAA  
 3241 AGTCCCTATT GGCCTTACTA TGGGAAACATA CGTCATTATT GACGTCAATG GGCAGGGGTC  
 3301 GTTGGCGGT CAGCCAGGCG GGCCATTAC CGTAAGTTAT GTAACGCCTG CAGGTTAATT  
 3361 AAGAACATGT GAGCAAAAGG CCAGCAAAAG GCCAGGAACG GTAAAAGGC CGCGTTGCTG  
 3421 GCGTTTTCC ATAGGCTCCG CCCCCCTGAC GAGCATCACA AAAATCGACG CTCAAGTCAG  
 3481 AGGTGGCGAA ACCCGACAGG ACTATAAAGA TACCAAGCGT TTCCCCCTGG AAGCTCCCTC  
 3541 GTGCGCTCTC CTGTTCCGAC CCTGCCGCTT ACCGGATACC TGTCCGCCTT TCTCCCTCG  
 3601 GGAAGCGTGG CGCTTTCTCA TAGCTCACGC TGTAGGTATC TCAGTTCGGT GTAGGTGTT  
 3661 CGCTCCAAGC TGGGCTGTGT GCACGAACCC CCCGTTCAAGC CCGACCGCTG CGCCTTATCC  
 3721 GGTAACTATC GTCTTGAGTC CAACCCGGTA AGACACGACT TATCGCCACT GGCAGCAGCC  
 3781 ACTGGTAACA GGATTAGCAG AGCGAGGTAT GTAGGCGGTG CTACAGAGTT CTTGAAGTGG  
 3841 TGGCCTAACT ACGGCTACAC TAGAAGAACAA GTATTTGGTA TCTGCGCTCT GCTGAAGCCA

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3901 GTTACCTTCG GAAAAAGAGT TGGTAGCTCT TGATCCGGCA AACAAACCAC CGCTGGTAGC  
 3961 GGTGGTTTT TTGTTGCAA GCAGCAGATT ACGCGAGAA AAAAGGATC TCAAGAAGAT  
 4021 CCTTTGATCT TTTCTACGGG GTCTGACGCT CAGTGGAACG AAAACTCACG TTAAGGGATT  
 4081 TTGGTCATGG CTAGTTAATT AACATTAAA TCAGCGGCCG CAATAAAAATA TCTTTATTTT  
 4141 CATTACATCT GTGTGTTGGT TTTTGTTGTG AATCGTAAC AACATACGCT CTCCATCAAA  
 4201 ACAAAACGAA ACAAAACAAA CTAGCAAAAT AGGCTGTCCC CAGTGCAAGT GCAGGTGCCA  
 4261 GAACATTCT CTATCGAA

## Amino acid sequence

(SEQ ID NO: 96)

MYRMQLLSCIALSLALVTNSISTEELRVSLASHLRKLRKRLRDLADDL

QKISAMVRSVECPAPPVAGPSVFLFPPPKPKDTLMISRPEVTCVVVDVSHE  
 DPEVQFNWYVDGMEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEY  
 KCKVSNKGLPAPIEKTIKTKQPREPQVYTLPPSREEMTKNQVSLTCLVKGF  
 YPSDIAWEWSNGQPENNYKTPPMILSDGSFFLYSKLTVDKSRWQQGNVFS  
 CSVMEALHNHYTQKSLSLSPGK

Example 5: CRISPR-Cas9 Mediated Editing and 25  
Base Editing of APOE

To introduce the R136S mutation in APOE using CRISPR-Cas9, gRNA sequences were designed (Table 7). In one example, a gRNA sequence is cloned into lentiCRISPR v2 using 2 oligos to form a linker containing the 20 base sequence that is cloned into the BsmB1 site downstream of the U6 promoter. To support repair, a template was designed with 2 additional silent mutations. The template has 50 bases flanking the area with the mutations. An exemplary template 30 sequence is as follows:

(SEQ ID NO: 65)  
 CGCCTGGTGCAGTACCGCGGCGAGGTGCAGGCCATGCTCGGCCAGAGCAC  
aGAGGAGCTcGGTGaGt CTCGCaq CCACCTGCGCAAGCTCGCTAAC  
 GGCTCCTCCGCGATGCCGATGACCTGC

where silent mutations to abolish PAM motifs are double underlined, the codon corresponding to the R136S mutation 45 is bolded, and silent mutation to generate SacI site for cleaving PCR products from clones that received the template is italicized.

TABLE 7

gRNA designs for introducing R136S mutation					
Plasmid	gRNA	SEQ ID NO:	Distance From DSB	ON target score	OFF target score
18401	CTTACGCGAGCTTGCGCAGGT	69	16	61.2	90.5
18402	GCTTGCGCAGGTGGGAGGCG	70	6	59.5	53.9
18403	ACGCAGCTTGCGCAGGTGGG	71	13	59.4	62.9
18404	CCAGAGCACCGAGGAGCTGC	72	9	49.3	42.7
Optional 18405	GCCAGAGCACCGAGGAGCTG	73	10	52.8	33.7
Optional 18406	GAGGCGCACCCGAGCTCCT	74	11	51.1	60.5

Without wishing to be bound by theory, a proposed mechanism for the APOE3ch mutation is loss of function (e.g. in binding to HSPG). Accordingly, gRNA sequences were designed to “knockout” APOE using CRISPR-Cas9 (Table 8). The gRNAs are designed to target exon 3 (amino acids 1-61) of ApoE. In an example, a gRNA sequence is cloned into lentiCRISPR v2 by ordering 2 oligos to form a linker containing the 20 base sequence that is cloned into BsmB1 site downstream of the U6 promoter. Repair is done by non-homologous end joining (NHEJ), which is an error-prone process and often results in short insertions or deletions leading to APOE knockout.

TABLE 8

gRNA designs for APOE knockout					
Plasmid	gRNA	SEQ ID NO:	Break at amino acid	ON target score	OFF target score
184Q1	AGCTGCGCCAGCAGACCGAG	75	18	66.3	74.4
184Q2	CCAGGCCAAGGTGGAGCAAG	76	3	65.6	49.3
184Q3	CACAGGATGCCAGGCCAAGG	77	1	65.4	44.5
184Q4	ACAGTGTCTGCACCCAGCGC	78	38	60.6	71.4
184Q5	GGCCAAGGTGGAGCAAGCGG	79	5	59.3	71.3

A R136H mutation in APOE is predicted to have a similar effect as the R136S mutation. Accordingly, to introduce a R136H mutation in APOE using base editing techniques, the following gRNA was designed (Table 9). The gRNA sequence GAGGCGCACCCGCAGCTCCT (SEQ ID NO: 74) is cloned into pLenti sgRNA (addgene 71409), using 2 oligos to form a linker containing the 20 base sequence that is cloned into BsmB1 site downstream of the U6 promoter. Plasmid Addgene base editor plasmid pCMV-BE3 (#73021) is used to produce base editing.

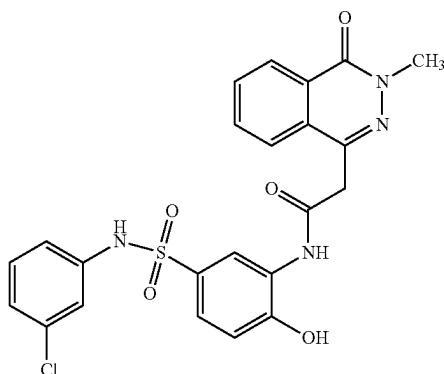
TABLE 9

gRNA design for APOE base editing				
gRNA	SEQ ID NO:	R136H change	Base editing score	OFF target score
GAGGCGCACCCGCAGCTCCT	80	CGC→CAC	4.6	60.5

#### Example 6: High-Throughput Screening of Molecules that Modify ApoE and Heparin Binding

To screen for molecules that affect ApoE and heparin binding, ApoE proteins are pre-incubated with candidate polypeptides, small molecules, nucleic acids, lipids or carbohydrates. The pre-incubated ApoE proteins are introduced to heparin-coated surfaces (such as plates or columns), allowed to bind to heparin/HSPG/GAG, and unbound ApoE and candidate molecules are washed off. Alternatively, heparin-coated surfaces (such as plates) can be pre-incubated with candidate molecules, before applying ApoE proteins. The levels of ApoE bound to heparin are detected using antibodies, protein assays, or fluorescence, and the effect of the candidate molecules on ApoE/heparin binding are assessed. Candidate molecules that reduce ApoE/heparin binding may represent novel therapeutics for prevention or treatment of cognitive decline associated with dementia

and/or mild cognitive impairment in a human subject in need of such treatments. An example of such molecules include EZ-482 (See, e.g. Mondal et al. Biochemistry 55 (18): 2613-21, 2016. The structure of EZ-482 is shown below).



#### Example 7: High-Throughput Screening of Molecules that Modify ApoE and Anti-ApoE Antibody Binding

To screen for molecules that affect ApoE and anti-ApoE antibody binding, ApoE proteins are pre-incubated with candidate polypeptides, small molecules, nucleic acids, lipids or carbohydrates. The pre-incubated ApoE proteins are introduced to surfaces (such as plates or columns) coated with antibodies that bind to the HSPG-binding sites of ApoE (any of the anti-ApoE antibodies as described herein), allowed to bind to the antibodies, and unbound ApoE and candidate molecules are washed off. Alternatively, heparin-coated surfaces (such as plates) can be pre-incubated with candidate molecules, before applying ApoE proteins. The levels of ApoE bound to anti-ApoE antibodies are detected

using antibodies, protein assays, or fluorescence, and the effect of the candidate molecules on the binding are assessed. Candidate molecules that increase or reduce ApoE/heparin binding may represent novel therapeutics for prevention or treatment of cognitive decline associated with dementia and/or mild cognitive impairment in a human subject in need of such treatments.

#### Example 8: Antibody Characterization

Antibodies that bind to wild type ApoE and ApoEch mutant were further evaluated using heparin-affinity chromatography, western blotting, subclones analysis, monoclonal antibody screening, screening for selectivity between huApoE3 and msApoE, and in vivo subretinal injections.

#### Methods

##### Chromatography Experiments

His-tagged recombinant ApoE peptide (50 µg/mL) was incubated 3 h R.T. with each antibody individually at 1:10 dilution in 20 mM Tris HCl buffer (pH 7.5). Samples were tested for heparin binding using the heparin sepharose column. Briefly, the column was allowed to reach R.T. and washed 5 times with 20 mM Tris-HCL. Protein input was loaded onto the column upon collecting 10 µL for WB experiments. Input was recycled through the column 5 times. Flow-through was collected and the column was subsequently washed 5 times and recovered fractions were labeled as “washes”. 1 mL fractions were retrieved for each 0.05 M step of the NaCl salt gradient from 0 to 1 M. 5 M fraction was also tested to ensure complete release of the protein from the column. WB or ELISA were used to test changes in ApoE binding to heparin.

##### Western Blotting

Samples for WB analyses were prepared by diluting 10 µL of each fraction in 4x sample buffer (Laemmli's SDS-Sample buffer, BP-110R, Boston bioproducts), 4 µL DTT (Sigma Aldrich), and 16 µL 1xRIPA buffer. Electrophoresis was performed under denaturing conditions, using a vertical electrophoretic chamber (Biorad). Bands separated on 4-20% precast gels (Biorad) using constant voltage (15' 70V, 1 h 100V). Transfer of the proteins was performed on nitrocellulose membranes (Millipore) at 70 V constant voltage for 1 h. Membranes were blocked 1 h R.T. using Odyssey blocking buffer (Licor) and membranes were washed 3×10' with TBS-0.05% Tween 20 (Thermo fisher) prior incubation with primary antibody (Anti-His, rb, 1:5000, Novus biological) and secondary antibody (Donkey anti-rb-800, 1:10000, Licor). Image acquisition was done using Odyssey scanner. Data was analyzed using Image J. Data was normalized by the input and expressed normalized intensities over fraction number (0=input, 1-27=increasing 0.05 M NaCl step gradient in 20 mM Tris HCl pH 7.5, 28=5 M NaCl in 20 mM Tris HCl pH 7.5).

##### ELISA

To test selectivity of the antibodies for huApoE3WT, huApoE3ch or msApoE, anti-his ELISA coated plates were incubated with 0.0025 µg/µL of the target protein for 2 h at R.T. under gentle shaking. Wells were washed 5 times with 1× wash buffer (R&D) and subsequently incubated with serial dilutions of Innovagen antibody of interest over night at 4° C. on a shaker (100 µL/well). The following day, wells were washed 5 times with sample buffer and incubated for 45 minutes using Rabbit-anti-mouse HRP-conjugated buffer (1:10,000; 100 µL/well; Abcam). After 5 more washes, plates were incubated with chromogen A+B 1:1 to initiate the colorimetric reaction (100 µL/well). The reaction was

stopped with 2 N sulfidric acid (R&D stop solution, 50 µL/well) and absorbance detected at 450 nm spectrophotically.

Antibodies designed against the heparin binding domain of APOE were tested for affinity to APOE3 and APOEch mutant recombinant protein using an ELISA. The Ni-NTA HisSorb Plates (Qiagen) plates were washed 3 times with wash buffer 1 (DY008), the APOE recombinant proteins were suspended in buffer (DY008) to give a final concentration of 0.5 ug/ml. The plates were incubated with 200 µl for 2 hours. The plate was then washed 5 times with 1× wash buffer (DY008), the plates were then incubated with antibodies in a serial dilution series from 1:1000 to 1:32000 and incubated overnight at 4° C. The plate is then washed 5 times in 1× wash buffer (DY008). The plates were then incubated with Anti-mouse HRP (Abcam; ab97046) (1:10000) for 45 minutes. The plate was then washed 5 times in 1× wash buffer to ensure complete removal of unbound secondary antibody. The Sulfuric acid from the ELISA reagent kit (DY008) was warmed to 37° C. prior to addition of 100 µl of tetramethylbenzidine (Millipore) initiating the detection phase of the reaction. After a 5-mins incubation, sulfuric acid was added to terminate the reaction. The plate was then read using Synergy 2 microplate reader (BioTek Instrument. Inc) and the Gen5 version1.11 software).

##### Results

Antibody 1H4 was evaluated using heparin-affinity chromatography and western blotting. ApoE3 was incubated either with negative control (vehicle, top blots) or 1H4 (bottom blots) and each fraction was subjected to heparin-affinity chromatography and western blotting (FIG. 18A). ApoE3 positive bands are indicated by the arrows and detected using the antibody anti his-tag (rb, 1:5,000) that specifically detects the his-tag of the recombinant human APOE. FIG. 18B shows quantification of WB blotting bands detected by the antibody anti hi-tag as shown in FIG. 18A. Intensities were normalized to the input. These results show that ApoE3 binding to heparin was reduced in the presence of the antibody, and that antibody 1H4 competes with ApoE for heparin binding. N=2 independent experiments.

Next subclone analysis of 1H4 serum was carried out. FIGS. 19A-19D show ELISA results of 1H4-2 serum tested with ApoE3 WT full-length protein (A), ApoE3 WT peptide (B), ApoE3ch full length protein (C), and ApoE3ch peptide (D). The results are expressed as optical density at 450 nm over dilution factor of the serum tested. FIG. 20 is a diagram comparing the results shown in FIGS. 19A-19D.

FIG. 21 shows representative ELISA profiles of serial dilutions of the antibody 1H4 incubated either with human recombinant ApoE3 or mouse recombinant ApoE3. The results show that the antibody preferentially binds to the human protein and not to the mouse, and that antibody 1H4 is selective for human ApoE. The results are shown as averaged optical densities detected at 450 nm±s.e.m. (n=2).

Next, monoclonal 1H4 antibody was purified from cloned hybridoma, and subjected to ELISA evaluation. FIG. 22 shows results from the ELISA experiments.

Antibody 7C11 was evaluated using heparin-affinity chromatography, western blotting, quantitative ELISA for chromatography fractions, and competitive ELISA for binding analyses.

Heparin affinity chromatography fractions of ApoE3 incubated either with negative control (vehicle, top blots) or the antibody 7C11 (bottom blots) and subjected to western blotting (FIG. 23A). ApoE3 positive bands are indicated by the arrows and detected using the antibody anti his-tag (rb, 1:5,000) that specifically detects the his-tag of the recom-

binant peptide. FIG. 23B shows quantification of the WB blotting bands detected by the antibody anti hi-tag as shown in FIG. 23A. Intensities were normalized to the input. These results show that ApoE3 binding to heparin was reduced in the presence of the antibody, and that 7C11 competes with ApoE for heparin binding.

Next, subclone analysis of 7C11-1 serum was carried out. FIGS. 24A-24D show ELISA results from testing the 7C11-1 serum with ApoE3 WT full-length protein (A), ApoE3 WT peptide (B), ApoE3ch full length protein (C), or ApoE3ch peptide (D). The results are shown as optical density at 450 nm over dilution factor of the serum tested. FIG. 25 is a diagram comparing the results shown in FIGS. 19A-19D. Next, monoclonal 7C11-1 antibody was purified from cloned hybridoma, and subjected to ELISA evaluation. FIG. 26 shows results from the ELISA experiments.

The 19G10-2 antibody was further evaluated using Heparin-Affinity chromatography, Western Blotting, Quantitative ELISA for chromatography fractions, and ELISA for binding analyses. ELISA screening of the 19G10-2 antibody was performed against the heparin binding domain of APOE3 Wild Type (WT) and APOE3ch Mutant recombinant protein. As shown in FIG. 27, the 19G10-2 antibody displays specificity towards both the full length and c-terminal domain of the APOE3ch (amino acids 125 to 299) mutant recombinant protein and some interaction with APOE3 WT.

Heparin affinity chromatography fractions of ApoE3 incubated either with negative control (vehicle, top blots) or the antibody 19G10-2 (bottom blots) were subjected to ELISA analysis (FIG. 28A). ApoE3 positive bands are indicated by the arrows and detected using the antibody anti his-tag (rb, 1:5,000) that specifically detects the his-tag of the recombinant peptide. FIG. 28B shows quantification of WB blotting bands detected by the antibody anti hi-tag as shown in FIG. 28A. Intensities were normalized to the input. These results show that despite being designed against the ApoE3ch-HSPG domain, 19G10-2 competes with wild type ApoE for heparin binding and resulted in reduced ApoE3 binding to heparin. Without wishing to be bound by theory, antibody 19G10-2 may recognize and/or stabilize a conformation specific feature of APOE (e.g. an APOE polymer or aggregate) that is less likely to bind heparin/HSPG/GAG.

FIG. 29 shows western blotting of ApoE3 WT incubated with 19G10-2 serum antibody. Top blots: membranes probed with secondary anti-mouse to detect 19G10-2 antibody. Bottom membranes were incubated with anti his-tag as described previously to detect ApoE3 positive fractions. This analysis demonstrates that antibody-APOE complexes (left side of the blots; top and bottom) do not bind to heparin, while free APOE bind to heparin with high affinity (right side of the blot; bottom).

FIG. 30 is representative ELISA showing the differences in binding of both serum and monoclonal antibody hybridoma supernatant 19G10-2 for ApoE3WT or ApoE3ch. Data confirms the preponderant selectivity of this antibody for the ApoE3ch variant. FIG. 31 is an enlargement of the Y axes showing some limited binding profiles of the antibody 19G10-2 (serum, grey profile; monoclonal, black binding profile) in the presence of ApoE3WT. Next, monoclonal 19G10-2 antibody was purified from cloned hybridoma, and subjected to ELISA evaluation. FIG. 32 shows results from the ELISA experiments. A signal of recognition of the full-length WT APOE higher than that of the WT ApoE peptide suggest binding of a conformation-specific feature.

The 25F1-2 antibody was further evaluated using Heparin-Affinity chromatography, Western Blotting, Quantitative ELISA for chromatography fractions, and ELISA for binding analyses. FIG. 33 shows ELISA screening of the 25F1-2 antibody against the heparin binding domain of APOE3 Wild Type (WT) and APOE3ch Mutant recombinant protein. As shown in FIG. 33, the 25F1-2 antibody shows high

affinity for the APOE3 mutant full length and c terminal protein, however, it does not appear to have strong binding to the c-terminus of the APOE3WT protein and showed limited interaction with APOE3 WT full length protein. The results are displayed as optical density at 450 nm over dilution factor of the serum tested.

Heparin affinity chromatography fractions of ApoE3 incubated either with negative control (vehicle, top blots) or the antibody 25F1-2 (bottom blots) were subjected to western blotting (FIG. 34A). ApoE3 positive bands are indicated by the arrows and detected using the antibody anti his-tag (rb, 1:5,000) that specifically detects the his-tag of the recombinant peptide. FIG. 34B shows quantification of WB blotting bands detected by the antibody anti hi-tag as shown in FIG. 34A. Intensities were normalized to the input. These results show that despite being designed against the ApoE3ch-HSPG domain, 25F1-2 competes with wild type ApoE for heparin binding and resulted in reduced ApoE3 binding to heparin.

FIG. 35 shows western blotting of ApoE3 WT incubated with the 25F1-2 monoclonal antibody. Top blots: membranes probed with secondary anti-mouse to detect 25F1-2. Bottom membranes were incubated with anti his-tag as described previously to detect ApoE3 positive fractions. This analysis demonstrates that antibody-APOE complexes (left blots; top and bottom) do not bind to heparin, while free ApoE bind to heparin with high affinity (right blot, bottom).

FIG. 36 is representative ELISA showing the differences in binding of both 25F1-2 serum and monoclonal antibody hybridoma supernatant 25F1-2 for ApoE3WT or ApoE3ch. These results confirms the preponderant selectivity of this antibody for the ApoE3ch variant. FIG. 37 is an enlargement of the Y axes of FIG. 36, showing the binding profiles of the antibody 25F1-2 in the presence of ApoE3WT. Next, monoclonal 25F1-2 antibody was purified from cloned hybridoma, and subjected to ELISA evaluation. FIG. 38 shows results from the ELISA experiments. A signal of some recognition of the full-length WT APOE higher than that of the WT ApoE peptide suggest binding of a conformation-specific feature.

The mouse antibody 1343ab (renamed from 23B2) was evaluated using heparin-affinity chromatography and western blotting, and quantitative ELISA for chromatography fractions. FIGS. 39 and 40 show ELISA screening of the 1343 antibody against the heparin binding domain of APOE3 Wild Type (WT) and APOE3ch Mutant recombinant protein. 1343 displayed reactivity to both the APOE3 WT and APOE3ch mutant C-Terminus and full-length recombinant APOE proteins (mutant refers to Christchurch mutant).

ApoE in protein fractions eluted from heparin columns using an increasing NaCl gradient in the presence or absence of the 1343 was subjected to western blotting (FIG. 41A). Individual blots were cropped between 25 to 50 kDa. Blank spaces separate individual blots. FT=flow through. An ELISA was carried out to quantify differences in the NaCl elution patterns of different ApoE in the presence and absence of 1343 (FIG. 41B). N=3 columns per isoform in independent experiments were analyzed side-by-side twice on different days to quantify differences. Error bars depict standard error of mean.

Upon validation, CDR sequences from mouse antibodies 1H4-2, 7C11-1, 19G10-2, 25F1-2, and 1343ab were grafted into human IgG backbones (IgG2 or IgG4) to generate humanized counterparts.

#### Example 9: In Vivo Validation of ApoE Antibodies

An intraocular model of inducible APOE-dependent Tau hyperphosphorylation (paired helical filament formation) was generated. This model was used to test the ability for the

ApoE antibodies to inhibit Tau pathology, which is a marker of neurodegeneration. FIG. 42A shows an exemplary experimental outline.

Briefly, his-tagged recombinant human APOE3 was injected intravitreally into a B6;C3-Tg (Pnpp-MAPT\*P301S) PS19Vle/J mouse (Jackson lab 008169) (Yoshiyama et al. 53 (3): 337-51, 2007). This mouse model contains a human tau P301S mutation and is a validated animal model for Alzheimer's disease and other tauopathies such as frontotemporal dementia (See e.g. Bugiani et al. 58 (6): 667-77, 1999). Mice injected with PBS were used as control.

As shown in FIG. 42B, in the control retina of 6-week old mice, paired helical filaments of phosphorylated tau (PHF) are absent from ganglion cells and their axon fibers (signal inside vessels labeled with isolectin B4 are background signal). In contrast, administration of recombinant human APOE3 (his tagged) triggered robust formation of PHF detected with the AT8 antibody. PHF are robust in ganglion cell axons (arrows) and in the ganglion cell bodies. Human APOE was detected around the ganglion cell bodies using anti-His antibody.

The mouse 1H4-2 antibody and the humanized 1343Ah antibody were injected intravitreally into the eye of mice from the above mouse model (final volume 2  $\mu$ L). The animals were sacrificed on day 3 post injection and retinas were dissected and immunolabeled. Retinas were stained with DAPI, Isolectin, and AT8 (pTAU), which recognizes phosphorylated paired helical filament tau (PHF tau). Retinas were imaged using the SP8 confocal microscope. As shown in FIGS. 43B, 43C, 43F and 43G, APOE3 WT resulted in a significant increase in PHF Tau, which is significantly reduced by 1H4-2 (\*\*p<0.001). Similarly, administration of the humanized 1H4-2 IgG2/kappa recombinant monoclonal antibody effectively reduced APOE-dependent induction of PHF tau pathology in vivo (FIG. 43H; \*\*p<0.01, \*\*\*p<0.001). As shown in FIGS. 43D and 43H, PHF Tau level was significantly reduced by the humanized 1343Ah (\*\*p<0.01, \*\*\*p<0.001).

The similarity of the efficacy between the mouse monoclonal antibody and the corresponding humanized antibody confirms the affinity of the binding domain for ApoE or ApoEch, and that the binding property is retained during humanization. This shows the binding properties of the CDRs are transferable from the original mouse IgG1 to other proteins including human IgG2.

The binding affinity between ApoE3 and the monoclonal antibody 1H4 (mAb 1H4) was determined using the advanced kinetic module of the BLItz system (Blitz Pro, FB-609928, ver. 1.3.1.3). Briefly, a protein A biosensor was loaded with mAb 1H4 and both association and dissociation constants were determined at increasing concentrations of the full length ApoE3 protein (Innovagen) from 0 to 571.4 nM. The following running settings were used: 30 s initial

baseline in the experimental media, 120 s loading of the ligand (mAb 1H4) on the biosensors, 30 s new baseline before association (120 s) and dissociation (120 s) steps. A total of 6 runs of 420 s at 2200 rpm and room temperature were conducted to determine the binding parameters of ApoE3. Global fitting and step corrections of the dissociation experiments were performed using the BLItz software (ver. 1.1.0.7). FIG. 44 shows representative binding measurements of increasing concentrations (nM) of ApoE3 protein to 1H4 on protein A biosensor. KD, Ka and Kd were measured (table 10) and calculated using the BLItz system. Top panel is representative of the association steps, the bottom panel is representative of the dissociation steps of the binding kinetic. The X and Y axes depicts time in second and binding in nM, respectively.

Run Index	Con. ApoE3 (nM)	KD (nM)	ka (1/Ms)	Ka Error	kd (1/s)	kd Error
1	0					
2	35.71	14.28	2900000	0.04142	0.001119	0.1543
3	71.43	14.28	2900000	0.04142	0.001119	0.1425
4	142.9	14.28	2900000	0.04142	0.001119	0.3063
7	285.7	14.28	2900000	0.04142	0.001119	0.09633
8	571.4	14.28	2900000	0.04142	0.001119	0.146

Run Index	Con. ApoE3 (nM)	Rmax	R
1	0		
2	35.71	0.1543	0.005199
3	71.43	0.1425	0.003305
4	142.9	0.3063	0.003587
7	285.7	0.09633	0.001949
8	571.4	0.146	0.001883

#### Example 10: In Vivo Validation of APOE Fragment Fusion Proteins

Next, a fusion protein containing an APOE fragment that includes the HSPG-binding domain, and the Fc region of a human IgG was tested using a similar in vivo model. Briefly, 0.78  $\mu$ g of recombinant full-length APOE was used to induce tau pathology. 0.14  $\mu$ g of the fusion protein was injected intravitreally to the mice. As shown in FIGS. 43E and 43I, the fusion protein diminished APOE-dependent tau pathology in neurons.

#### Example 11: Sequences of Chimeric Antibodies

The sequences of the chimeric antibodies where CDRs were transferred from mouse to human IgG2 or IgG4 are shown below:

```

Normal font = vector
Italicized = Signal peptide
Underlined = VL/VH
Double underlined = Constant part (human Kappa/IgG4/IgG2)
Sequences of expression vectors for mAb 1H4 IgG2/kappa:
>p1H4.VL.hk
GTTAGGCCTTGCGCTGCTCGCGATGTACGGCCAGATATACCGCTGACATTGATTATT

GACTAGTTATTAATAGTAATCAATTACGGGTCTAGTCATAGCCCATATATGGAGTTCC
GCGTTACATAACTTACGGTAAATGGCCCGCTGGCTGACCGCCAAACGACCCCCGCCATTG
ACGTCATAATGACGTATGTCCTAGTAACGCCATAGGGACTTCCATTGACGTCAATG
GGTGGAGTATTACGGTAAACTGCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTA
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 GAATTCAGACACAGCTGTGACCAGAGCCCTGCCAGCCTGGTTCATCTGGGACAGAGAG  
 CCACCATCAGCTGCAAGGCCAGCCAGCGTTGACTACGACGGCAGCTACATGAACTGG  
 TATCAGCAGAACGCCGGCCAGCCACCTAAGGTGTTCATCTACGCCGCAGCACCTGGAAAG  
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 TCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACCCCTCCAATCGGGTAACTCC  
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Sequences of expression vectors for mAb 1343Ah IgG2/kappa:

>p1343Ah.VL.hk

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**139****140**

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**146**

**147****148**

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## Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

## SEQUENCE LISTING

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														10	15

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Arg	Lys	Arg	Leu	Leu	Arg	Asp	Ala	Asp	Asp	Leu	Gln	Lys	Arg	Leu	Ala		
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Val	Tyr	Gln	Ala	Gly	Ala	Arg	Glu	Gly	Ala	Glu	Arg	Gly	Leu	Ser	Ala	
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<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 3

Thr Glu Glu Leu Arg Val Arg Leu Ala Ser His Leu Arg Lys  
1 5 10

<210> SEQ ID NO 4  
<211> LENGTH: 15  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 4

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn  
1 5 10 15

<210> SEQ ID NO 5  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 5

Ala Ala Ser Asn Leu Glu Ser  
1 5

<210> SEQ ID NO 6  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 6

Gln Gln Ser Asn Glu Asp Pro Trp Thr  
1 5

<210> SEQ ID NO 7  
<211> LENGTH: 5  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 7

Ser Tyr Thr Met Ser  
1 5

<210> SEQ ID NO 8  
<211> LENGTH: 17  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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## peptide

&lt;400&gt; SEQUENCE: 8

Lys	Ile	Arg	Asn	Gly	Gly	Gly	Ile	Thr	Tyr	Tyr	Leu	Asp	Thr	Leu	Lys
1				5			10				15				

Gly

&lt;210&gt; SEQ ID NO 9

&lt;211&gt; LENGTH: 11

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 9

His	Tyr	Tyr	Gly	Ser	Glu	Asp	Tyr	Phe	Asp	Tyr
1				5			10			

&lt;210&gt; SEQ ID NO 10

&lt;211&gt; LENGTH: 393

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 10

atggagacag	acacaatcct	gctatgggtg	ctgctgctct	gggttccagg	ctccactgg	60
gacaatgtgc	tgacccaatc	tccagcttct	ttggctgtgt	ctctagggca	gagggccacc	120
atctcctgca	aggccagcca	aagtgttcat	tatgtatgg	atagttatat	gaactggta	180
caacagaaac	caggacagcc	acccaaagtc	ttcatctatg	ctgcatccaa	tctagaatct	240
gggatcccag	ccaggtttag	tggcagtggg	tctgggacag	acttcaccct	caacatccat	300
cctgtggagg	aggaggatgc	tgcaacctat	tactgtcagc	aaagtaatga	ggatccgtgg	360
acgttcggtg	gaggcaccaa	gctggaaatc	aaa			393

&lt;210&gt; SEQ ID NO 11

&lt;211&gt; LENGTH: 417

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 11

atgaatttcg	ggctcagctt	gatttcctt	gtccttgttt	taaaagggtgt	cctgtgtgaa	60
gtgaagctgg	tggaatctgg	gggaggtgtg	gtgcagcctg	gagggtccct	gaaactctcc	120
tgtgcagcct	ctggattcac	tttcagtagc	tataccatgt	cttgggttcg	tcagactcca	180
gagaagaggc	tggagtgggt	cgaaaaatt	cgtaatgg	gtggtatcac	ctactattta	240
gacactttaa	agggccgatt	caccatctcc	agagacaacg	ccaagaacac	cctataacctg	300
caaatacgac	gtctgaagtc	tgaagacacg	gccatattt	tctgtgoaag	acattactac	360
ggtagcgagg	actacttga	ctactggggc	caaggcacca	ctctcacagt	ctccctca	417

&lt;210&gt; SEQ ID NO 12

&lt;211&gt; LENGTH: 131

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

-continued

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 12

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

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

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

Val	Asp	Tyr	Asp	Gly	Asp	Ser	Tyr	Met	Asn	Trp	Tyr	Gln	Gln	Lys	Pro
						50		55		60					

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

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

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

Gln	Gln	Ser	Asn	Glu	Asp	Pro	Trp	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu
						115		120			125				

Glu	Ile	Lys
		130

&lt;210&gt; SEQ ID NO 13

&lt;211&gt; LENGTH: 139

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 13

Met	Asn	Phe	Gly	Leu	Ser	Leu	Ile	Phe	Leu	Val	Leu	Val	Leu	Lys	Gly
1						5		10			15				

Val	Leu	Cys	Glu	Val	Lys	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln
					20			25			30				

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

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

Glu	Trp	Val	Ala	Lys	Ile	Arg	Asn	Gly	Gly	Ile	Thr	Tyr	Tyr	Leu
					65			70		75		80		

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

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

Tyr	Phe	Cys	Ala	Arg	His	Tyr	Tyr	Gly	Ser	Glu	Asp	Tyr	Phe	Asp	Tyr
					115			120			125				

Trp	Gly	Gln	Gly	Thr	Thr	Leu	Thr	Val	Ser	Ser
					130			135		

&lt;210&gt; SEQ ID NO 14

&lt;211&gt; LENGTH: 15

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 14

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn  
1               5               10               15

<210> SEQ ID NO 15

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 15

Ala Ala Ser Asn Leu Glu Ser  
1               5

<210> SEQ ID NO 16

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 16

Gln Gln Ser Asn Glu Asp Pro Trp Thr  
1               5

<210> SEQ ID NO 17

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 17

Arg Tyr Thr Met Ser  
1               5

<210> SEQ ID NO 18

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 18

Lys Ile Arg Asn Val Gly Gly Ile Thr Tyr Tyr Pro Asp Thr Val Lys  
1               5               10               15

Gly

<210> SEQ ID NO 19

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 19

His Tyr Tyr Gly Ser Glu Asp Tyr Phe Asp Tyr  
1               5               10

<210> SEQ ID NO 20

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<211> LENGTH: 417  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 20

```
atgaatttcg ggctcagcgt gattttcctt gtccttgtt taaaagggtgt cctgtgtgaa      60
gtgaagctgg tggagtctgg gggagggtta gtgcagcctg gagggtccct gaaactctcc      120
tgtgcagcct ctggattcac tttagttagg tataccatgt ctgggttcg gcagactcca      180
gagaagaggc tggagtgggt cgaaaaatt cgtaatgttg gtggatcac ctactatcca      240
gacactgtaa agggccgatt caccatctcc agagacaacg ccaagaacac ccttacctg      300
caaatgagca gtctgaagtc tgaagacacg gccatgtatt actgtgcaag acattattac      360
ggtagcgagg actacttga ctactgggc caaggcacca ctctcacagt ctctca      417
```

<210> SEQ ID NO 21  
<211> LENGTH: 393  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 21

```
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactgg      60
gacaatgtgc tgacccaatc tccagcttct ttggctgtgt ctctaggcga gaggccacc      120
atctcctgca aggccagcca aagtgttcat tatgtatggtg atagttatat gaactggtag      180
caacagaaac caggacagcc acccaaagtc ttcatctatg ctgcacatccaa tctagaatct      240
ggatcccag ccaggtttag tggcagtggg tctgggacaa acttcaccct caacatccat      300
cctgtggagg aggaggatgc tgcaacctat tactgtcagc aaagtaatga ggatccgtgg      360
acgttcggtg gaggcaccaa gctggaaatc aaa      393
```

<210> SEQ ID NO 22  
<211> LENGTH: 139  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 22

Met	Asn	Phe	Gly	Leu	Ser	Val	Ile	Phe	Leu	Val	Leu	Val	Leu	Lys	Gly
1															
Val	Leu	Cys	Glu	Val	Lys	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln
Pro	Gly	Gly	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe
Ser	Arg	Tyr	Thr	Met	Ser	Trp	Val	Arg	Gln	Thr	Pro	Glu	Lys	Arg	Leu
Glu	Trp	Val	Ala	Lys	Ile	Arg	Asn	Val	Gly	Gly	Ile	Thr	Tyr	Tyr	Pro
Asp	Thr	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn
Thr	Leu	Tyr	Leu	Gln	Met	Ser	Ser	Leu	Lys	Ser	Glu	Asp	Thr	Ala	Met
100															
105															
110															

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Tyr Tyr Cys Ala Arg His Tyr Tyr Gly Ser Glu Asp Tyr Phe Asp Tyr  
 115 120 125

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser  
 130 135

<210> SEQ ID NO 23  
 <211> LENGTH: 131  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 23

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

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

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

Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro  
 50 55 60

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

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asn Phe Thr  
 85 90 95

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

Gln Gln Ser Asn Glu Asp Pro Trp Thr Phe Gly Gly Thr Lys Leu  
 115 120 125

Glu Ile Lys  
 130

<210> SEQ ID NO 24  
 <211> LENGTH: 15  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 24

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn  
 1 5 10 15

<210> SEQ ID NO 25  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 25

Ala Ala Ser Asn Leu Glu Ser  
 1 5

<210> SEQ ID NO 26  
 <211> LENGTH: 9  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 26

Gln Gln Ser Asn Val Asp Pro Trp Thr  
1 5

<210> SEQ ID NO 27

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 27

Asp Tyr His Met His  
1 5

<210> SEQ ID NO 28

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 28

Trp Ile Asp Pro Glu Asn Gly Asn Thr Met Tyr Asp Pro Lys Phe Gln  
1 5 10 15

Gly

<210> SEQ ID NO 29

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 29

Gly Thr Ala Arg Ala Ser Phe Asp Tyr  
1 5

<210> SEQ ID NO 30

<211> LENGTH: 393

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 30

atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactgg 60

gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc 120

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttatat gaattggtag 180

caacagaata caggacagcc acccaaactc ctcatactat ctgcatacaa tctagaatct 240

gggatcccag ccagggttag tggcagtggg tctgggacag acttcacctt caacatccat 300

cctgtggagg aggaggatgc tgcaacctat tactgtcagc aaagtaatgt ggatccgtgg 360

acgttcggtg gaggcaccaa gctggaaatc aaa 393

<210> SEQ ID NO 31

-continued

<211> LENGTH: 411  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 31

```
atgaaatgca gctgggtcat cttttcctg atggcagtgg ttacaggggt caattcagag      60
gttcagtcgc agcagtctgg ggctgagctt gtgaggccag gggccttagt caagttgtcc      120
tgcaaagctt ctgggttcaa cattaaagac taccatatgc actgggtgaa ggagaggcct      180
gaacaggccc tggagtggat tggatggatt gatcctgaga atggtaatac tatgtatgac      240
ccgaagttcc agggcaaggc cagttataaca gcagacacat cctccaacac agcctacctg      300
cagctcagca gcctgacatc tgaggacact gccgtctatt actgtgttag ggggacagct      360
cgggcttccct ttgactactg gggccaaggc accactctca cagtctccctc a      411
```

<210> SEQ ID NO 32  
<211> LENGTH: 131  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 32

Met	Glu	Thr	Asp	Thr	Ile	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	Lys	Ala	Ser	Gln	Ser
					35			40			45				

Val	Asp	Tyr	Asp	Gly	Asp	Ser	Tyr	Met	Asn	Trp	Tyr	Gln	Gln	Lys	Ser
	50				55			60							

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

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

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

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

Glu	Ile	Lys
	130	

<210> SEQ ID NO 33  
<211> LENGTH: 137  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 33

Met	Lys	Cys	Ser	Trp	Val	Ile	Phe	Phe	Leu	Met	Ala	Val	Val	Thr	Gly
1					5			10				15			

Val	Asn	Ser	Glu	Val	Gln	Leu	Gln	Ser	Gly	Ala	Glu	Leu	Val	Arg
					20			25			30			

Pro	Gly	Ala	Leu	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Asn	Ile
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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35                    40                    45

Lys Asp Tyr His Met His Trp Val Lys Glu Arg Pro Glu Gln Gly Leu  
 50                    55                    60

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

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

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

Tyr Tyr Cys Val Arg Gly Thr Ala Arg Ala Ser Phe Asp Tyr Trp Gly  
 115                  120                  125

Gln Gly Thr Thr Leu Thr Val Ser Ser  
 130                  135

&lt;210&gt; SEQ ID NO 34

&lt;211&gt; LENGTH: 15

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 34

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Thr Tyr Met Asn  
 1                    5                    10                    15

&lt;210&gt; SEQ ID NO 35

&lt;211&gt; LENGTH: 7

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 35

Thr Ala Ser Asn Leu Glu Ser  
 1                    5

&lt;210&gt; SEQ ID NO 36

&lt;211&gt; LENGTH: 9

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 36

Gln Gln Ser Asn Glu Asp Pro Trp Thr  
 1                    5

&lt;210&gt; SEQ ID NO 37

&lt;211&gt; LENGTH: 5

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 37

Asp Tyr His Ile His  
 1                    5

&lt;210&gt; SEQ ID NO 38

&lt;211&gt; LENGTH: 17

-continued

<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 38

Trp	Ile	Asp	Pro	Glu	Ile	Asp	Lys	Thr	Leu	Tyr	Asp	Pro	Lys	Phe	Gln
1				5				10					15		

Gly

<210> SEQ ID NO 39  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 39

Gly	Thr	Ala	Arg	Ala	Ser	Phe	Asp	Tyr
1					5			

<210> SEQ ID NO 40  
<211> LENGTH: 393  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 40

atggagacag	acacaatcct	gctatgggtg	ctgctgctct	gggttccagg	ctccactgg	60
gacattgtgc	tgacccaatc	tccagcttct	ttggctgtgt	ctctaggcca	gagggccacc	120
atctcctgca	aggccagcca	aagtgttcat	tatgtggtg	atacttatat	gaactggtag	180
caacagaaac	caggacagcc	acccaaactc	ctcatctata	ctgcataccaa	tctagaatct	240
gggatcccag	ccaggtttag	tggcagtgaaa	tctgggacag	acttcaccct	caacatccat	300
cctgtggagg	agggtggatgc	tgcaacctat	tactgtcagc	aaagtaatga	ggatccatgg	360
acgttcggtg	gaggcaccaa	gctggaaatc	aaa			393

<210> SEQ ID NO 41  
<211> LENGTH: 411  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 41

atgaaatgca	gctgggtcat	cttcttcctg	atggcagtg	ttacaggggt	caattcagag	60
gttcagctgc	agcagtctgg	ggctgagctt	gtgaggccag	gggccttagt	caagtggtcc	120
tgcaaagctt	ctggcttcaa	cattaaagac	taccatatac	actgggtgaa	acagaggcct	180
gaacagggcc	tggactggat	tggatggatt	gatcctgaga	ttgataaaac	tctatatgac	240
ccgaagttc	aggcaaggc	cagaataaca	gcagacacat	cctccaatac	agcctacctg	300
cagctcagca	gcctgacatc	tgaagacact	gccgtctatt	actgtgccag	ggggacagct	360
cgggcttct	ttgactactg	gggccaaggc	accactctca	cagtctccctc	a	411

&lt;210&gt; SEQ ID NO 42

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-continued

<211> LENGTH: 131  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 42

Met	Glu	Thr	Asp	Thr	Ile	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	Lys	Ala	Ser	Gln	Ser
	35				40				45						

Val	Asp	Tyr	Asp	Gly	Asp	Thr	Tyr	Met	Asn	Trp	Tyr	Gln	Gln	Lys	Pro
	50				55				60						

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

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

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

Gln	Gln	Ser	Asn	Glu	Asp	Pro	Trp	Thr	Phe	Gly	Gly	Thr	Lys	Leu	
	115				120			125							

Glu	Ile	Lys													
	130														

<210> SEQ ID NO 43  
<211> LENGTH: 137  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 43

Met	Lys	Cys	Ser	Trp	Val	Ile	Phe	Phe	Leu	Met	Ala	Val	Val	Thr	Gly
1				5		10			15						

Val	Asn	Ser	Glu	Val	Gln	Leu	Gln	Ser	Gly	Ala	Glu	Leu	Val	Arg	
	20			25				30							

Pro	Gly	Ala	Leu	Val	Lys	Trp	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Asn	Ile
	35			40				45							

Lys	Asp	Tyr	His	Ile	His	Trp	Val	Lys	Gln	Arg	Pro	Glu	Gln	Gly	Leu
	50			55				60							

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

Pro	Lys	Phe	Gln	Gly	Lys	Ala	Arg	Ile	Thr	Ala	Asp	Thr	Ser	Ser	Asn
	85			90				95							

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

Tyr	Tyr	Cys	Ala	Arg	Gly	Thr	Ala	Arg	Ala	Ser	Phe	Asp	Tyr	Trp	Gly
	115			120				125							

Gln	Gly	Thr	Thr	Leu	Thr	Val	Ser	Ser							
	130			135											

<210> SEQ ID NO 44  
<211> LENGTH: 15  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 44

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Glu Asn Tyr Met Asn  
 1               5                   10                   15

<210> SEQ ID NO 45  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 45

Val Ala Ser Asn Leu Glu Ser  
 1               5

<210> SEQ ID NO 46  
 <211> LENGTH: 9  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 46

Gln Gln Ser Asn Leu Asp Pro Trp Thr  
 1               5

<210> SEQ ID NO 47  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 47

Gly Phe Asn Ile Lys Asp Tyr  
 1               5

<210> SEQ ID NO 48  
 <211> LENGTH: 6  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 48

Asp Pro Glu Asn Gly Asn  
 1               5

<210> SEQ ID NO 49  
 <211> LENGTH: 9  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 49

Gly Thr Ala Arg Ala Ser Phe Asp Tyr  
 1               5

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<210> SEQ ID NO 50  
<211> LENGTH: 317  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 50

Met	Lys	Val	Leu	Trp	Ala	Ala	Leu	Leu	Val	Thr	Phe	Leu	Ala	Gly	Cys
1															15
5															

Gln	Ala	Lys	Val	Glu	Gln	Ala	Val	Glu	Thr	Glu	Pro	Glu	Pro	Glu	Leu
20															30

Arg	Gln	Gln	Thr	Glu	Trp	Gln	Ser	Gly	Gln	Arg	Trp	Glu	Leu	Ala	Leu
35															45

Gly	Arg	Phe	Trp	Asp	Tyr	Leu	Arg	Trp	Val	Gln	Thr	Leu	Ser	Glu	Gln
50															60

Val	Gln	Glu	Leu	Leu	Ser	Ser	Gln	Val	Thr	Gln	Glu	Leu	Arg	Ala	
65															80

Leu	Met	Asp	Glu	Thr	Met	Lys	Glu	Leu	Lys	Ala	Tyr	Lys	Ser	Glu	Leu
85															95

Glu	Glu	Gln	Leu	Thr	Pro	Val	Ala	Glu	Glu	Thr	Arg	Ala	Arg	Leu	Ser
100															110

Lys	Glu	Leu	Gln	Ala	Ala	Gln	Ala	Arg	Leu	Gly	Ala	Asp	Met	Glu	Asp
115															125

Val	Cys	Gly	Arg	Leu	Val	Gln	Tyr	Arg	Gly	Glu	Val	Gln	Ala	Met	Leu
130															140

Gly	Gln	Ser	Thr	Glu	Glu	Leu	Arg	Val	Ser	Leu	Ala	Ser	His	Leu	Arg
145															160

Lys	Leu	Arg	Lys	Arg	Leu	Leu	Arg	Asp	Ala	Asp	Asp	Leu	Gln	Lys	Arg
165															175

Leu	Ala	Val	Tyr	Gln	Ala	Gly	Ala	Arg	Glu	Gly	Ala	Glu	Arg	Gly	Leu
180															190

Ser	Ala	Ile	Arg	Glu	Arg	Leu	Gly	Pro	Leu	Val	Glu	Gln	Gly	Arg	Val
195															205

Arg	Ala	Ala	Thr	Val	Gly	Ser	Leu	Ala	Gly	Gln	Pro	Leu	Gln	Glu	Arg
210															220

Ala	Gln	Ala	Trp	Gly	Glu	Arg	Leu	Arg	Ala	Arg	Met	Glu	Glu	Met	Gly
225															240

Ser	Arg	Thr	Arg	Asp	Arg	Leu	Asp	Glu	Val	Lys	Glu	Gln	Val	Ala	Glu
245															255

Val	Arg	Ala	Lys	Leu	Glu	Glu	Gln	Ala	Gln	Gln	Ile	Arg	Leu	Gln	Ala
260															270

Glu	Ala	Phe	Gln	Ala	Arg	Leu	Lys	Ser	Trp	Phe	Glu	Pro	Leu	Val	Glu
275															285

Asp	Met	Gln	Arg	Gln	Trp	Ala	Gly	Leu	Val	Glu	Lys	Val	Gln	Ala	Ala
290															300

Val	Gly	Thr	Ser	Ala	Ala	Pro	Val	Pro	Ser	Asp	Asn	His			
305															

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<210> SEQ ID NO 52
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 52
```

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

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
                  20                         25                         30

Gly Glu Asn Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro  
           35                 40                 45

Lys Leu Leu Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala  
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His  
65                   70                   75                   80

Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Asn  
85 90 95

Leu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg  
100 105 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln  
           115                 120                 125

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr  
 130 135 140

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln  
 145                    150                    155                    160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr  
                  165                   170                   175

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg  
           180                  185                  190

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro  
195 200 205

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys  
210 215

```
<210> SEQ ID NO 53
<211> LENGTH: 442
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide
```

<400> SEQUENCE: 53

Glu	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Leu	Val	Arg	Pro	Gly	Ala
1				5					10						15

Leu Val Lys Leu Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Tyr  
 20 25 30

His Leu His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile  
35 40 45

Gly Trp Ile Asp Pro Glu Asn Gly Asn Val Ile Tyr Asp Pro Lys Phe  
50 55 60

Gln Gly Lys Ala Thr Met Thr Val Val Thr Ser Ser Asn Thr Ala Tyr  
 65                    70                    75                    80

Leu Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys

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85	90	95	
Thr Arg Gly Thr Ala Arg Ala Ser Phe Asp Tyr Trp Gly Gln Gly Thr			
100	105	110	
Ser Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro			
115	120	125	
Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly			
130	135	140	
Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn			
145	150	155	160
Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln			
165	170	175	
Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr			
180	185	190	
Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser			
195	200	205	
Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro			
210	215	220	
Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro			
225	230	235	240
Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys			
245	250	255	
Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp			
260	265	270	
Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu			
275	280	285	
Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met			
290	295	300	
His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser			
305	310	315	320
Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly			
325	330	335	
Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln			
340	345	350	
Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe			
355	360	365	
Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu			
370	375	380	
Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe			
385	390	395	400
Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn			
405	410	415	
Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr			
420	425	430	
Glu Lys Ser Leu Ser His Ser Pro Gly Lys			
435	440		

```

<210> SEQ_ID NO 54
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER_INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<400> SEQUENCE: 54

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-continued

Cys	Thr	Glu	Glu	Leu	Arg	Val	Arg	Leu	Ala	Ser	His	Leu	Arg	Lys
1				5				10					15	

<210> SEQ ID NO 55  
<211> LENGTH: 15  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
<400> SEQUENCE: 55

Cys	Thr	Glu	Glu	Leu	Arg	Val	Ser	Leu	Ala	Ser	His	Leu	Arg	Lys
1				5				10				15		

<210> SEQ ID NO 56  
<211> LENGTH: 954  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide  
<400> SEQUENCE: 56

atgaagggttc	tgtgggctgc	gttgctggc	acattcctgg	caggatgcc	ggccaagg	tg	60
gagcaagcg	gg	ggagacaga	gcccggagcc	gagctgcgc	agcagaccg	gtggcagagc	120
ggccagcg	ct	ggaaactggc	actgggctgc	ttttgggatt	acctgcgc	gttgcagaca	180
ctgtctgagc	gg	gttgcagga	ggagctgctc	agctcccagg	tcacccagg	actgaggcg	240
ctgatggacg	ag	accatgaa	ggagttgaag	gcctacaat	cggaaactg	ggaacaactg	300
accccggtgg	cg	ggaggagac	cgccggcacgg	ctgtccaagg	agctgcaggc	ggcgcaggcc	360
cg	ggctggcg	ggacatgga	ggacgtgtc	ggccgcctgg	tgcagtaccc	cgccgagg	420
caggccatgc	tc	ggccagag	caccgaggag	ctgcgggtga	gcctcgcc	ccacctgc	480
aagctgcgt	a	gcggctcct	ccgcgtatgc	gatgac	ctgc	agaagcgct	540
caggccgggg	cc	cgcgaggg	cgccgagc	ggcctcagcg	ccatccgc	gcgcctggg	600
ccccctgg	aa	caggcgcc	cgtgcggggcc	gccactgtgg	gtccctggc	cggccagcc	660
ctacaggagc	gg	ggcccgaggc	ctggggcgag	cggtgcgc	cgcggatg	ggagatggc	720
agccggaccc	gc	gaccgcct	ggacgagg	aggagcagg	tggcggaggt	gcgcgc	780
ctggaggagc	gg	ggcccgagc	gatacgct	caggccagg	ccttccagg	ccgcctca	840
agctggttcg	ac	ccccctgg	ggaagacat	cagcgc	ggccgggt	ggtggaga	900
gtgcaggctg	cc	gtgggcac	cagegcgc	cctgtgccc	gcgacaat	cta	954

<210> SEQ ID NO 57  
<211> LENGTH: 29  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 57

Ser	Thr	Glu	Glu	Leu	Arg	Val	Arg	Leu	Ala	Ser	His	Leu	Arg	Lys	Leu
1				5				10				15			

Arg	Lys	Arg	Leu	Leu	Arg	Asp	Ala	Asp	Asp	Leu	Gln	Lys		
			20									25		

<210> SEQ ID NO 58  
<211> LENGTH: 29  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 58

Ser	Thr	Glu	Glu	Leu	Arg	Val	Ser	Leu	Ala	Ser	His	Leu	Arg	Lys	Leu
1		5			10									15	
Arg	Lys	Arg	Leu	Leu	Arg	Asp	Ala	Asp	Asp	Leu	Gln	Lys			
	20				25										

<210> SEQ ID NO 59  
 <211> LENGTH: 31  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Arg	Leu	Val	Gln	Tyr	Arg	Gly	Glu	Val	Gln	Ala	Met	Leu	Gly	Gln	Ser
1			5			10								15	
Thr	Glu	Glu	Leu	Arg	Val	Arg	Leu	Ala	Ser	His	Leu	Arg	Lys	Leu	
	20			25										30	

<210> SEQ ID NO 60  
 <211> LENGTH: 31  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 60

Arg	Leu	Val	Gln	Tyr	Arg	Gly	Glu	Val	Gln	Ala	Met	Leu	Gly	Gln	Ser
1			5			10								15	
Thr	Glu	Glu	Leu	Arg	Val	Ser	Leu	Ala	Ser	His	Leu	Arg	Lys	Leu	
	20			25										30	

<210> SEQ ID NO 61  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Unknown  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Unknown:  
 nuclear localization sequence

<400> SEQUENCE: 61

Pro	Lys	Lys	Lys	Arg	Lys	Val
1				5		

<210> SEQ ID NO 62  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Simian virus 40

<400> SEQUENCE: 62

Pro	Lys	Lys	Lys	Arg	Arg	Val
1				5		

<210> SEQ ID NO 63  
 <211> LENGTH: 16  
 <212> TYPE: PRT  
 <213> ORGANISM: Unknown  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Unknown:  
 nucleoplasmin NLS sequence

<400> SEQUENCE: 63

-continued

Lys	Arg	Pro	Ala	Ala	Thr	Lys	Lys	Ala	Gly	Gln	Ala	Lys	Lys	Lys	Lys
1						5				10					15

<210> SEQ ID NO 64  
<211> LENGTH: 60  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 64  
tagcaataaa ggatcgaaaa ttttcattgg aagcgtgtgt tggttttttg atcaggcgcg 60

<210> SEQ ID NO 65  
<211> LENGTH: 127  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 65  
cgccctgggtgc agtaccggcg cgaggtgcag gccatgctcg gccagagcac agaggagctc 60  
cgcggtgagtc tcgcaagccca cctgcgcgaag ctgcgttaagg ggctctccg cgatgccat 120  
gacactgc 127

<210> SEQ ID NO 66  
<211> LENGTH: 264  
<212> TYPE: DNA  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66  
aagggtcgccc aggaagaggg cctatttccc atgattcctt catatttgcata tatacgatac 60  
aaggctgtta gagagataat tagaattaat ttgactgtaa acacaaagat attagtacaa 120  
aataacgtgac gtagaaaagta ataatttctt gggtagtttgc cagttttaaa attatgttt 180  
aaaaatggact atcatatgct taccgttaact tgaaaagtatt tcgatttctt ggctttat 240  
atcttgtgaa aaggacgaaa cacc 264

<210> SEQ ID NO 67  
<211> LENGTH: 25  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 67  
agcccttctc cccgcctccc actgt 25

<210> SEQ ID NO 68  
<211> LENGTH: 25  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 68  
ctccggccacc tgctccctca cctcg 25

<210> SEQ ID NO 69

-continued

<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 69

cttacgcagc ttgcgcagg

20

<210> SEQ ID NO 70  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 70

gcttgcgca g tggggaggcg

20

<210> SEQ ID NO 71  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 71

acgcagctg cgcagggtgg

20

<210> SEQ ID NO 72  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 72

ccagagcacc gaggagctgc

20

<210> SEQ ID NO 73  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 73

gccagagcac cgaggagctg

20

<210> SEQ ID NO 74  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 74

gaggcgcacc cgcagctcct

20

<210> SEQ ID NO 75  
<211> LENGTH: 20

-continued

<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 75

agctgcgcca gcagaccgag

20

<210> SEQ ID NO 76  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 76

ccaggccaag gtggagcaag

20

<210> SEQ ID NO 77  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 77

cacaggatgc caggccaagg

20

<210> SEQ ID NO 78  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 78

acagtgtctg cacccagcgc

20

<210> SEQ ID NO 79  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 79

ggccaagggtg gagcaagcgg

20

<210> SEQ ID NO 80  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 80

gaggcgcacc cgcaagtcct

20

<210> SEQ ID NO 81  
<211> LENGTH: 4290  
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 81

ggatctgcga tcgctccgtt gcccgtcagt gggcagagcg cacatcgccc acagtccccg	60
agaagttggg gggaggggtc ggcaattgaa cgggtgccta gagaagggtgg cgccgggtaa	120
actgggaaag tgatgtcggt tactggctcc gccttttcc cgagggtggg ggagaaccgt	180
atataagtgc agtagtcgcc gtgaacgttc ttttcgcaa cgggtttgcc gccagaacac	240
agctgaagct tcgaggggct cgcacatctc cttcacgcgc cccgcgcct acctgaggcc	300
gccatccacg ccgggttgagt cgcggtctgc cgcgtccgc ctgtggtgcc tcctgaactg	360
cgtccgcgcgt ctaggttaagt tttaaagctca ggtcgagacc gggccttgtt ccggcgctcc	420
cttggagcct acctagactc agccggctct ccacgctttg cctgaccctg cttgtcaac	480
tctacgttctt tgtttgcgtt tctgttctgc gccgttacag atccaagctg tgaccggcgc	540
ctacctgaga tcacccggcga aggagggcca ccatgtacag gatgcaactc ctgttgcga	600
ttgcactaag tcttgcactt gtcacgaatt cggcacctct ctagcgccttgc tctgtgtcg	660
agtgcggcacc gtgcccagca ccacactgtgg caggaccgtc agtcttctc ttccccccaa	720
aacccaagga caccctcatg atctccggaa cccctgaggt cacgtgcgtg gtggtgacg	780
ttagccacga agaccccgag gtccagttca actggtaacgt ggacggcgtg gaggtgcata	840
atgccaagac aaagccacgg gaggaggact tcaacacgcac gttccgtgtg gtcagcgctcc	900
tcaccgttgc acccaggac tggctgaacg gcaaggagta caagtgcgaag gtctccaaca	960
aaggcctccc agcccccatac gagaaaacca tctccaaac caaaggcag ccccgagaac	1020
cacagggtgtt caccctgccc ccacccggg aggagatgac caagaaccag gtcagcctga	1080
cctgcctgtt caaaggcttc tacccageg acatcgccgt ggagtggag agcaatggc	1140
agccggagaa caactacaag accacgcctc ccatgtcgaa ctccgacggc tccttctcc	1200
tctacagcaa gtcacccgtg gacaagagca ggtggcagca ggggaacgtc ttctcatgt	1260
ccgtgatgca tgagggtctg cacaaccact acacgcagaa gagcctctcc ctgtctccgg	1320
gtgcacgtac ggcctgggt cagtaccgtcg gcgagggtgcg ggcgcgtc ggcgcggca	1380
ccgaggagct gccccgtcgc ctgcctccc acctgcgcac gctgtatat ctgcgtactg	1440
ctggccagac atgataagat acattgtga gtttggacaa accacaacta gaatgcgtg	1500
aaaaaaaaatgc ttatattgtt aaatttgtga tgctattgtt ttatattgtt ccattataag	1560
ctgcaataaa caagttaaaca acaacaattt cattcatttt atgtttcagg ttcaggggaa	1620
ggtgtgggg gttttttaaa gcaagtaaaa cctctacaaa tgggttatgg attaattct	1680
aaaaatacagc atagcaaaac tttaacctcc aaatcaagcc tctacttgaa tcctttctg	1740
agggtatgaat aaggcatagg catcaggggc tggcatttgc tggcatttgc	1800
ctcaccttctt ttcatggagt ttaagatata gtgtatccc ccaagggtttg aactagctct	1860
tcattttttt atgttttaaa tgcactgacc tcccacattc cttttttgtt aaaatattca	1920
gaaataattt aaatacatca ttgcaatgaa aataaatgtt ttttattagg cagaatccag	1980
atgctcaagg cccttcataa tatccccccat ttttagtagt ggacttaggg aacaaaggaa	2040
cctttaatag aaattggaca gcaagaaago gagttcttag cttatccca gtcctgcgtcc	2100
tctgccacaa agtgcacgcgca gttgccggcc gggtcgcgcgca gggcgaactc ccgcggccac	2160

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<210> SEQ ID NO 82  
<211> LENGTH: 284  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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203

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-continued

polypeptide

&lt;400&gt; SEQUENCE: 82

Met	Tyr	Arg	Met	Gln	Leu	Leu	Ser	Cys	Ile	Ala	Leu	Ser	Leu	Ala	Leu
1				5				10					15		

Val	Thr	Asn	Ser	Ala	Pro	Leu	Glu	Arg	Lys	Ser	Ser	Val	Glu	Cys	Pro
	20					25						30			

Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro
	35					40					45				

Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr
	50				55				60						

Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn
65						70		75			80				

Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg
	85					90			95						

Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val
	100					105				110					

Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser
	115					120			125						

Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys
	130					135			140						

Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu
145				150			155			160					

Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe
	165					170			175						

Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu
	180					185			190						

Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe
	195					200			205						

Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly
	210				215			220							

Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr
	225					230			235			240			

Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Ala	Arg	Thr	Arg	Leu	Val
	245					250			255						

Gln	Tyr	Arg	Gly	Glu	Val	Gln	Ala	Met	Leu	Gly	Gln	Ser	Thr	Glu	Glu
	260				265			270							

Leu	Arg	Val	Arg	Leu	Ala	Ser	His	Leu	Arg	Lys	Leu				
	275					280									

&lt;210&gt; SEQ ID NO 83

&lt;211&gt; LENGTH: 4290

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 83

ggatctgcga tcgctccgggt gccccgtcagt gggcagagcg cacatcgccc acagtccccg 60

agaagttggg gggagggggtc ggcaattgaa cgggtgccta gagaagggtgg cgcggggtaa 120

actggggaaag tcatgtcggt tactggctcc gccttttcc cgagggtggg ggagaaccgt 180

ataataagtgc agtagtcgccc gtgaacgttc ttttcgcaa cgggttgcc gcccagaacac 240

agctgaagct tcgaggggtc cgcatctctc ctgcacgcgc ccggccgcctt acctgaggcc 300

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cgggaccgcc gaaactgcgag gggacgtggc tagggcggct tcttttatgg tgccggcc 2760
ctcggaggca gggcgctcg ggaggccatcg cggccaatct cgggtggcag gaggcggggc 2820
cgaaggccgt gcctgaccaa tccggagcac ataggagtct cagccccccg ccccaaagca 2880
aggggaaatgc acgcgcctgt agcgcgcagcg tgggtgaaa tgggggcttg ggggggttgg 2940
ggccctgact agtcaaaaaca aactcccatt gacgtcaatg gggtggagac ttggaaatcc 3000
ccgtgagtc aaccgcgtatc cacgcccatt gatgtactgc caaaaccgca tcatacatgg 3060
aatagcgatg actaataacgt agatgtactg ccaagtagga aagtccata aggtcatgt 3120
ctgggcataa tgccaggcgg gccatttacc gtcattgacg tcaatagggg gcgtacttgg 3180
catatgatac acttgatgt  ctgccaagtg ggcagttac cgtaaatact ccaccattg 3240
acgtcaatgg aaagtcccta ttggcgttac tatggaaaca tacgtcat  ttgacgtcaa 3300
tgggcggggg tcgttggcg gtcagccagg cggccattt accgtaagtt atgtaacgccc 3360
tgcagggttaa ttaagaacat gtgagcaaaa ggccagcaaa aggccaggaa ccgtaaaaag 3420
gcgcgcgttgc tggcggtttt ccataggctc cgcggccctg acgagcatca caaaatcg 3480
cgctcaagtc agagggtggcg aaacccgaca ggactataaa gataccaggc gttccccct 3540
ggaagctccc tcgtgcgtc tccgttccg accctgcgc ttaccggata cctgtccgc 3600
tttctccctt cgggaagcgt ggccgtttct catagctac gctgttaggt tctcagttcg 3660
gtgttaggtcg ttgcgtccaa gctgggtgt gtgcacgaac ccccggttca gcccgcacgc 3720
tgccgcctt ccggtaacta tcgtctttag tccaaccggg taagacacga cttatcgcca 3780
ctggcagcag ccactggtaa caggatttagc agagcgaggt atgtaggcg tgctacagag 3840
ttcttgaagt ggtggctaa ctacggctac actagaagaa cagttttgg tatctgcgt 3900
ctgctgaagc cagttacctt cggaaaaaga gttggtagct cttgatccgg caaacaacc 3960
accgctggta gcgggtggttt tttgtttgc aagcagcaga ttacgcgcag aaaaaagga 4020
tctcaagaag atcccttgc ttttctacg gggctgtacg ctcagtgaa cgaaaactca 4080
cgtaaggga ttttggtcat ggctagttaa ttaacattt aatcagcggc cgcaataaaa 4140
tatcttatt ttcattacat ctgtgtgtt gtttttgtt tgaatcgtaa ctaacatacg 4200
ctctccatca aaacaaaacg aaacaaaaca aactagcaaa ataggctgc cccagtgc 4260
gtgcagggtgc cagaacattt ctctatcgaa 4290

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<210> SEQ_ID NO 84
<211> LENGTH: 284
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

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<400> SEQUENCE: 84
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Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

```

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Val Thr Asn Ser Ala Pro Leu Glu Arg Lys Ser Ser Val Glu Cys Pro
20 25 30

```

```

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
35 40 45

```

```

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
50 55 60

```

```
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
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65	70	75	80
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg			
85		90	95
Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val			
100		105	110
Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser			
115		120	125
Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys			
130		135	140
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu			
145		150	155
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe			
165		170	175
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu			
180		185	190
Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe			
195		200	205
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly			
210		215	220
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr			
225		230	235
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Thr Arg Leu Val			
245		250	255
Gln Tyr Arg Gly Glu Val Gln Ala Met Leu Gly Gln Ser Thr Glu Glu			
260		265	270
Leu Arg Val Ser Leu Ala Ser His Leu Arg Lys Leu			
275		280	

<210> SEQ ID NO 85  
 <211> LENGTH: 4284  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 85

ggatctgcga tcgctccgtt gcccgtcagt gggcagagcg cacatcgccc acagtccccg	60
agaagttggg gggaggggtc ggcaattgaa cgggtgccta gagaagggtgg cgcgggtaa	120
actggaaag ttagtgcgtg tactggctcc gccttttcc cgagggtggg ggagaaccgt	180
atataagtgc agtagtcgcc gtgaacgttc ttttcgcaa cgggtttgcc gccagaacac	240
agctgaagct tcgaggggct cgcacgtc cttcacgcgc cccgcgcct acctgaggcc	300
cccatccacg ccgggttgagt cgcggtctgc cgccctccgc ctgtggtgcc tcctgaactg	360
cgtccgcgtt ctaggttaagt tttaagctca ggtagatcgacc gggcccttgtt cccggcgctcc	420
cttggagactt accttagactc agccggctct ccacgttttgc cctgaccctg cttgtctcaac	480
tctacgtctt tggttcgttt tctgttctgc gccgttacag atccaagctg tgaccggcgc	540
ctacctgaga tcaccggcga aggagggcca ccatgtacag gatgcaactc ctgtcttgca	600
ttgcactaag tcttgcactt gtcacgaatt cgatacgcctt ggtgcagttac cgccggcagg	660
tgccaggccat gtcggccag agtactgagg agctgcgggtt ggcgcctggcc tccacacctgc	720
gcaagctgat atcggccatg gtttagatctg tggagtgccc accttgccca gcaccacctg	780
tggcaggacc ttcagtccttc ctcttccccca caaaacccaa ggacaccctg atgatctcca	840

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gaacccctga ggtcacgtgc gtgggtgg acgtgagcca cgaagacccc gaggtccagt	900
tcaactggta cgtggacggc atggagggtgc ataatgcca gacaaagcca cggggaggac	960
agttcaacag cacgttccgt gtggtcagec tcctcaccgt cgtcaccag gactggctga	1020
acggcaagga gtacaagtgc aaggctcca acaaaggcc cccagcccc atcgagaaaa	1080
ccatctccaa aaccaaaggc cagccccag aaccacagggt gtacaccctg ccccatccc	1140
ggggaggat gaccaagaac caggtcagec tgacctgcct ggtcaaaggc ttctaccctt	1200
gcgacatgc cgtggagtgg gagagcaatg ggtagccggaa gaacaactac aagaccacac	1260
c当地ccatgtc ggactccgac ggctccttct tcctctacag caagctcacc gtggacaaga	1320
gcaggtggca gcaggggaac gtcttctcat gctccgtat gcatgaggct ctgcacaacc	1380
actacacaca gaagagccctc tccctgtctc cgggttaatg agtgccacgg cttagtggcc	1440
agacatgata agatacattt atgagtttgg acaaaccaca actagaatgc agtggaaaaaa	1500
atgttttatt tttttttttt gtgtatgtat tgcttttattt gtaaccatata taagctgca	1560
taaacaagtt aacaacaaca attgcattca ttttatgtttt caggttcagg gggaggtgt	1620
ggaggttttt taaagcaagt aaaacctcta caaatgtggat atggattaa ttctaaaata	1680
cagcatagca aaacttaac ctccaaatca agcctctact tgaatcattt tctgaggat	1740
gaataaggca taggcatttc gggctgttgc caatgtcat tagctgtttt cagcctcacc	1800
ttctttcatg gagttttaaga tatagtgtat tttcccaagg tttgaacttag ctcttcattt	1860
ctttatgttt taaatgcact gaccccccattttt tagtaaaaattt ttcagaaata	1920
atttaaatac atcattgcaaa tgaaataaaa tgttttttat taggcagaat ccagatgtc	1980
aaggcccttc ataataatccc ccagttttagt agttggactt agggaaacaaa ggaaccttta	2040
atagaaattt gacagcaaga aagegagctt ctatgttatac ctcagtcctg ctctctgcc	2100
acaaagtgc cgccatggcc ggccgggtcg cgccaggcga actcccgccc ccacggctgc	2160
tcgcccgtatc cggcatggc cggccggag gggtccggag agttcgatggc cacgaccctcc	2220
gaccactcg cgtacagctc gtccaggccg cgccacccaca cccaggccag ggtgttgtcc	2280
ggcaccaccc ggtcttggac cgcgtatgtt aacagggtca cgtcgcccg gaccacacccg	2340
gegaagtcgt cttccacgaa gtccggggag aacccgagcc ggtcgggtcca gaactcgacc	2400
gctccggcga cgtcgccgc ggtgagcacc ggaacggcactt ggcatgtatg	2460
gctccctctg tcaggagagg aaagagaaga aggttagtac aattgtata gtgagttgtat	2520
ttatactatg cagatataact atgccaatga ttaattgtca aactagggttgc gcaagggttca	2580
tagtgccact tttccctgcac tgcccatct cctgcccacc cttccagg catagacagt	2640
cagtgactta ccaaactcac aggagggaga aggccagaac ttgagacaga cccgcggac	2700
cgccgaactg cgagggggacg tggcttagggc ggcttctttt atgggtgcggcc ggccctcgga	2760
ggcaggggcgc tcggggagggc ctagcggcca atctcggttgc gcaggaggcg gggccgaagg	2820
ccgtgcctga ccaatccgga gcacatagga gtctcagccc cccgccccaa agcaaggga	2880
agtcaacgcgc ctgttagcgcc agcgtgtgtt gaaatgggggg cttggggggg ttggggccct	2940
gacttagtca aacaaactcc cattgacgtc aatgggggtgg agacttggaa atccccgtga	3000
gtcaaaaccgc tatccacgccc cattgtatgtt ctgccaaac cgcacatcatca tggtaatagc	3060
gtatgactaat acgttagatgt actgccaagt agggaaagtcc cataagggtca ttttttttttgc	3120
ataatgcacggc cggggccatt taccgtcatt gacgtcaata gggggcgtac ttggcatatg	3180

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atacacttga tgtactgcca agtgggcagt ttaccgtaaa tactccaccc attgacgtca 3240
atggaaagtc cctattggcg ttactatggg aacatacgctt attattgacg tcaatggcg 3300
ggggtcgttg ggcggtcagc caggcgggcc atttaccgta agttatgtaa cgccgtcagg 3360
ttaattaaga acatgtgagc aaaaggccag caaaaggcca ggaaccgtaa aaaggcccg 3420
ttgctggcgt ttttccatag gctccgcccc cctgacgagc atcacaaaaa tcgacgctca 3480
agtcagaggt ggcgaaaccc gacaggacta taaagatacc aggcgtttcc ccctggaagc 3540
tccctcgtgc gctctctgt tccgaccctg ccgcttaccg gatacctgtc cgcccttctc 3600
ccttcggaa gcgtggcgct ttctcatago tcacgctgtaa ggtatcttag ttccggtag 3660
gtcgttcgct ccaagctggg ctgtgtgcac gaacccccc ttcagccga ccgctgcgcc 3720
ttatccggta actatcgctc tgagtccaa cccggttaagac acgacttatac gccactggca 3780
gcagccactg gtaacaggat tagcagagcg aggtatgttag gcggtgtac agagttctg 3840
aagtggggc ctaactacgg ctacactaga agaacagtat ttggtatctg cgctctgtc 3900
aagccagttt ctttcggaaa aagagttgtt agctcttgat ccggcaaaaca aaccaccgt 3960
ggtagcgggt gttttttgtt ttgcaagcag cagattacgc gcagaaaaaa aggatctcaa 4020
gaagatcctt ttagtctttt tacggggct gacgctcgtt ggaacgaaaa ctcacgttaa 4080
gggattttgg tcatggctag ttaattaaca tttaaatcag cggccgcaat aaaatatctt 4140
tattttcatt acatctgtgt tttttttttt tttgtgtaaatc gtaactaaca tacgctctcc 4200
atcaaaacaa aacgaaacaa aacaaactag caaaataggc tttttttttt gcaagtgcag 4260
gtgccagaac atttctctat cgaa 4284

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<210> SEQ ID NO 86  
<211> LENGTH: 282  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
polypeptide

&lt;400&gt; SEQUENCE: 86

Met	Tyr	Arg	Met	Gln	Leu	Leu	Ser	Cys	Ile	Ala	Leu	Ser	Leu	Ala	Leu
1				5				10					15		

Val	Thr	Asn	Ser	Ile	Arg	Leu	Val	Gln	Tyr	Arg	Gly	Glu	Val	Gln	Ala
				20				25				30			

Met	Leu	Gly	Gln	Ser	Thr	Glu	Glu	Leu	Arg	Val	Arg	Leu	Ala	Ser	His
					35			40			45				

Leu	Arg	Lys	Leu	Ile	Ser	Ala	Met	Val	Arg	Ser	Val	Glu	Cys	Pro	Pro
				50			55			60					

Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
65					70				75			80			

Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
				85				90			95				

Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp
				100			105			110					

Tyr	Val	Asp	Gly	Met	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
				115			120			125					

Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val
				130			135			140					

His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
145				150			155			160					

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Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly  
165 170 175

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu  
180 185 190

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr  
195 200 205

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn  
210 215 220

Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe  
225 230 235 240

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn  
245 250 255

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr  
260 265 270

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
275 280

<210> SEQ ID NO 87  
<211> LENGTH: 4284  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 87

ggatctgcga	tcgctccgggt	gccegtcagt	gggcagagcg	cacategccc	acagtccccg	60
agaagttggg	gggagggggtc	ggcaattgaa	cgggtgccta	gagaagggtgg	cgcggggtaa	120
actggggaaag	tgtatgtcggt	tactggctcc	gccttttcc	cgagggtggg	ggagaaccgt	180
atataaagtgc	agtagtcgcc	gtgaacgttc	tttttcgaa	cgggttgcc	gccagaacac	240
agctgaagct	tcgaggggct	cgcacatctc	cttcacgegc	cggccgcct	acctgaggcc	300
gccatccacg	ccgggttgggt	cgcgttctgc	cgcctccgc	ctgtggtgcc	tcctgaactg	360
cgtccgcgcgt	ctaggtaagt	ttaaaagctca	ggtcgagacc	gggcctttgt	ccggcgctcc	420
cttggagccct	acctagactc	agcgggtct	ccacgctttg	cctgaccctg	cttgcataac	480
tctacgtctt	tgtttcggtt	tctgttctgc	gccgttacag	atccaagctg	tgaccggcgc	540
ctacctgaga	tcacccggcga	aggagggcca	ccatgtacag	gatgcaactc	ctgtttgca	600
ttgcactaag	tcttgcactt	gtcacgaatt	cgatacgcct	ggtgcagttac	cgcggcgagg	660
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gcaagctgat	atcgcccatg	gttagatctg	tggagtgccc	accttgccca	gcaccacctg	780
tggcaggacc	ttcagtcttc	ctcttccccc	caaaccacaa	ggacaccctg	atgatctcca	840
gaacccctga	ggtcacgtgc	gtgggtgggg	acgtgagcca	cgaagacccc	gagggtccagt	900
tcaactggta	cgtggacggc	atggaggtgc	ataatgccaa	gacaaagcca	cgggaggagc	960
agttcaacag	cacgttccgt	gtggtcagec	tcctcaccgt	cgtgcaccag	gactggctga	1020
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ccatctccaa	aaccaaaggg	cagccccgag	aaccacagg	gtacaccctg	cccccatccc	1140
gggaggagat	gaccaagaac	caggtcagcc	tgacctgcct	ggtcaaaggc	ttctaccctt	1200
cgacatcg	cgtggagtgg	gagagcaatg	ggcagccgga	gaacaactac	aagaccacac	1260
ctcccatgtc	ggactccgac	ggctccttct	tcctctacag	caagctcacc	gtggacaaga	1320

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cgagggtggca gcaggggaac gtcttctcat gtcgcgtat gcatgaggct ctgcacaacc 1380  
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agacatgata agatacatgt atgagtttg acaaaccaca actagaatgc agtaaaaaaaa 1500  
atgcatttatt tgtgaaattt gtgatgctat tgctttattt gtaaccatta taagctgcaa 1560  
taaacaaagt aacaacaaca attgcattca tttatgttt caggttcagg gggaggtgtg 1620  
ggaggtttt taaagcaagt aaaacctcta caaatgtggt atggaattaa ttctaaaata 1680  
cagcatagca aaacttaac ctccaaatca agcctctact tgaatcctt tctgagggat 1740  
gaataaggca taggcattcag gggctgttgc caatgtgcatt tagctgtttt cagccctacc 1800  
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ctttatgttt taaatgcact gaccccacccatcccttt tagtaaaaata ttcagaaata 1920  
attnaaatac atcattgcaaa tgaaaataaa tgtttttat taggcagaat ccagatgctc 1980  
aaggcccttc ataatatccc ccagtttagt agttggactt agggacaaaa ggaaccttta 2040  
atagaaattt gacagcaaga aagcgagctt ctatgttatac ctcaatcttgc ctcccttgcc 2100  
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cagtgaactt ccaaactcac aggagggaga aggacagaagc ttgagacaga cccggggac 2700  
cgccgaactt cgaggggacg tggcttagggc ggctttttt atggtgcggcc ggccttgg 2760  
ggcaggggcgc tcggggaggc ctageggca atctgcggtg gcaaggaggcg gggccgaagg 2820  
ccgtgcctga ccaatccgga gcacatagga gtctcgecc cccggccaa agcaagggga 2880  
agtcaacgcg cttgtcgcc acgtgttgc gaaatggggg cttggggggg ttggggccct 2940  
gactagtcaa aacaaactcc cattgacgtc aatgggggtgg agacttgaa atccccgtga 3000  
gtcaaaacccgc tatccacgca cattgtatgtc ctgcacaaac cgcacatcatca tggtaatgc 3060  
gtgactatac acgttagatgt actgccaagt aggaaagtcc cataaggctca tggactggc 3120  
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tccctcggtc gctctccctgt tccgaccctg ccgttaccg gataccctgtc cgccttctc 3600  
ccttcggaa ggcgtggcgct ttctcatagc tcacgtgttca ggtatctcag ttgggtgttag 3660  
gtcggtcgctt ccaagctggg ctgtgtgcac gaaccccccgg ttcagcccgaa cgcgtgcgc 3720

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ttatccggtta actatcgctc tgagtccaa cccggtaagac acgacttatac gccactggca 3780
gcagccactg gtaacaggat tagcagagcg aggttatgtac gcccgtgtac agagtttttg 3840
aagtgggtggc ctaactacgg ctacactaga agaacagtat ttggtatctg cgctctgctg 3900
aagccagttt ccttcggaaa aagagttgtt agtcttgcgat ccggcaaaaca aaccaccgct 3960
ggtagcggtg gttttttgtt ttgcaagcag cagattacgc gcagaaaaaa aggatctcaa 4020
gaagatcctt tcatcttttac cgggggtct gacgctcgtt ggaacgaaaaa ctcacgtttaa 4080
gggatttgg tcatggcttag ttaattaaca tttaaatcag cggccgcaat aaaatatctt 4140
tattttcattt acatctgtgtt gttgggtttt tttgtgtaaatcataa ttcacgttcc 4200
atcaaaaacaa aacgaaaacaa aacaaaactag caaaaataggc tttccccagt gcaagtgcag 4260
gtgccagaac atttctctat cgaa 4284

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<210> SEQ ID NO 88  
<211> LENGTH: 282  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 88

Met	Tyr	Arg	Met	Gln	Leu	Leu	Ser	Cys	Ile	Ala	Leu	Ser	Leu	Ala	Leu
1				5			10			15					

Val	Thr	Asn	Ser	Ile	Arg	Leu	Val	Gln	Tyr	Arg	Gly	Glu	Val	Gln	Ala
				20			25			30					

Met	Leu	Gly	Gln	Ser	Thr	Glu	Glu	Leu	Arg	Val	Ser	Leu	Ala	Ser	His
				35			40			45					

Leu	Arg	Lys	Leu	Ile	Ser	Ala	Met	Val	Arg	Ser	Val	Glu	Cys	Pro	Pro
				50			55			60					

Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
				65			70			75			80		

Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
				85			90			95					

Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp
				100			105			110					

Tyr	Val	Asp	Gly	Met	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
				115			120			125					

Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val
				130			135			140					

His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
				145			150			155			160		

Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly
				165			170			175					

Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu
				180			185			190					

Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
				195			200			205					

Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
				210			215			220					

Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
				225			230			235			240		

Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
				245			250			255			255		

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Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr  
 260 265 270

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 275 280

<210> SEQ ID NO 89  
 <211> LENGTH: 4284  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 89

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agaagttggg	gggaggggtc	ggcaattgaa	cgggtgccta	gagaagggtgg	cgcggggtaa	120
actggggaaag	tgtatgtcggt	tactggctcc	gccttttcc	cgagggtggg	ggagaaccgt	180
atataagtgc	agtatgtcgcc	gtgaacgttc	tttttcgcaa	cgggtttgcc	gccagaacac	240
agctgaagct	tcgaggggct	cgcacatctc	cttcacgcgc	ccggccgcct	acctgaggcc	300
gccatccacg	ccgggttgggt	cgcgttctgc	cgccctccgc	ctgtggtgcc	tcctgaactg	360
cgtccggccgt	ctaggtaagt	ttaaaagctca	ggtcgagacc	gggcctttgt	ccggcgctcc	420
cttggagccct	accttagactc	agccggctct	ccacgctttg	cctgaccctg	cttgcgtcaac	480
tctacgtctt	tgtttcggtt	tctgttctgc	gccgttacag	atccaagctg	tgaccggcgc	540
ctacctgaga	tcacccggcga	aggagggcca	ccatgtacag	gtgcgtactc	ctgtcttgca	600
ttgcactaag	tcttgcactt	gtcacgaatt	cggcacctct	cgagcgcaaa	tctagtgtcg	660
agtggccacc	gtggccagca	ccacctgtgg	caggaccgtc	agtcttcctc	ttccccccaa	720
aacccaagga	caccctcatg	atctcccgga	cccttgaggt	cacgtgcgtg	gtggtgacg	780
tgagccacga	agaccccgag	gtcccgatca	actggtaactg	ggacggcggt	gaggtgcata	840
atgccaagac	aaagccacgg	gaggagcagt	tcaacacgac	gttccgtgtg	gtcagcgctcc	900
tcaccgttgt	gcaccaggac	tggctgaacg	gcaaggagta	caagtgcgaa	gtctccaaaca	960
aaggcctccc	agcccccatac	gagaaaacca	tctccaaaac	caaaggcgag	ccccgagaac	1020
cacaggtgta	caccctgccc	ccatccggg	aggagatgac	caagaaccag	gtcagcctga	1080
cctgcctgg	caaaggcttc	taccccgacg	acatcgccgt	ggagtggag	agcaatggc	1140
agccggagaa	caactacaag	accacgcctc	ccatgctgg	ctccgcggc	tccttctcc	1200
tctacagcaa	gtcaccgtg	gacaagagca	ggtggcagca	ggggAACGTC	ttctctatgt	1260
ccgtgatgca	tgaggctctg	cacaaccact	acacgcagaa	gagcctctcc	ctgtctccgg	1320
gtgcacgtac	gagcaccggag	gagctgcggg	tgcgcctcgc	ctcccacctg	cgcaagctgc	1380
gtaaagcggt	cctcccgat	gccgtgacc	tgcagaagtg	atatctcgag	ctagctggcc	1440
agacatgata	agatacattg	atgagtttg	acaaccaca	actagaatgc	agtaaaaaa	1500
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taaacaaagt	aacaacaaca	attgcattca	tttatgttt	caggttcagg	gggagggtgt	1620
ggaggttttt	taaagcaagt	aaaacctcta	caaatgtgg	atggaattaa	ttctaaaata	1680
cacgcata	aaactttaac	ctccaaatca	agectctact	tgaatcctt	tctgagggt	1740
gaataaggca	taggcata	gggctgttgc	caatgtgc	tagctgttg	cagcctcacc	1800
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ctttatgttt taaatgcact gacctccac attcccttt tagaaaata ttcagaaata 1920  
 atttaaatac atcattgcaa tgaaaataaa tgtttttat taggcagaat ccagatgctc 1980  
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 atagaaattg gacagcaaga aagcgagctt cttagttatc ctcagtcctg ctcctctgcc 2100  
 acaaagtgca cgcaagttgcc ggccgggtcg cgcaaggcgca actcccgccc ccacggctgc 2160  
 tcgcccgtct cggcatggc cgccccggag gctgtcccgaa agttcggtga cacgaccc 2220  
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 ccgtgcctga ccaatccgga gcacatagga gtctcageccc cccgccccaa agcaagggg 2880  
 agtcacgcgc ctgttagcgcc agcgtgtgt gaaatggggg cttggggggg ttggggccct 2940  
 gactagtcaa aacaaactcc cattgacgtc aatgggggtgg agacttggaa atccccgtga 3000  
 gtcaaacccgc tatccacgccc cattgtatgtc ctgccaaac ccgtatcatca tggtaatacg 3060  
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 atacacttgc tggactgcgc agtggggcagt ttaccgtaaa tactccaccc attgacgtca 3240  
 atggaaagtcc ctattggcg ttactatggg aacatacgctt attattgacgc tcaatggcg 3300  
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 gaagatcctt tgatctttc tacggggctt gacgctcagt ggaacggaaa ctcacgtt 4080  
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 tattttcatt acatctgtgtt gttgggtttt tgggtgttac gtaactaaca tacgctctcc 4200

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gtgccagaac atttctctat cgaa 4284

<210> SEQ ID NO 90

<211> LENGTH: 282

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 90

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Val Thr Asn Ser Ala Pro Leu Glu Arg Lys Ser Ser Val Glu Cys Pro  
20 25 30

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro  
35 40 45

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr  
50 55 60

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn  
65 70 75 80

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg  
85 90 95

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val  
100 105 110

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser  
115 120 125

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys  
130 135 140

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu  
145 150 155 160

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe  
165 170 175

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu  
180 185 190

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe  
195 200 205

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly  
210 215 220

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr  
225 230 235 240

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Thr Ser Thr Glu  
245 250 255

Glu Leu Arg Val Arg Leu Ala Ser His Leu Arg Lys Leu Arg Lys Arg  
260 265 270

Leu Leu Arg Asp Ala Asp Asp Leu Gln Lys  
275 280

<210> SEQ ID NO 91

<211> LENGTH: 4284

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 91

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228

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actgggaaag tgatgtcgta tactggctcc gccttttcc cgagggtggg ggagaaccgt	180
atataagtgc agtagtcgac gtgaacgttc ttttcgcaa cgggttgcc gccagaacac	240
agctgaagct tcgaggggtc cgcatctc cttcacgcgc ccggccgcct acctgaggcc	300
ccatccacg ccgggttgagt cgcggttcgc cgccgtccgc ctgtgggcc tcctgaactg	360
cgtccgcgtt ctaggttaagt tttaagctca ggtcgagacc gggccttgtt ccggggctcc	420
cttggagccct accttagactc agccggctct ccacgcttgc cctgaccctg cttgtcaac	480
tctacgttctt tgtttcgttt tctgttctgc gccgttacag atccaagctg tgaccggcgc	540
ctacctgaga tcacccggca aggagggcca ccatgtacag gatgcacactc ctgtcttgc	600
ttgcactaag tcttgcactt gtcacgaatt cggcacctct cgagcgaaaa tctagtgtcg	660
agtggccacc gtggccagca ccacccgtgg caggaccgtc agtcttccctc ttccccccaa	720
aacccaagga caccctcatg atctcccgga cccctgaggt cacgtgogtg gtggtgacg	780
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aaggccctccc agcccccatac gagaaaacca tctccaaac caaaggccag ccccgagaac	960
cacaggtgta caccctgccc ccatccggg aggagatgac caagaaccag gtcagcctga	1020
cctgccttgtt caaaggcttc taccctcageg acatcgccgt ggagtggag agcaatggc	1080
agccggagaa caactacaag accacgcctc ccacgtgtgg ctccgacggc tccttctcc	1140
tctacagcaa gtcaccgtg gacaagagca ggtggcagca ggggaacgtc ttctcatgt	1200
ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc ctgtctccgg	1260
gtgcacgtac gagcaccgtg gagctgcggg tgagcctcgcc ctcccacctg cgcaagctgc	1320
gtaaagccgtt cctccgcgtt gccgtatgacc tgcagaagtg atatctcgag ctatgtggcc	1380
agacatgata agatacattt atgagtttttgg acaaaccaca actagaatgc agtaaaaaaaa	1440
atgctttattt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt	1500
taaacaagttt aacaacaaca attgcattca ttttatgtttt caggttcagg gggaggtgt	1560
ggaggtttttt taaagcaagt aaaacctcta caaatgtggg atggattaa ttctaaaata	1620
cacccatagca aaacttaac ctccaaatca agccctact tgaatccctt tctgaggat	1680
gaataaggca taggcattcag gggctgttgc caatgtgcatt tagctgtttt cagcctcacc	1740
ttttttcatg gagttttaaga tatagtgtat tttcccaagg tttgaacttag ctcttcattt	1800
ctttatgtttt taaatgtact gaccccccac attccctttt tagtaaaaata ttcaaaaaata	1860
atttaaatac atcattgcaaa tgaaaataaa tgttttttat taggcagaat ccagatgtc	1920
aaggcccttc ataatatccc ccagtttagt agttggactt agggaaacaaa ggaacctta	1980
atagaaattt gacagcaaga aagcgagctt ctatgttatac ctatgttgc ctatgttgc	2040
acaaagtgcg cgcacgttgcc ggccgggtcg cgccaggccgc actccggccc ccacggctgc	2100
tcggccatct cggcgtatggc cggccggag ggcgtccggg agttcggtgg cacgaccc	2160
gaccactcggtt cgtacagctc gtccaggccgc cgccacccaca cccaggccag ggtgtgtcc	2220
ggcaccacccctt ggtccctggac cgccgtatggc aacagggtca cgtcgcccg gaccaccc	2280
ggcaccacccctt ggtccctggac cgccgtatggc aacagggtca cgtcgcccg gaccaccc	2340

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gccaaggcgt cctccacgaa gtcggggag aacccgagcc ggtcggtcca gaactcgacc	2400
gctccggcga cgtcgcgcc ggtgagcacc ggaacggcac tggtaactt ggccatgtg	2460
gctccctctg tcaggagagg aaagagaaga aggttagtac aattgtata gtgagttgt	2520
ttatactatg cagataact atgccaatga ttaattgtca aactagggtgcaggggtca	2580
tagtgccact tttccgtcac tgccccatct cctgcccacc ctttcccagg catagacagt	2640
cagtgaactt ccaaactcac aggagggaga aggacagaac ttgagacaga cccgegggac	2700
cgccgaactg cgaggggacg tggctaggc ggcttcttt atggtgccg ggcctcgga	2760
ggcagggcgc tcggggaggc cttagggcca atctcggtg gcaggaggcg gggccgaagg	2820
ccgtgcctga ccaatccgga gcacatagga gtctcagccc cccgccccaa agcaagggga	2880
agtcacgcgc ctgtagcgcc agcgttgtgt gaaatggggg cttgggggg ttggggccct	2940
gactagtcaa aacaaactcc cattgacgtc aatgggtgg agacttggaa atccccgtga	3000
gtcaaacccgc tatccacgccc cattgatgtc ctgccaaaac cgcacatcatca tggtaatagc	3060
gatgactaat acgttagatgt actgccaagt aggaaagtcc cataagggtca tgtactggc	3120
ataatgccag gggggccatt taccgtcatt gacgtcaata gggggcgtac ttggcatatg	3180
atacacttga tgtactgcca agtggggcagt ttaccgtaaa tactccaccc attgacgtca	3240
atggaaagtc cctattggcg ttactatggg aacatacgcc attattgacg tcaatggcg	3300
ggggtcgttg ggccgtcagc caggccggcc atttaccgtaa agttatgtaa cgcctgcagg	3360
ttaattaaga acatgtgagc aaaaggccag caaaaggccca ggaaccgtaa aaaggccgc	3420
ttgctggcgt tttccatag gctccggccc cctgacgagc atcacaaaaa tcgacgctca	3480
agtcagaggt ggcgaaaccc gacaggacta taaagatacc aggcgtttcc ccctggaaagc	3540
tccctcggtc gtcctctgt tccgaccctg ccgttaccg gatacctgtc cgccttctc	3600
ccttcggaa gcgtggcgct ttctcatagc tcacgctgtaa ggtatctcag ttccgtgt	3660
gtcggtcgct ccaagctggg ctgtgtgcac gaacccccc ttcagccga cgcgtcgcc	3720
ttatccggta actatcgctc tgagtccaaac ccggtaagac acgacttatac gccactggca	3780
gcagccactg gtaacaggat tagcagagcg aggtatgttag gcggtgtac agagttctg	3840
aagtgggtgc ctaactacgg ctacactaga agaacagttatc ttggtatctg cgctctgt	3900
aagccaggtt ctttcggaaa aagagttgtt agctcttgc cccgcaaaaca aaccaccgt	3960
ggtagcggtg gttttttgtt ttgcagcagc cagattacgc gcagaaaaaaa aggatctcaa	4020
gaagatcctt tgatctttt tacggggct gacgctcgt ggaacgaaaaa ctcacgtttaa	4080
gggatttgg tcatggctag ttaattaaca tttaaatcag cggccgcaat aaaatatctt	4140
tattttcatt acatctgtgtt gttgggtttt tgggtgtatc gtaactaaca tacgtctcc	4200
atcaaaaaca aacgaaaacaa aacaaactag caaaataggc tgcggccact gcaagtgcag	4260
gtgccagaac atttctctat cgaa	4284

<210> SEQ ID NO 92  
 <211> LENGTH: 282  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 92

Met	Tyr	Arg	Met	Gln	Leu	Leu	Ser	Cys	Ile	Ala	Leu	Ser	Leu	Ala	Leu
1					5			10				15			

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Val Thr Asn Ser Ala Pro Leu Glu Arg Lys Ser Ser Val Glu Cys Pro  
20 25 30

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro  
35 40 45

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr  
50 55 60

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn  
65 70 75 80

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg  
85 90 95

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val  
100 105 110

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser  
115 120 125

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys  
130 135 140

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu  
145 150 155 160

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe  
165 170 175

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu  
180 185 190

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe  
195 200 205

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly  
210 215 220

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr  
225 230 235 240

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Thr Ser Thr Glu  
245 250 255

Glu Leu Arg Val Ser Leu Ala Ser His Leu Arg Lys Leu Arg Lys Arg  
260 265 270

Leu Leu Arg Asp Ala Asp Asp Leu Gln Lys  
275 280

<210> SEQ ID NO 93  
<211> LENGTH: 4278  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 93

ggatctgcga tcgctccggt gccccgtcagt gggcagagcg cacatcgccc acagtcccc 60  
agaagttggg gggaggggtc ggcaattgaa cgggtgccta gagaagggtgg cgcggggtaa 120  
actggaaag ttagtgcgtg tactggctcc gccttttcc cgagggtgg ggagaaccgt 180  
atataagtgc agtagtcgcc gtgaacgttc ttttcgcaa cgggttgcc gccagaacac 240  
agctgaagct tcgagggct cgcacgtctc cttcacgcgc cggccgcctt acctgaggcc 300  
ggcatccacg ccgggttggat cgcgttctgc cgcctccgc ctgtggtgcc tcctgaactg 360  
cgtccggcgt ctaggttaat tttaaagctca ggtcgagacc gggccttgtt ccggcgctcc 420  
cttggagctt accttagactc agccggctct ccacgcttgc cctgaccctg cttgtcaac 480

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tctacgtctt tgtttcgttt tctgttctgc gccggttacag atccaagctg tgaccggcgc	540
ctacacctgaga tcacccggcga aggagggcca ccatgtacag gatgcaactc ctgtcttgca	600
ttgcactaag tcttgcactt gtcacgaatt cgataagcac cgaggagctg cgggtgcgcc	660
tcgcctccca cctgcgcgaag ctgcgttaago ggctcctccg cgatgcgcgat gacctgcaga	720
agatatacgcc catggttaga tctgtggagt gcccaccttgc cccagcacca cctgtggcag	780
gaccccttca gtttcccttc cccccaaaccc caaggacac cctgtatgtc tccagaaccc	840
ctgagggtcac gtgcgtggtg gtggacgtga gccacgaaga ccccgaggc cagttcaact	900
ggtagcgtgga cggcatggag gtgcataatg ccaagacaaa gccacgggag gaggcgttca	960
acagcacgtt ccgtgtggc acgtcctca ccgtcgtgca ccaggactgg ctgaacggca	1020
aggagtacaa gtgcaaggc tccacaacaa gcttcccagc ccccatcgag aaaaccatct	1080
ccaaaaaccaa agggcagccc cgagaaccac aggtgtacac cctgccccca tcccgagg	1140
agatgaccaa gaaccaggc acgctgaccc gcctggtaaa aggcttctac cccagcgaca	1200
tcgcccgtgga gtggggagac aatgggcagc cggagaacaa ctacaagacc acacccca	1260
tgctggactc cgacggctcc ttcttccttc acagcaagct caccgtggac aagagcagg	1320
ggcagcaggg gaacgtcttc tcatgtctcg tgatgtatgaa ggctctgcac aaccactaca	1380
cacagaagag cctctccctg tctccggta aatgagtgc acggctagct ggccagacat	1440
gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa aaaaatgctt	1500
tatttgtgaa atttgtgatg ctattgtttt atttgtaacc attataagct gcaataaaca	1560
agttaacaac aacaattgca ttcattttat gtttcaggtt cagggggagg tgtgggagg	1620
tttttaaagc aagtaaaacc tctacaaatg tggatggaa ttaattctaa aatacagcat	1680
agcaaaaactt taacccctcaa atcaagcctc tacttgaatc cttttctgag ggtatgtaa	1740
ggcataggca tcaggggctg ttgcaatgt gcattagctg tttgcagcct caccccttt	1800
catggagttt aagatatagt gtatccc aaggtttggaa ctatcttc atttttttat	1860
tttttaaatg cactgaccc ccacattccc ttttagtaa aatattcaga aataattaa	1920
atacatcatt gcaatgaaaa taaatgtttt ttattaggca gaatccagat gctcaaggcc	1980
tttcataata tccccagtt tagtagttgg acttagggaa caaaggaaacc ttaatagaa	2040
attggacagc aagaaaagcga gcttcgtatc tatttcgtt cctgccttc tgccacaag	2100
tgcacgcagt tgccggccgg gtcgcgcagg gcgaactccc gccccacgg ctgcgcgg	2160
atctcggtca tggccggccc ggaggcgtcc cggaaagttcg tggacacgc ctccgaccac	2220
tcggcgtaca gtcgtccag gcccgcacc cacacccagg ccagggtgtt gtccggcacc	2280
acctggctt ggaccgcgtt gatgaacagg gtcacgtcg cccggaccac accggcgaag	2340
tctgtcccca cgaagtcccc ggagaaccccg agccggtcgg tccagaactc gaccgctccg	2400
gcgcacgtcgc ggcgggtgag caccggaaacg gcaactgtca acttggccat gatggctct	2460
cctgtcagga gagggaaagag aagaaggta gtacaattgc tatagtgagt tgtattatac	2520
tatgcagata tactatgcca atgattaatt gtcaaaactag ggctgcagggtt ttcatatgtc	2580
cacttttccct gcaactgcccc atctccctgcc cacccttcc caggcataga cagtcagtga	2640
cttaccaaacc tacacaggagg gagaaggcag aagcttggaa cagaccccg ggaccgcga	2700
actgcggagg gacgtggcta gggcggttc tttatggtg cggccggccct cggaggcagg	2760
gcgcgtcgaaa aggccctagcg gccaatctgc ggtggcagga ggcggggccg aaggccgtgc	2820
ctgaccaatc cggagcacat aggagtctca gccccccgc ccaaagcaag gggaaagtca	2880

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gcccctgtag	cgcacgcgtg	ttgtgaaatg	ggggcttggg	ggggttgggg	ccctgactag	2940
tcaaaaacaaa	ctccccattga	cgtcaatggg	gtggagact	ggaaatcccc	gtgagtcaaa	3000
ccgctatcca	cgcattgtatc	tgtactgc	aaaccgcac	atcatggtaa	tagcgatgac	3060
taatacgtat	atgtactgcc	aatggggaaa	gtcccaataag	gtcatgtact	gggcataatg	3120
ccaggcgggc	catttaccgt	cattgacgtc	aatagggggc	gtacttggca	tatgatacac	3180
ttgatgtact	gccaagtggg	cagtttaccgt	taataactcc	accattgac	gtcaatggaa	3240
agtccttatt	ggcgttacta	tgggaacata	cgtcattatt	gacgtcaatg	ggcgggggtc	3300
gttggggcgt	cagccaggcg	ggccatttac	cgttaagttt	gtacgcctg	caggtaatt	3360
aagaacatgt	gagcaaaagg	ccagcaaaag	gccaggaacc	gtaaaaaggc	cgcgttgctg	3420
gcgttttcc	ataggctccg	ccccctgcac	gagcatcaca	aaaatcgacg	ctcaagtctag	3480
aggtggcgaa	acccgacagg	actataaaga	taccaggcg	ttccccctgg	aagctccctc	3540
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ggaagcgtgg	cgttttctca	tagtcacgc	tgttaggtatc	tcaagttcggt	gttaggtcggt	3660
cgttccaagg	tgggctgtgt	gcacgaaacc	cccggtcagc	ccgacccgtg	cgccttatcc	3720
ggtaactatc	gttttgcgt	caacccggta	agacacgact	tatcgcoact	ggcagcagcc	3780
actggtaaca	ggataggcag	agcggaggat	gtaggcgggt	ctacagagtt	cttgaagtgg	3840
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ggtgtttttt	ttgtttgcaa	gcagcagatt	acgcgcagaa	aaaaaggatc	tcaagaagat	4020
cctttgtatct	tttctacggg	gtctgacgt	cagtggaaac	aaaactcact	ttaagggatt	4080
tttgttcatgg	ctagtttaatt	aacattaaa	tcaagcggcc	caataaaata	tctttat	4140
cattacatct	gtgtgttggt	tttttgtgt	aatcgtaact	aacatacgct	ctccatcaaa	4200
acaaaacgaa	acaaaacaaa	ctagcaaaat	aggctgtccc	cagtcaagt	gcaggtgcca	4260
gaacatttct	ctatcgaa					4278

<210> SEQ ID NO 94  
 <211> LENGTH: 280  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 94

Met	Tyr	Arg	Met	Gln	Leu	Leu	Ser	Cys	Ile	Ala	Leu	Ser	Leu	Ala	Leu
1				5			10					15			

Val	Thr	Asn	Ser	Ile	Ser	Thr	Glu	Glu	Leu	Arg	Val	Arg	Leu	Ala	Ser
				20			25			30					

His	Leu	Arg	Lys	Leu	Arg	Lys	Arg	Leu	Leu	Arg	Asp	Ala	Asp	Asp	Leu
				35			40			45					

Gln	Lys	Ile	Ser	Ala	Met	Val	Arg	Ser	Val	Glu	Cys	Pro	Pro	Cys	Pro
				50			55			60					

Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro
				65			70		75		80				

Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
				85			90			95					

Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val
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100	105	110
Asp	Gly	Met
Glu	Val	His
Asn	Ala	Lys
Thr	Lys	Pro
Arg	Glu	Glu
115	120	125
Phe	Asn	Ser
Thr	Phe	Arg
Val	Val	Ser
Val	Leu	Thr
130	135	140
Asp	Trp	Leu
Asn	Gly	Lys
Glu	Tyr	Lys
Cys	Val	Ser
Asn	Lys	Gly
145	150	155
Leu	Pro	Ala
Pro	Ile	Glu
Lys	Thr	Ile
Ser	Lys	Thr
165	170	175
Arg	Glu	Pro
Pro	Gln	Val
Tyr	Thr	Leu
Leu	Pro	Pro
180	185	190
Lys	Asn	Gln
Val	Ser	Leu
Thr	Cys	Leu
Val	Lys	Gly
195	200	205
Phe	Tyr	Pro
Asp	Ile	Ala
Val	Glu	Trp
Glu	Ser	Asn
Gly	Gln	Pro
210	215	220
Lys	Thr	Thr
Pro	Pro	Met
Leu	Asp	Ser
Asp	Gly	Ser
Phe	Phe	Leu
225	230	235
Ser	Lys	Leu
Thr	Val	Asp
Lys	Ser	Arg
Trp	Gln	Gln
Gly	Asn	Val
245	250	255
Ser	Cys	Ser
Val	Met	His
Glu	Ala	Leu
His	Asn	His
Tyr	Thr	Gln
260	265	270
Ser	Leu	Ser
Leu	Ser	Pro
Gly	Lys	
275	280	

&lt;210&gt; SEQ ID NO 95

&lt;211&gt; LENGTH: 4278

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 95

ggatctgcga	tcgctccgggt	gcccgtagt	gggcagagcg	cacatgcgcc	acagtccccg	60
agaagttggg	gggagggggtc	ggcaattgaa	cgggtgccta	gagaagggtgg	cgcggggtaa	120
actggaaag	tgtatgtcggt	tactggctcc	gccttttcc	cgagggtggg	ggagaaccgt	180
atataaagtgc	agtagtcgccc	gtgaacgttc	ttttcgcaa	cgggttgcc	gccagaacac	240
agctgaagct	tcgaggggct	cgcacatctc	cttcacgcgc	ccggccgcct	acctgaggcc	300
ccatccacg	ccgggtttagt	cgcgttctgc	cgcctccgc	ctgtggtggc	tcctgaactg	360
cgtccgcgt	ctaggtaagt	ttaaagctca	ggtcgagacc	gggcctttgt	ccggcgctcc	420
cttggagccct	accttagactc	agccggctct	ccacgcttgc	cctgaccctg	cttgctcaac	480
tctacgttct	tgttctgttt	tctgttctgc	gccgttacag	atccaagctg	tgaccggcgc	540
ctacctgaga	tcacccggcga	aggaggggcca	ccatgtacag	gatgcaactc	ctgtttgca	600
ttgcactaag	tcttgcactt	gtcacgaatt	cgataagcac	cgaggagctg	cggttgagcc	660
tcgcctccca	cctgcgcgaag	ctgcgttccgc	ggctcctccg	cgatgccat	gacctgcaga	720
agatatacgcc	catgggtttaga	tctgtggagt	gcccaccttgc	cccagcacca	cctgtggcag	780
gacccatgtt	cttcctcttc	ccccaaaaac	ccaaggacac	cctgtatgtc	tccagaaccc	840
ctgagggtcac	gtgcgtgggt	gtggacgtga	gccacgaaga	ccccggggc	cagttcaact	900
ggtaacgttga	cggcatggag	gtgcataatg	ccaagaca	gccacggggag	gagcagtca	960
acagcacgtt	ccgtgtggc	agcgtcctca	ccgtcgtgca	ccaggactgg	ctgaacggca	1020

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aggagtacaa gtgcaaggc tccaaacaaag gcctcccagc ccccatcgag aaaaccatct	1080
ccaaaaccaa agggcagccc cgagaaccac aggtgtacac cctgccccca tcccggagg	1140
agatgaccaa gaaccaggc acgcgtaccc gcctggtaaa aggcttctac cccagcgaca	1200
tccggctgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc acaccccca	1260
tgctggactc cgacggctcc ttcttcctct acagcaagct caccgtggac aagagcagg	1320
ggcagcggg gAACGCTTC tcatgctcc tgatgcata ggctctgcac aaccactaca	1380
cacagaagag cctctccctg tctccggta aatgagtgcc acggctagct ggccagacat	1440
gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa aaaaatgctt	1500
tatttgtgaa atttgtgatg ctattgtttt atttgtaacc attataagct gcaataaaca	1560
agttaacaac aacaattgca ttcattttat gtttcaggtt cagggggggg tgggggggt	1620
tttttaaagc aagtaaaacc tctacaaatg tggtatggaa ttaattctaa aatacagcat	1680
agaaaaactt taacctccaa atcaaggcctc tacttgaatc cttttctgag ggtgaataa	1740
ggcataggca tcaggggctg ttgcoaatgt gcattagctg tttgcagcct cacttcttt	1800
catggagttt aagatatagt gtatccc aagggttggaa ctagcttcc atttctttat	1860
gttttaatg cactgaccc tcacattccc ttttagtaa aatattcaga aataatttaa	1920
atacatcatt gcaataaaaaa taaatgtttt ttattaggca gaatccagat gctcaaggcc	1980
cttcataata tccccagtt tagtagttgg acttagggaa caaaggaacc tttatagaa	2040
attggacagc aagaaagcga gcttctagct tatcctcagt cctgctcc tcggcacaaaag	2100
tgcacgcagt tgcggccgg gtcgcgcagg gcgaactccc gccccacgg ctgctccgg	2160
atctcggtca tggccggccc ggaggcggtcc cggaaagttc tggacacgg ctccgaccac	2220
tcggcgtaca gctgtccag gccgcgcacc cacacccagg ccagggtgtt gtccggcacc	2280
acctggctt ggaccccgct gatgaacagg gtcacgttgtt cccggaccac accggcgaag	2340
tgcgtccca cgaagtcggc ggagaaccccg agccggctcg tccagaactc gaccgctccg	2400
gacacgtcgc ggcgggtgag cacccggaaac gcactggtaa acttggccat gatggctcct	2460
cctgtcagga gagaaagag aagaaggta gtacaattgc tatagtgagt tgtattatac	2520
tatgcagata tactatgcca atgattaatt gtcaaaactag ggctgcagggtt ttcatagtgc	2580
cactttctt gcaactgcccc atctctgtcc cacccttcc caggcataga cagtcaatgc	2640
cttaccaaac tcacaggagg gagaaggcag aagcttgaga cagaccccg ggaccggcga	2700
actgcgaggg gacgtggcta gggccggcttc ttttatggtg cgccggccct cggaggcagg	2760
gacgtcgcccc aggccctagcg gcaaatctgc ggtggcaggaa ggccggcccg aaggccgtgc	2820
cttaccaatcc cggagcacat aggagtctca gccccccgc ccaaagcaag gggaaagtac	2880
gcccctgtcg cgcacgtgt ttgtgaaatg ggggttgggg ggggttgggg ccctgactag	2940
tcaaaaacaaa ctccccattga cgtcaatggg gtggagactt ggaaatcccc gtgagtcaaa	3000
ccgttatcca cggccattga ttttactgcca aaaccgcacat atcatggtaa tagcgatgc	3060
taatacgtatgtactgccc aatggggggc gtacttggca tatgatacac	3120
ccaggcgggc catttaccgt catttgcgtc aataggggggc gtacttggca tatgatacac	3180
ttgtatgtact gccaagggtgg cagtttaccgt taaatactcc acccatttgc gtcataatggaa	3240
agtccctatt ggcgttacta tggaaacata cgtcatttatt gacgtcaatg ggcgggggtc	3300
gttgggggtt cagccaggcgc ggccattttac cgtaagttat gtaacgcctg caggtaatt	3360

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aagaacatgt gagcaaaagg ccagcaaaag gccaggaacc gtaaaaaggc cgcggtgctg	3420
gcgttttcc ataggctcg cccccctgac gagcatcaca aaaatcgacg ctcaagttag	3480
aggtggcgaa acccgacagg actataaaga taccaggegt ttccccctgg aagctccctc	3540
gtgcgccttc ctgttccgac cctgccgtt accggatacc tgtccgcctt tctccctcg	3600
ggaagcgtgg cgcttctca tagtcacgc tgtaggtatc tcagttcggt gtaggtcggt	3660
cgcctcaagc tgggctgtgt gcacgaaacc cccgttcagc cgcacggctg cgccttatcc	3720
ggtaactatc gtcttgagtc caacccggta agacacgact tatcgccact ggcagcagcc	3780
actggtaaca ggattagcag agcgaggat gtaggcgggt ctacagagtt cttgaagtgg	3840
tggcctaact acggctacac tagaagaaca gtatttggta tctgcgtct gctgaaggcca	3900
tttacccctcg gaaaaagagt tggtagctct tgatccggca aacaaaccac cgctggtagc	3960
ggtggttttt ttgttgcaa gcagcagatt acgcgcagaa aaaaaggatc tcaagaagat	4020
cctttgtatct tttctacggg gtctgacgct cagtggaacg aaaactcacg ttaaggatt	4080
tttggatggat ctagttattt aacatttaaa tcagcggccg caataaaata tctttatattt	4140
cattacatct gtgtgttggt tttttgtgtg aatcgtaact aacatacgct ctccatcaaa	4200
acaaaacgaa acaaaacaaa ctagcaaat aggctgtccc cagtgcaagt gcaggtgcca	4260
gaacatttct ctatcgaa	4278

&lt;210&gt; SEQ ID NO 96

&lt;211&gt; LENGTH: 280

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 96

Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu			
1	5	10	15

Val Thr Asn Ser Ile Ser Thr Glu Glu Leu Arg Val Ser Leu Ala Ser			
20	25	30	

His Leu Arg Lys Leu Arg Lys Arg Leu Leu Arg Asp Ala Asp Asp Leu			
35	40	45	

Gln Lys Ile Ser Ala Met Val Arg Ser Val Glu Cys Pro Pro Cys Pro			
50	55	60	

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro			
65	70	75	80

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val			
85	90	95	

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val			
100	105	110	

Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln			
115	120	125	

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln			
130	135	140	

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly			
145	150	155	160

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro			
165	170	175	

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr			
180	185	190	

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Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
195															205

Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr
210															220

Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
225															240

Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe
245															255

Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys
260															270

Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
275							280

&lt;210&gt; SEQ\_ID NO 97

&lt;211&gt; LENGTH: 6773

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 97

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ttgactagtt	atataatagta	atcaattacg	gggtcattag	ttcatagccc	atatatggag	120
ttccgcgtta	cataacttac	ggtaaatggc	ccgcctggct	gaccgcocaa	cgacccccgc	180
ccattgacgt	caataatgac	gtatgttccc	atagtaacgc	caataggac	tttccatgt	240
cgtcaatggg	tggagtattt	acggtaaact	gcccaactgg	cagtagatca	agtgtatcat	300
atgccaagta	cgccccctat	tgacgtcaat	gacggtaataat	ggcccgctg	gcattatgcc	360
cagtagatga	ccttatggga	ctttctact	tggcagttaca	tctacgtatt	agtcatcgct	420
attaccatgg	tgtatgeggtt	ttggcagttac	atcaatgggc	gtggatagcg	gtttgactca	480
cggggatttc	caagtctcca	ccccattgac	gtcaatggga	gtttgttttgc	acccaaaaat	540
caacgggact	ttccaaatgt	tcgtaacaac	tccggcccat	tgacgcaaat	gggcggtagg	600
cgtgtacggt	gggaggtcta	tataaggaga	gctcgtttag	tgaacccgtca	gatcgctgg	660
agacgcccattc	cacgctgttt	tgacctccat	agaagacacc	gggacccatgc	cagcctccgg	720
actcttagagg	atcgaaaccct	taagcttgc	accatgtaca	ggatgcaact	cctgtctgc	780
attgcactaa	gtcttgact	tgtcacgaat	tcagacaacg	tgcgtacaca	gagccctgcc	840
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gactacgacg	gcgacagacta	catgaactgg	tatcagcaga	agccggccca	gccacctaag	960
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aaatctggaa	ctgcctctgt	tgtgtgcctg	ctgaataact	tctatccatg	agaggccaaa	1260
gtacagtggaa	aggtggataa	cgcctccaa	tcgggtaact	cccaggagag	tgtcacagag	1320
caggacagca	aggacagcac	ctacagccctc	agcagcaccc	tgacgtcgag	caaaggccac	1380
tacgagaaac	acaaagtcta	cgcctgcgaa	gtcacccatc	agggcctgag	ctcgcccgtc	1440
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aggcaacgtg	gctgtgtgtg	cactgtgttt	gctgacgcaa	ccccactgg	ttggggcatt	1800
gccaccacat	gtcagtcct	ttceggact	ttcgctttcc	ccctccctat	tgccacggcg	1860
gaactcatcg	ccgcctgcct	tgcgcgtgc	tggacagggg	ctcgctgtt	gggcactgac	1920
aattccgtgg	tgttgtcggt	gaagtgacg	tcctttccat	ggctgtcgc	ctgtgttgcc	1980
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taattctgtg	gaatgtgtgt	cagttagggt	gtggaaagtc	cccaggctcc	ccagcaggca	2940
gaagtatgca	aagcatgcat	ctcaatttgc	cagcaaccag	gtgtggaaag	tccccaggct	3000
ccccagcagg	cagaagttatg	caaagcatgc	atctcaatta	gtcagcaacc	atagtccgc	3060
cccttaactcc	gccccatcccc	ccccctactc	cgcccagttc	cgccccattt	ccgccccatg	3120
gctgactaat	ttttttattt	tatgcagagg	ccgaggccgc	ctctgcctct	gagctattcc	3180
agaagtagtg	aggaggcttt	tttggaggcc	taggtttttg	caaaaagctc	ccggggagctt	3240
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aagatggatt	gcacgcaggt	tctccggccg	cttgggtggaa	gaggctattt	ggctatgact	3360
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ggctcgcc	agccgaactg	ttcgccaggc	tcaaggcgcg	catgcccgc	ggcgaggatc	3840
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ctggattcat cgactgtggc cggctgggtg tggcggaccg ctatcaggac atagcgttgg 3960  
 ctacccgtga tattgtgaa gagctggcg gcgaatgggc tgaccgcttc ctcgtgttt 4020  
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 aggaacccgtaa aaaaggccgc gttgtggcgt tttttccata ggctccgccc ccctgacgg 4860  
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 ggataacctgtt cccctttctt cccttcgggaa agegtggcgt tttctcaatg ctcacgctgt 5040  
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 gttcagcccg accgctgcgc cttatccgtt aactatcgctc ttgagtccaa cccggtaaga 5160  
 cacgacttat cgcactggc agcagccact ggtaacaggta ttagcagacg gaggtatgt 5220  
 ggcgggtcta cagagttctt gaagttggcgtt cctaactacg gctacactag aaggacagta 5280  
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 tccggcaaac aaaccaccgc tggtagcggg ggttttttgc tttgcaagca gcagattacg 5400  
 cgcagaaaaaa aaggatctca agaagatctt ttgatctttt ctacgggtc tgacgctcag 5460  
 tggAACAAA actcacgatc agggattttgcgtt gtcgttgcgtt tatcaaaaag gatcttcacc 5520  
 tagatccttt taaattaaaa atgaatctt aaatcaatctt aaagttatata tgagtaact 5580  
 tggtctgaca gttaccaatg cttatcaatgtt gaggcaccta ttcgttgcgtt ctgttctt 5640  
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 tcagcaataa accagccagc cggaaaggcc gaggcgcggaa gtggcgttgc aactttatcc 5820  
 gcctccatcc agtcttattaa ttgttgcggg gaagcttagag taagtagtgc ggcagttat 5880  
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 gtgttatcatc tcaatgggtat ggcagactg cataattctc ttactgtcat gccatccgt 6120  
 agatgctttt ctgtgtactgg tgagttactca accaagtcat tctgagaata gtgtatgcgg 6180  
 cgaccgagtt gtccttgccc ggcgtcaata cggataataa cgcgcacaca tagcagaact 6240

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ttaaaaagtgc tcatcatggg	aaaacgttct tcggggcgaa	aactctcaag gatcttaccg	6300
ctgttgagat ccagttcgat	gtaacccact cgtgcaccca	actgatctc agcatcttt	6360
actttcacca gcgttctgg	gtgagaaaa acaggaaggc	aaaatgccgc aaaaaaggga	6420
ataagggcga cacggaaatg	ttgaataactc atactcttc	ttttcaata ttattgaagc	6480
atttatcagg gttattgtct	catagcgga tacatattt	aatgtattta gaaaaataaa	6540
caaatagggg ttccgegcac	atttccccga aaagtgcac	ctgacgtcga cgatcgaaa	6600
gatctccgaa tcccctatgg	tcgactctca gtacaatctg	ctctgatgcc gcatagttaa	6660
gccgatctc gtcctctgt	tgtgttgtgg aggtcgctga	gtatgtcgcg agcaaaattt	6720
aagctacaac aaggcaaggc	ttgaccgaca attgcatgaa	aatctgctt agg	6773

&lt;210&gt; SEQ\_ID NO 98

&lt;211&gt; LENGTH: 7452

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 98

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ttgactagtt attaatagta	atcaattacg gggtcattag	ttcatagccc atatatggag	120
ttccgcgtta cataacttac	ggtaaatggc ccgcctggct	gaccgcocaa cgaccccccgc	180
ccattgcacgt caataatgac	gtatgttccc atagaacgc	caatagggac tttccatgaa	240
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atgccaagta cgccccctat	tgacgtcaat gacggtaataa	ggccgcctg gcattatgcc	360
cagtagatca ctttatggga	ctttctact tggcagtaca	tctacgtatt agtcatcgct	420
attaccatgg ttagtgggtt	ttggcagtac atcaatgggc	gtggatagcg gtttgactca	480
cggggatttc caagtctcca	ccccattgac gtcaatggga	gtttgttttgcacaaaaat	540
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ggtgttgttc agcctggcg	atctctgaag ctgagctgt	ccgcccagcg cttcacctt	900
agcagctaca caatgagctg	ggtccgacag acccctgaga	agagactgg aatgggtcgcc	960
aaagatccgga acggcgagg	catcacctac tacctggata	ccctgaaggg cagattcacc	1020
atcagccggg acaacgccaa	gaacaccctg tacctgcaga	tgagcagcct gaagtccgag	1080
gacaccgcca tctacttttgc	cgccagacac tactacggca	gcgaggacta cttcgactat	1140
tggggccagg gcaccacact	gaccgttagc tctgctagca	ccaagggccc atcggtttc	1200
ccctggcgcc cttgcgtccag	gagcacctcc gagagcaca	cgccctggg ctgcgtggc	1260
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gtgcacacact tcccagctgt	cctacagtc tcaggactct	actccctcag cagcgtgg	1380
accgtgcctt ccagcaactt	cggcacccag acctacac	gcaacgtaga tcacaagccc	1440
agcaacacca aggtggacaa	gacagtttag cgcacaaatgtt	gtgtcgagtg cccaccgtgc	1500

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**251****252**

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ccacgggaggc agcagttcaa cagcacgttc cgtgtggta cggtcctcac cggtgtgcac	1740
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cccatcgaga aaaccatctc caaaaacccaa gggcagcccc gagaaccaca ggtgtacacc	1860
ctgccccat cccgggagga gatgaccaag aaccaggctca gcctgacctg cctggtaaaa	1920
ggcttctacc ccagcgacat cgccgtggag tggagagca atgggcagcc ggagaacaac	1980
tacaagacca cgcctccat gctggactcc gacggctctc tcttctctca cagcaagctc	2040
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gctctgcaca accactacac gcagaagago ctctccctgt ctccggtaaa atgaccttagc	2160
gtggcatctca gacactctcg agaagggttc gatccctacc ggtagtaat gagttgata	2220
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**257****258**

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What is claimed is:

1. An isolated antibody or antigen binding domain thereof that binds to Apolipoprotein E (ApoE), wherein the antibody or antigen binding domain thereof comprises a heavy chain variable region (VH) comprising a VHCDR1, a VHCDR2, and a VHCDR3; and a light chain variable region (VL) comprising a VLCDR1, a VLCDR2, and a VLCDR3, wherein the VHCDR1, the VHCDR2, the VHCDR3, the VLCDR1, the VLCDR2, and the VLCDR3 comprise the amino acid sequences of SEQ ID NOS: 17, 18, 19, 14, 15, and 16, respectively.

2. The antibody or antigen binding domain thereof of claim 1, wherein the antibody or antigen binding domain thereof binds to an epitope that comprises or consists of the amino acid sequence TEELRVRLASHLRK (SEQ ID NO:3).

3. The antibody or antigen binding domain thereof of claim 1, wherein the antibody or antigen binding domain thereof binds to one or more HSPG-binding sites of ApoE2, ApoE3, or ApoE4.

4. The antibody or antigen binding domain thereof of claim 1, wherein the antibody or antigen binding domain thereof does not bind to a mutant ApoE protein comprising the amino acid sequence TEELRVSLASHLRK (SEQ ID NO: 2).

5. The antibody or antigen binding domain thereof of claim 4, wherein the antibody or antigen binding domain thereof binds to an epitope that comprises or consists of the amino acid sequence TEELRVRLASHLRK (SEQ ID NO:3).

6. The antibody or antigen binding domain thereof of claim 1, wherein the antibody or antigen binding domain thereof competes with and/or binds a same epitope as a reference anti-ApoE antibody comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL of the reference antibody comprise: (i) the amino acid sequence of SEQ ID NO: 13 and the amino acid sequence of SEQ ID NO:12, respectively; (ii) the amino acid sequence of SEQ ID NO:22 and the amino acid sequence of SEQ ID NO:23, respectively; (iii) the amino acid sequence of SEQ ID NO:33 and the amino acid sequence of SEQ ID NO:32, respectively; or (iv) the amino acid sequence of SEQ ID NO:43 and the amino acid sequence of SEQ ID NO:42, respectively.

7. The antibody or antigen binding domain thereof of claim 1, wherein the antibody or antigen binding domain thereof comprises a mouse IgG1, IgG2a, IgG2b, IgG2c, or IgG3 heavy chain constant region.

8. The antibody or antigen binding domain thereof of claim 1, wherein the antibody or antigen binding domain thereof is an antibody and comprises a human IgG1, IgG2, IgG3, or IgG4 heavy chain constant region.

9. The antibody or antigen binding domain thereof of claim 1, wherein the antibody or antigen binding domain thereof comprises a human kappa or human lambda light chain constant region.

10. The antibody or antigen binding domain thereof of claim 1, wherein the antibody is a whole antibody, a monoclonal antibody, a humanized antibody, or a chimeric antibody, and wherein the antigen-binding domain is a Fv, a scFv, an sc(Fv)2, an Fab, or an F(ab')2.

11. The antibody or antigen binding domain thereof of claim 1, further comprising one or more of: a half-life extending moiety, a blood-brain barrier penetrating moiety, or a detectable label.

12. A pharmaceutical composition comprising the antibody or antigen binding domain thereof of claim 1.

13. An anti-ApoE antibody or antigen binding domain thereof comprising a VH comprising VHCDR1, VHCDR2, and VHCDR3, and a VL comprising VLCDR1, VLCDR2, and VLCDR3, wherein the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences of SEQ ID NOS: 17, 18, 19, 14, 15, and 16, respectively.

14. The antibody or antigen binding domain thereof of claim 13, wherein the VH comprises the amino acid sequence that is at least 80% identical to the amino acid sequences of SEQ ID NO: 22 and comprises VHCDR1, VHCDR2 and VHCDR3 having the amino acid sequences of SEQ ID NOS: 17, 18 and 19, respectively; and the VL comprises the amino acid sequence that is at least 80% identical to the amino acid sequence of SEQ ID NO:23 and comprises VLCDR1, VLCDR2 and VLCDR3 having the amino acid sequences of SEQ ID NOS: 14, 15 and 16, respectively.

15. The antibody of claim 14, wherein the VH comprises the amino acid sequence with at least 90% sequence identity to the amino acid sequences of SEQ ID NO: 22 and comprises VHCDR1, VHCDR2 and VHCDR3 having the

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amino acid sequences of SEQ ID NOs: 17, 18 and 19, respectively; and the VL comprises the amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO:23 and comprises VLCDR1, VLCDR2 and VLCDR3 having the amino acid sequences of SEQ ID NOs: 14, 15 and 16, respectively.

**16.** The antibody or antigen binding domain thereof of claim **13**, wherein (i) the VH comprises the amino acid sequence with at least 80% sequence identity to amino acids 20-139 of the amino acid sequence of SEQ ID NO: 22 and comprises VHCDR1, VHCDR2 and VHCDR3 having the amino acid sequences of SEQ ID NOs: 17, 18 and 19, respectively; and (ii) the VL comprise the amino acid sequence with at least 80% sequence identity to amino acids 21-131 of the amino acid sequence of SEQ ID NO: 23 and comprises VLCDR1, VLCDR2, and VLCDR3 having the amino acid sequences of SEQ ID NOs: 14, 15 and 16, respectively.

**17.** The antibody or antigen binding domain thereof of claim **16**, wherein (i) the VH comprises the amino acid sequence with at least 90% sequence identity to amino acids 20-139 of the amino acid sequence of SEQ ID NO: 22 and comprises VHCDR1, VHCDR2 and VHCDR3 having the amino acid sequences of SEQ ID NOs: 17, 18 and 19, respectively; and (ii) the VL comprise the amino acid sequence with at least 90% sequence identity to amino acids 21-131 of the amino acid sequence of SEQ ID NO: 23 and

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comprises VLCDR1, VLCDR2, and VLCDR3 having the amino acid sequences of SEQ ID NOs: 14, 15 and 16, respectively.

**18.** The antibody or antigen binding domain thereof of claim **17**, wherein (i) the VH comprises the amino acid sequence with at least 95% sequence identity to amino acids 20-139 of the amino acid sequence of SEQ ID NO: 22 and comprises VHCDR1, VHCDR2 and VHCDR3 having the amino acid sequences of SEQ ID NOs: 17, 18 and 19, respectively; and (ii) the VL comprise the amino acid sequence with at least 95% sequence identity to amino acids 21-131 of the amino acid sequence of SEQ ID NO: 23 and comprises VLCDR1, VLCDR2 and VLCDR3 having the amino acid sequences of SEQ ID NOs: 14, 15 and 16, respectively.

**19.** The antibody or antigen binding domain thereof of claim **18**, wherein (i) the VH comprises the amino acid sequence of amino acids 20-139 of the amino acid sequence of SEQ ID NO: 22, and (ii) the VL comprise the amino acid sequence of amino acids 21-131 of the amino acid sequence of SEQ ID NO: 23.

**20.** An isolated polynucleotide or polynucleotides encoding the antibody or antigen binding domain thereof of claim **1**.

**21.** A vector or vectors comprising the polynucleotide or polynucleotides of claim **20**.

**22.** An isolated host cell comprising the vector or vectors of claim **21**.

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