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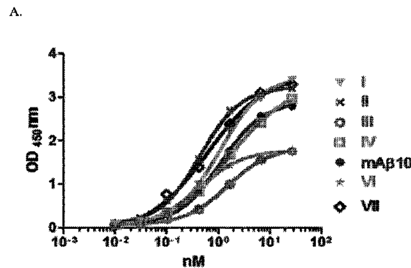
(54) **Titre : ANTICORPS ANTI-ABETA ET LEURS UTILISATIONS**
(54) **Title: ANTI-ABETA ANTIBODIES AND USES THEREOF**

A.



B.

$A\beta_{1-42}$ DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO: 28)

SEQ ID NO: 29 1. biotin- DAEFRHDSGYGSG
SEQ ID NO: 30 2. biotin- SGSGEFRHDSGYEV
SEQ ID NO: 31 3. biotin- SGSGRHDSGYEVHH
SEQ ID NO: 32 4. biotin- SGSGDSGYEVHHQK
SEQ ID NO: 33 5. biotin- SGSGGYEVHHQKLV
SEQ ID NO: 34 6. biotin- SGSGEVHHQKLVFF
SEQ ID NO: 35 7. biotin- SGSGHHQKLVFFAE
SEQ ID NO: 36 8. biotin- SGSG QKLVFFAEDV
SEQ ID NO: 37 9. biotin- SGSG LVFFAEDVGS
SEQ ID NO: 38 10. biotin- SGSG FFAEDVGSNK
SEQ ID NO: 39 11. biotin- SGSG AEDVGSNKGA
SEQ ID NO: 40 12. biotin- SGSG DVGSNKGAIIG
SEQ ID NO: 41 13. biotin- SGSG GSNKGAIIGLM
SEQ ID NO: 42 14. biotin- SGSG NKGAIIGLMVG
SEQ ID NO: 43 15. biotin- SGSG GAIIGLMVGGV
SEQ ID NO: 44 16 biotin- SGSG IIGLMVGGVV
SEQ ID NO: 45 17. biotin- SGSGGLMVGGVVIA

C.

Antibodies /isotype	CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
I/IgG2a	SEQ ID NO: 1 CRSSQTIVHSNGNTYLE	SEQ ID NO: 2 KVSNRFS	SEQ ID NO: 3 FQGSHVPLT	SEQ ID NO: 4 TSGMNVG	SEQ ID NO: 5 HIWWDDDKYYNPSLKS	SEQ ID NO: 6 RR**SIR--GSDYFDY**
II/IgG1	SEQ ID NO: 7 CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 8 FQGSLVPLT	SEQ ID NO: 9 TSGMGVG	HIWWDDDKYYNPSLKS	SEQ ID NO: 10 RR**ALRNVVADAMDY**
III/IgG3	CRSSQSIVHSNGNTYLE	KVSNRFS	FQGSHVPLT	SEQ ID NO: 11 TSAVGVS	SEQ ID NO: 12 HIYWDDDKRYNPSLKS	SEQ ID NO: 13 RR**PYYRYDVDAMDY**
IV/IgG2b	SEQ ID NO: 14 CRSSQNIVHSNGNTYLE	SEQ ID NO: 15 TVSNRFS	FQGSHVPLT	SEQ ID NO: 16 SSVLGVS	SEQ ID NO: 17 HIYWDDDRRYNPSLKS	SEQ ID NO: 18 RR**GKMGRGLDAMDY**
V(mAβ-10)/IgG2a	CRSSQNIVHSNGNTYLE	TVSNRFS	FQGSHVPLT	SSVLGVS	SEQ ID NO: 19 HIYWDDDRRYNPSLRS	SEQ ID NO: 20 RR**GKMGRGLDALDF**
VI/IgG2b	CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 21 FQGSRVPLT	TSGMGVG	SEQ ID NO: 22 HIWWDDDKYFNPSLKS	SEQ ID NO: 23 RR**SLK--WLDAMDY**
VII/IgG1	CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 24 FQSSRVPLT	SEQ ID NO: 25 TSGMGVS	SEQ ID NO: 26 HIYWDDDKSYNPSLKS	SEQ ID NO: 27 RR**RNW-VITDAMEY**

(57) **Abrégé/Abstract:**
An isolated antibody, comprising a light-chain CDR1 (L-CDR1) having the sequence of SEQ ID NO: 1, SEQ ID NO: 7, or SEQ ID NO: 14; a light-chain CDR2 (L-CDR2) having the sequence of SEQ ID NO: 2 or SEQ ID NO: 15; a light-chain CDR3 (L-CDR3) having the sequence of SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 21, or SEQ ID NO: 24; a heavy-chain CDR1 (H-CDR1) having the sequence of SEQ ID NO: 4, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 16, or SEQ ID NO: 25; a heavy-chain CDR2 (H-CDR2) having the sequence of SEQ ID NO: 5, SEQ ID NO: 12, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 22, or SEQ ID NO: 26; and a heavy-chain CDR3 (H-CDR3) having the sequence of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 23, or SEQ ID NO: 27, wherein the antibody specifically binds to $A\beta_{1-42}$ or an N-terminal modified form thereof.

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A61P 25/28 (2006.01) *C07K 16/46* (2006.01)

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(72) Inventors: **SHIE, Feng-Shiun**; No. 35 Keyan Road, Zhunan Town, Miaoli County 35053 (TW). **HSU, Tsu-An**; No. 35 Kean Road, Zhunan Town, Miaoli County 35053 (TW). **SHEN, Santai**; No. 31 Huaxing Street, Toufen City Miaoli County 35163 (TW).

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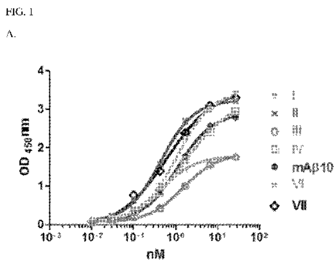
(54) Title: ANTI-ABETA ANTIBODIES AND USES THEREOF

(57) Abstract: An isolated antibody, comprising a light-chain CDR1 (L-CDR1) having the sequence of SEQ ID NO: 1, SEQ ID NO: 7, or SEQ ID NO: 14; a light-chain CDR2 (L-CDR2) having the sequence of SEQ ID NO: 2 or SEQ ID NO: 15; a light-chain CDR3 (L-CDR3) having the sequence of SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 21, or SEQ ID NO: 24; a heavy-chain CDR1 (H-CDR1) having the sequence of SEQ ID NO: 4, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 16, or SEQ ID NO: 25; a heavy-chain CDR2 (H-CDR2) having the sequence of SEQ ID NO: 5, SEQ ID NO: 12, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 22, or SEQ ID NO: 26; and a heavy-chain CDR3 (H-CDR3) having the sequence of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 23, or SEQ ID NO: 27, wherein the antibody specifically binds to $A\beta_{1-42}$ or an N-terminal modified form thereof.

FIG. 1

A.



B.

$A\beta_{1-42}$ DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO: 28)

SEQ ID NO: 29 1. biotin- DAEFRHDSGYGSG
SEQ ID NO: 30 2. biotin- SGSGEFRHDSGYEV
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SEQ ID NO: 32 4. biotin- SGSGDSGYEVHHQK
SEQ ID NO: 33 5. biotin- SGSGGYEVHHQKLV
SEQ ID NO: 34 6. biotin- SGSGEVHHQKLVFF
SEQ ID NO: 35 7. biotin- SGSGHHQKLVFFAE
SEQ ID NO: 36 8. biotin- SGSG QKLVFFAEDV
SEQ ID NO: 37 9. biotin- SGSG LVFFAEDVGS
SEQ ID NO: 38 10. biotin- SGSG FFAEDVGSNK
SEQ ID NO: 39 11. biotin- SGSG AEDVGSNKGA
SEQ ID NO: 40 12. biotin- SGSG DVGSNKGAIIG
SEQ ID NO: 41 13. biotin- SGSG GSNKGAIIGLM
SEQ ID NO: 42 14. biotin- SGSG NKGAIIGLMVG
SEQ ID NO: 43 15. biotin- SGSG GAIIGLMVGGV
SEQ ID NO: 44 16 biotin- SGSG IIGLMVGGVV
SEQ ID NO: 45 17. biotin- SGSGGLMVGGVVIA

C.

Antibodies /isotype	CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
I/IgG2a	SEQ ID NO: 1 RSSQTIVHSNGNTYLE	SEQ ID NO: 2 KVSNRFS	SEQ ID NO: 3 FQGSHVPLT	SEQ ID NO: 4 TSGMGVG	SEQ ID NO: 5 HIWWDDDKYYNPSLKS	SEQ ID NO: 6 RRSIR--GSLYFDY
II/IgG1	SEQ ID NO: 7 RSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 8 FQGSLVPLT	SEQ ID NO: 9 TSGVGVG	HIWWDDDKYYNPSLKS	SEQ ID NO: 10 RR**ALRNVVALAMD**Y
III/IgG3	RSSQAIVHSNGNTYLF	KVSNRFS	FQGSHVPLT	SEQ ID NO: 11 TSAVGVS	SEQ ID NO: 12 HIYWDDDSRYNPSLKS	SEQ ID NO: 13 RR**PYYRYDVLAMD**Y
IV/IgG2b	SEQ ID NO: 14 RSSQNIVHSNGNTYLE	SEQ ID NO: 15 IVSNRFS	FQGSHVPLT	SEQ ID NO: 16 SSVLGVS	SEQ ID NO: 17 HIYWDDDSRYNPSLKS	SEQ ID NO: 18 RR**GKMGRGLLAMD**Y
V (mAβ-10) /IgG2a	RSSQNIVHSNGNTYLE	IVSNRFS	FQGSHVPLT	SSVLGVS	SEQ ID NO: 19 HIYWDDDRRYNPSLKS	SEQ ID NO: 20 RR**GKMGRGLDALDF**
VI/IgG2b	RSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 21 FQGSRVPLT	TSGMGVG	SEQ ID NO: 22 HIWWDDDKYYNPSLKS	SEQ ID NO: 23 RR**SLK--WLLAMD**Y
VII/IgG1	RSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 24 FQGSRVPLT	SEQ ID NO: 25 TSGMGVS	SEQ ID NO: 26 HIYWDDDKSYNPSLKS	SEQ ID NO: 27 RR**RNW VITLAME**Y

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ANTI-Abeta ANTIBODIES AND USES THEREOF

5

BACKGROUND

Alzheimer's Disease (AD) is characterized clinically by progressive memory
10 loss and cognitive dysfunction. Extracellular senile amyloid plaques constituted predominantly of Aβ are some of its pathological hallmarks. See, e.g., Wang et al., Nat Rev Neurol. 2017, 13(10):612-623. The majority of AD cases are sporadic and the etiology of AD remains largely unclear due to its multiplicity of disease origin. Current treatments targeting temporary symptomatic relief do not cure the disease.

15 In AD, Aβ deposits in the brain instigate pro-inflammatory modes of glial activation and the uncontrolled accumulation of Aβ exacerbates the consequential neuro-inflammation and promotes Tau hyper-phosphorylation, leading to neuronal loss. To date, there is no cure for this devastating disease. Among many disease-modifying approaches, passive immunotherapy using antibody against Aβ is a
20 promising approach to prevent or delay the pathogenesis of AD. See, e.g., Barrera-Ocampo A and Lopera F. Colomb Med (Cali). 2016 Dec 30;47(4):203-212; US 2009/0142270A1; and US 2015/0315267A1. The beneficial effects are believed to be attributed to the antibody's effects on alleviating Aβ accumulation via promoting microglial phagocytosis toward Aβ. However, many clinical trials of immunotherapy
25 failed to validate the therapeutic benefits largely due to the lack of improved Aβ clearance and/or the occurrence of the severe adverse effects.

As mentioned above, microglia are thought to play an important role in the pathogenesis of AD, where they become activated and are characterized by morphological changes and by productions of various effectors; some combination of
30 which can be beneficial or detrimental for brain functioning. There is growing consensus that a favorable combination of diminished microglia-mediated neuro-inflammation and enhanced Aβ clearance may be critical in AD therapy. Any means that possess anti-inflammatory properties, while promoting microglial phagocytic

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activity and neuronal functionality, should be beneficial for treating the diseases. Many strategies for prevention and treatment of AD have aimed to prevent amyloid accumulation or to enhance its clearance. Indeed, systematic delivery of an Aβ monoclonal antibody, 3D6, was shown to have therapeutic efficacy in transgenic mouse models. See, e.g., Bacskai BJ *et al.*, J Neurosci. 2002 Sep 15;22(18):7873-8. Although the humanized version of this antibody, bapineuzumab, in clinical trials did show lower Aβ burden in the brain by amyloid PET imaging, the clinical trials failed due to no significant clinical benefits and the occurrence of severe adverse effects. Furthermore, subtle but significant neuro-inflammation might appear in the brain many years before the clinical manifestations of AD become detectable. The chronic and self-propelling neuro-inflammation has severely compromised the brain functioning by then, which makes AD treatment more difficult. Thus, intervention at the early stage of the disease with multi-functional effects is emerging as a promising therapeutic paradigm. However, an early diagnosis of AD at preclinical stages and an effective treatment for AD are not available.

To fulfill the unmet needs in AD therapy, novel antibodies are needed that possess multifaceted functionality for attenuating the AD-like pathology, e.g., enhancing Aβ clearance *in vitro* and *in vivo*, and promoting neuronal functioning in animals.

SUMMARY

In one aspect, described herein is an isolated antibody. The antibody contains a light-chain CDR1 (L-CDR1) having the sequence of SEQ ID NO: 1, SEQ ID NO: 7, or SEQ ID NO: 14; a light-chain CDR2 (L-CDR2) having the sequence of SEQ ID NO: 2 or SEQ ID NO: 15; a light-chain CDR3 (L-CDR3) having the sequence of SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 21, or SEQ ID NO: 24; a heavy-chain CDR1 (H-CDR1) having the sequence of SEQ ID NO: 4, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 16, or SEQ ID NO: 25; a heavy-chain CDR2 (H-CDR2) having the sequence of SEQ ID NO: 5, SEQ ID NO: 12, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 22, or SEQ ID NO: 26; and a heavy-chain CDR3 (H-CDR3) having the sequence of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 23, or SEQ ID NO: 27, wherein the antibody specifically binds to $A\beta_{1-42}$ or an N-terminal modified form thereof. In some embodiments, the N-

terminal modified Aβ1-42 is pyro-glutamate Aβ (pE-Aβ3-42). The antibody can containing an Fc region, an Fab fragment, an Fab' fragment, an F(ab')2 fragment, a single-chain antibody, an scFV multimer, a monoclonal antibody, a monovalent antibody, a multispecific antibody, a humanized antibody, or a chimeric antibody.

5 In some embodiments, the H-CDR1 has the sequence of SEQ ID NO: 16, the H-CDR2 has the sequence of SEQ ID NO: 19, the H-CDR3 has the sequence of SEQ ID NO: 20, the L-CDR1 has the sequence of SEQ ID NO: 14, the L-CDR2 has the sequence of SEQ ID NO: 15, and the L-CDR3 has the sequence of SEQ ID NO: 3.

In some embodiments, the H-CDR1 has the sequence of SEQ ID NO: 4, the 10 H-CDR2 has the sequence of SEQ ID NO: 5, the H-CDR3 has the sequence of SEQ ID NO: 6, the L-CDR1 has the sequence of SEQ ID NO: 1, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 3.

In some embodiments, the H-CDR1 has the sequence of SEQ ID NO: 9, the H-CDR2 has the sequence of SEQ ID NO: 5, the H-CDR3 has the sequence of SEQ 15 ID NO: 10, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 8.

In some embodiments, the H-CDR1 has the sequence of SEQ ID NO: 11, the H-CDR2 has the sequence of SEQ ID NO: 12, the H-CDR3 has the sequence of SEQ ID NO: 13, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the 20 sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 3.

In some embodiments, the H-CDR1 has the sequence of SEQ ID NO: 16, the H-CDR2 has the sequence of SEQ ID NO: 17, the H-CDR3 has the sequence of SEQ ID NO: 18, the L-CDR1 has the sequence of SEQ ID NO: 14, the L-CDR2 has the sequence of SEQ ID NO: 15, and the L-CDR3 has the sequence of SEQ ID NO: 3.

25 In some embodiments, the H-CDR1 has the sequence of SEQ ID NO: 9, the H-CDR2 has the sequence of SEQ ID NO: 22, the H-CDR3 has the sequence of SEQ ID NO: 23, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 21.

In some embodiments, the H-CDR1 has the sequence of SEQ ID NO: 25, the 30 H-CDR2 has the sequence of SEQ ID NO: 26, the H-CDR3 has the sequence of SEQ ID NO: 27, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 24.

In another aspect, provided herein is a pharmaceutical composition that contains any of the antibodies described herein and a pharmaceutically acceptable carrier.

In yet another aspect, described herein is a nucleic acid construct that encodes any of the antibodies described herein or a component thereof.

In one aspect, described herein is a recombinant cell comprising the nucleic acid construct.

In another aspect, contemplated herein is a method for treating Alzheimer's disease in a subject, the method including identifying a subject suffering from Alzheimer's disease and administering to the subject an effective amount of any of the antibodies described herein.

In some embodiments, the identifying step includes administering to the subject any of the antibodies described herein, and measuring a peripheral blood level of Aβ protein in the subject, wherein the peripheral blood level positively correlates with the level of cerebral Aβ protein.

In yet another aspect, described herein is a method for detecting cerebral Aβ protein in a subject, the method including administering to the subject any of the antibodies described herein, and measuring a peripheral blood level of Aβ protein in the subject, wherein the peripheral blood level positively correlates with the level of cerebral Aβ protein.

In one aspect, described herein is a method for labeling an Aβ plaque in a subject, the method includes labeling any of the antibodies described herein with a detectable label, administering the labeled antibody to a subject, and detecting a location of the label in the subject. In some embodiments, the label is radioactive and the detection is carried out by positron emission tomography.

The details of one or more embodiments are set forth in the accompanying drawing and the description below. Other features, objects, and advantages of the embodiments will be apparent from the description and drawing, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the properties of antibodies against Aβ from mouse monoclonal hybridoma. Seven different clones of hybridoma secreting antibodies specific for Aβ were generated. ELISA was performed to evaluate the Aβ binding affinity of the

antibodies (A). These antibodies shared a similar binding epitope at $A\beta_{N3-10}$ (B), and contained all murine IgG isotypes with seven unique sequence combinations in CDR-H3 (C).

FIG. 2 shows the properties of chimeric antibodies. IgG variable domains of mouse antibodies were constructed into a human IgG1 backbone to generate chimeric antibodies. The binding affinity of the chimeric antibodies was evaluated by surface plasmon resonance (SPR) (A). Microglial Aβ uptake was evaluated and the lead antibody in chimeric version, chAβ10, showed the highest score in Aβ uptake (B).

FIG. 3 shows properties of humanized version of the lead antibody: hzAβ-10. Solubility of the lead antibody was examined by FPLC (A). Binding affinity was evaluated by ELISA (B) and SPR (C).

FIG. 4 shows that the lead antibody also recognized pE-$A\beta_{3-42}$. Molecular dynamic modeling predicted binding to pE-$A\beta_{3-42}$ (A), which was confirmed by SPR (B) and by ELISA (C).

FIG. 5 shows that [^{124}I]mAβ-10 detected cerebral Aβ. Positron Emission Tomography/Computed Tomography analysis showed that mAβ-10 crossed the blood brain barrier and could be a diagnostic probe for Aβ deposition in the brain.

FIG. 6 shows that the lead antibody could be used to predict Aβ levels in the brain by monitoring antibody-induced Aβ in circulation. Intraperitoneal injection of the lead antibody instigated a robust efflux of cerebral Aβ into the blood. The increased Aβ levels in the serum were positively correlated with the cerebral Aβ levels in APP/PS1 mice with or without the presence of Aβ plaques.

FIG. 7 summarizes NextGen™ RNA sequencing analysis of gene expressions in the hippocampus from mice injected with mAβ-10. Surprisingly, antibody treatments triggered many genes beneficial against AD, while no indication of neuro-inflammation was found.

FIG. 8 shows comparisons between Aducanumab and the lead antibody. CDR sequence identity (A), binding affinity to Aβ by ELISA (B), detection of Aβ plaques (C), and microglial Aβ phagocytosis (D) were compared.

DETAILED DESCRIPTION

Described herein are novel antibodies that recognize a variety of Aβ species and an N-terminally modified pyro-glutamate Aβ.

The antibodies each include a light-chain CDR1 (L-CDR1) having the sequence of SEQ ID NO: 1, SEQ ID NO: 7, or SEQ ID NO: 14; a light-chain CDR2 (L-CDR2) having the sequence of SEQ ID NO: 2 or SEQ ID NO: 15; a light-chain CDR3 (L-CDR3) having the sequence of SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 21, or SEQ ID NO: 24; a heavy-chain CDR1 (H-CDR1) having the sequence of SEQ ID NO: 4, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 16, or SEQ ID NO: 25; a heavy-chain CDR2 (H-CDR2) having the sequence of SEQ ID NO: 5, SEQ ID NO: 12, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 22, or SEQ ID NO: 26; and a heavy-chain CDR3 (H-CDR3) having the sequence of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 23, or SEQ ID NO: 27. The antibodies each specifically bind to Aβ1-42 or an N-terminal modified form thereof.

The term "antibody" as used herein includes various antibody structures that have an antigen-binding activity, including but not limited to monoclonal antibodies, polyclonal antibodies, full-length antibodies or fragments thereof, antibodies that contain an Fc region, Fab fragments, Fab' fragments, F(ab')2 fragments, single-chain antibodies, scFV multimers, monovalent antibodies, multivalent antibodies, humanized antibodies, and chimeric antibodies.

Based on the antibody CDR sequences disclosed herein, a skilled practitioner would be able to produce an anti-Aβ antibody in various forms using methods known in the art, e.g., recombinant methods.

Data described below suggest that these antibodies can be used to treat AD and for early detection of cerebral Aβ levels. N-terminally modified pyro-glutamate Aβ (pE-Aβ3-42) is highly prone to aggregation and might be critical for Aβ plaque formation. It was shown that the binding epitopes of these antibodies are mapped to the N-terminus of Aβ peptide specifically recognizing various forms of Aβ species and pE-Aβ3-42. Thus, these antibodies may be more effective in Aβ clearance.

For example, data demonstrated that at least one of the antibodies possesses multifaceted functionality in attenuating the AD-like pathology in APP/PS1 mice and engages Aβ plaques in the brain across the blood-brain barrier, while transforming over-activated microglia into ramified microglia with a healthy and functional morphology. The data further indicated that treatment with the antibody can enhance microglial Aβ phagocytosis and improved neuronal function.

Further, it was shown that intraperitoneal injection of one of the antibodies triggered a robust efflux of cerebral Aβ into the circulation, whereby the increased Aβ levels in the blood were positively correlated with the Aβ levels in the brains of Aβ plaque-loaded or non-Aβ plaque-bearing APP/PS1 mice. In other words, an elevated level of peripheral blood Aβ indicates an elevated cerebral Aβ level. Therefore, measuring the Aβ level in the peripheral blood (e.g., in a serum or plasma sample) induced by the antibody can be used to predict cerebral Aβ level at all disease stages of AD. This innovative approach can serve as a preclinical diagnosis for patients at risk of AD and assist to monitor the status of Aβ pathology in AD patients under intervention. Findings from mechanistic study further revealed that glial rejuvenation and increased astrocytic transthyretin might, at least partly, contribute to the dual efficacy of both treatment and early diagnosis. The studies set out below suggest that the novel antibodies have theranostic potential for AD.

To diagnose AD or determine AD disease stages in a subject, after a subject has been administered one of the antibodies described herein, the peripheral blood Aβ level can be determined. The determined level can be compared to a control level (e.g., a level found in subjects without AD or Aβ plaques) or a level determined in the subject at an earlier time point. Based on the comparison, whether the subject has AD or the severity of AD can be assessed. To monitor the efficacy of an AD treatment in a subject, the peripheral blood Aβ level in the subject can be determined, using the method described herein, before the start of the treatment and at one or more points during the treatment. A decreasing peripheral blood Aβ level indicates that the treatment is effective.

Any of the anti-Aβ antibodies described herein can be formulated as a pharmaceutical composition suitable for various routes of administration, e.g., intravenous, intraarticular, conjunctival, intracranial, intraperitoneal, intrapleural, intramuscular, intrathecal, or subcutaneous route of administration. The pharmaceutical composition can be an aqueous solution or lyophilized formulation. It can contain a pharmaceutically acceptable carrier, e.g., a buffer, excipient, stabilizer, or preservative. The pharmaceutical composition can include other active ingredients that work together with the anti-Aβ antibody, e.g., another therapeutic agent or an adjuvant.

Without further elaboration, it is believed that one skilled in the art can, based on the description above, utilize the present invention to its fullest extent. The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

5

Example 1: Production of seven clones of antibodies specific for Aβ from hybridoma.

To generate hybridoma, oligomeric Aβ (oAβ) was used for mouse immunization. Synthetic $A\beta_{1\text{-}42}$ was dissolved in 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) followed by evaporation. Dry membrane was re-dissolved in 1X PBS followed by centrifugation to remove fibrillary and aggregated Aβ. The prepared oAβ oligomers were characterized by Western blot using a commercially available Aβ antibody, 6E10. Results showed that the prepared oAβ oligomers constituted a mixture of Aβ species, including monomers, dimers, and various orders of structure of oAβ species with molecular weights ranging from 37 to 250 kDa. The prepared oAβ oligomers were stored at -80°C until immunization was performed by LTK Biolaboratories for production of monoclonal hybridoma. Antibodies were subjected to analysis for Aβ binding affinity by ELISA (Fig. 1A) and by immunohistochemistry (data not shown). Epitope mapping of the antibodies was performed. See Fig. 1B. Seven different clones of hybridoma that secret antibodies specific for Aβ were generated. Results showed that these antibodies were all IgG isotypes with a similar binding epitope at $A\beta_{N3\text{-}10}$. Hybridoma sequencing was carried out to determine the entire CDR sequences of each monoclonal antibody. The isotypes and CDR sequences are shown in Fig. 1C.

25

Example 2: Generation of chimeric antibodies

Mouse IgG variable domains were inserted into a human IgG1 backbone to generate chimeric antibodies. Surface Plasmon Resonance (SPR) by Biacore™ was performed to evaluate the Aβ binding affinity of 7 chimeric antibodies. See Fig. 2A. Antibody-enhanced microglial Aβ uptake *in vitro* was performed. Data indicate that all antibodies enhanced microglial Aβ uptake, while the lead antibody appears to have the highest score on the assay. See Fig. 2B.

Example 3: Humanization of mAβ-10

A humanized version of the lead antibody (hzAβ-10) was constructed from chimeric antibody using human IgG1 framework. Fast protein liquid chromatography (FPLC) was used for analysis of protein solubility (Fig. 3A) and characters of Aβ binding were examined by immunofluorescent histochemistry on APP/PS1 mouse brain sections (data not shown), ELISA (Fig. 3B), and SPR (Fig. 3C). Data indicated that hzAβ-10 exhibited an excellent Aβ binding affinity and an exceptional property of very high protein solubility, which is suitable for cell line development.

Example 4: Novel Aβ antibodies also recognize pE-Aβ3-42

N-terminally modified pyro-glutamate Aβ (pE-$Aβ_{3-42}$) is highly prone to aggregation and might be critical for Aβ plaque formation. The binding epitopes of these antibodies are mapped to N-terminus of Aβ peptide specifically recognizing various forms of Aβ species and pE-$Aβ_{3-42}$ as predicted in the molecular dynamic modeling. See Fig. 4A. Data from Biacore™ (Fig. 4B) and ELISA (Fig. 4C) confirmed that the lead antibody targeted $Aβ_{1-42}$ and pE-$Aβ_{3-42}$, suggesting that it would be more effective in Aβ clearance.

Example 5: [^{124}I]mAβ-10 detected cerebral Aβ

APP/PS1 transgenic mice received isotope-labelled antibody ([^{124}I]mAβ-10) through i.p. and were subjected to PET/CT analysis. As shown in Fig. 5, results indicated that mAβ-10 crossed the blood-brain barrier and could engage Aβ plaques, suggesting that mAβ-10 could be developed as a diagnostic probe for Aβ deposition in the brain.

Example 6: Early AD diagnosis by measuring antibody-induced Aβ in the serum

A robust transport of cerebral Aβ into the blood was triggered by two doses of mAβ-10 treatments and the escalating serum Aβ levels were highly correlated with the corresponding Aβ levels in Aβ plaques-laden and non-Aβ plaques-bearing APP/PS1 mice. See Fig. 6. Through examining the blood samples, use of this novel antibody could indicate the amount of cerebral Aβ at various stages of the disease and predict the appearance of Aβ plaque formation by evaluating serum Aβ. Furthermore, serum Aβ declined as the circulating antibody descended, suggesting the involvement

of the antibody in the clearance of peripheral Aβ. See Fig. 6. This innovative approach might implement the development of early diagnosis for patients at risk of AD or at preclinical stages and aid in monitoring the status of Aβ pathology in AD patients under intervention.

5

Example 7: Transcriptome analysis

NextGen™ Sequencing RNA-seq analysis, i.e., transcriptome analysis, of the hippocampus was performed to examine the gene expression profile after injection of mAβ-10. Results showed that a total of 47,717 genes showed increased or decreased
10 expression levels. As presented in Fig. 7, many genes with significant upregulation appeared to be beneficial for AD, while genes involved in toxicity and stress were down-regulated.

Example 8: Treatments with hzAβ-10 rejuvenated microglia in APP/PS1 mice
15 Confocal imaging show that the presence of frustrated microglia without apparent phagocytic activity was observed in aged APP/PS1 mice, while treatment with hzAβ-10 at a dose of 30 mg/kg via i.p. injection for 4 doses (in a period of 17 days) escalated Iba1 immunoreactivity with dramatic changes in morphology resembling functional/ramified microglia (data not shown). These results indicated
20 that treatment of hzAβ-10 rejuvenated microglia and promoted clearance of Aβ plaques *in vivo*.

Example 9: Treatment with mAβ-10 increased astrocytic TTR, improved neuronal functionality, and reduced amyloid plaques in APP/PS1 mice
25 Confocal images showed that treatments with mAβ-10 at 30 mg/kg via ip injection for two doses increased levels of astrocytic transthyretin (TTR), while low abundance of TTR was observed in astrocytes in age-matched APP/PS1 mice (data not shown). Co-localization data also confirmed the localization of TTR within astrocyte end-feet (data not shown). The results suggested that the antibody-induced-
30 TTR in astrocytes could be involved in the Aβ efflux triggered by mAβ-10. Surprisingly, mAβ-10 also increased immunoreactivity of MAP2 and PSD95 in the hippocampus of APP/PS1, suggesting that mAβ-10 enhanced neuronal functions (data not shown). Further, treatment with mAβ-10 once per week for 39 weeks led to a reduction of amyloid plaques in APP/PS1 mice (data not shown).

Example 10: Comparisons between Aducanumab and the lead antibody

Aducanumab (BIIB037 by Biogen™) is currently in Phase III clinical trial for AD therapy. The CDR sequences of hzAβ-10 and those of Aducanumab shared very low identity. See Fig. 8A. Compared to Aducanumab (purchased from Creative
5 Biolabs), the lead antibody in either mouse or human versions had stronger affinity for oligomeric Aβ (oAβ) and aggregated Aβ. See Fig. 8B. In contrast to Aducanumab's binding preference to aggregated Aβ, the lead antibody exhibited similar binding affinity for both forms of Aβ. See Fig. 8B. Fluorescent histochemistry followed by confocal Imaging was used to detect Aβ plaques in the
10 brain of APP/PS1 mice at the age of 14 months. See Fig. 8C. Consecutive sections were used for the comparisons between the two antibodies (at 0.2 or 1 mg/ml). Results showed that hzAβ-10 was more sensitive than Aducanumab in detecting cerebral Aβ plaques. Microglial Aβ phagocytosis was evaluated by flow cytometry following the treatments of soluble or aggregated Aβ-FITC for 24hr. Results showed
15 that hzAβ-10 performed better than Aducanumab in enhancing microglial Aβ phagocytosis. See Fig. 8D.

OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any
20 combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the
25 essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the scope of the following claims.

IN THE CLAIMS:

1. An isolated antibody, comprising a light-chain CDR1 (L-CDR1); a light-chain CDR2 (L-CDR2); a light-chain CDR3 (L-CDR3); a heavy-chain CDR1 (H-CDR1); a heavy-chain CDR2 (H-CDR2); and a heavy-chain CDR3 (H-CDR3), wherein the antibody specifically binds to $A\beta_{1-42}$ or an N-terminal modified form of $A\beta_{1-42}$, and wherein:

(i) the H-CDR1 has the sequence of SEQ ID NO: 16, the H-CDR2 has the sequence of SEQ ID NO: 17 or 19, the H-CDR3 has the sequence of SEQ ID NO: 18 or 20, the L-CDR1 has the sequence of SEQ ID NO: 14, the L-CDR2 has the sequence of SEQ ID NO: 15, and the L-CDR3 has the sequence of SEQ ID NO: 3;

(ii) the H-CDR1 has the sequence of SEQ ID NO: 4, the H-CDR2 has the sequence of SEQ ID NO: 5, the H-CDR3 has the sequence of SEQ ID NO: 6, the L-CDR1 has the sequence of SEQ ID NO: 1, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 3;

(iii) the H-CDR1 has the sequence of SEQ ID NO: 9, the H-CDR2 has the sequence of SEQ ID NO: 5, the H-CDR3 has the sequence of SEQ ID NO: 10, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 8;

(iv) the H-CDR1 has the sequence of SEQ ID NO: 11, the H-CDR2 has the sequence of SEQ ID NO: 12, the H-CDR3 has the sequence of SEQ ID NO: 13, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 3;

(v) the H-CDR1 has the sequence of SEQ ID NO: 9, the H-CDR2 has the sequence of SEQ ID NO: 22, the H-CDR3 has the sequence of SEQ ID NO: 23, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 21; or

(vi) the H-CDR1 has the sequence of SEQ ID NO: 25, the H-CDR2 has the sequence of SEQ ID NO: 26, the H-CDR3 has the sequence of SEQ ID NO: 27, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 24.

2. The isolated antibody of claim 1, wherein the H-CDR1 has the sequence of SEQ ID NO: 16, the H-CDR2 has the sequence of SEQ ID NO: 19, the H-CDR3 has the sequence of SEQ ID NO: 20, the L-CDR1 has the sequence of SEQ ID NO: 14, the L-CDR2 has the sequence of SEQ ID NO: 15, and the L-CDR3 has the sequence of SEQ ID NO: 3.

3. The isolated antibody of claim 1, wherein the N-terminal modified $A\beta_{1-42}$ is pyro-glutamate $A\beta$ ($pE-A\beta_{3-42}$).

4. The isolated antibody of claim 2, wherein the N-terminal modified $A\beta_{1-42}$ is pyro-glutamate $A\beta$ ($pE-A\beta_{3-42}$).

5. The isolated antibody of claim 1, wherein the H-CDR1 has the sequence of SEQ ID NO: 4, the H-CDR2 has the sequence of SEQ ID NO: 5, the H-CDR3 has the sequence of SEQ ID NO: 6, the L-CDR1 has the sequence of SEQ ID NO: 1, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 3.

6. The isolated antibody of claim 1, wherein the H-CDR1 has the sequence of SEQ ID NO: 9, the H-CDR2 has the sequence of SEQ ID NO: 5, the H-CDR3 has the sequence of SEQ ID NO: 10, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 8.

7. The isolated antibody of claim 1, wherein the H-CDR1 has the sequence of SEQ ID NO: 11, the H-CDR2 has the sequence of SEQ ID NO: 12, the H-CDR3 has the sequence of SEQ ID NO: 13, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 3.

8. The isolated antibody of claim 1, wherein the H-CDR1 has the sequence of SEQ ID NO: 16, the H-CDR2 has the sequence of SEQ ID NO: 17, the H-CDR3 has the sequence of SEQ ID NO: 18, the L-CDR1 has the sequence of SEQ ID NO: 14, the L-CDR2 has the sequence of SEQ ID NO: 15, and the L-CDR3 has the sequence of SEQ ID NO: 3.

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9. The isolated antibody of claim 1, wherein the H-CDR1 has the sequence of SEQ ID NO: 9, the H-CDR2 has the sequence of SEQ ID NO: 22, the H-CDR3 has the sequence of SEQ ID NO: 23, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 21.

10. The isolated antibody of claim 1, wherein the H-CDR1 has the sequence of SEQ ID NO: 25, the H-CDR2 has the sequence of SEQ ID NO: 26, the H-CDR3 has the sequence of SEQ ID NO: 27, the L-CDR1 has the sequence of SEQ ID NO: 7, the L-CDR2 has the sequence of SEQ ID NO: 2, and the L-CDR3 has the sequence of SEQ ID NO: 24.

11. The isolated antibody of claim 1, wherein the antibody is an antibody containing an Fc region, an Fab fragment, an Fab' fragment, an F(ab')2 fragment, a single-chain antibody, an scFV multimer, a monoclonal antibody, a monovalent antibody, a multispecific antibody, a humanized antibody, or a chimeric antibody.

12. A pharmaceutical composition, comprising the isolated antibody of claim 1 and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12, wherein the antibody comprises H-CDR1 having the sequence of SEQ ID NO: 16, H-CDR2 having the sequence of SEQ ID NO: 19, H-CDR3 having the sequence of SEQ ID NO: 20, L-CDR1 having the sequence of SEQ ID NO: 14, L-CDR2 having the sequence of SEQ ID NO: 15, and L-CDR3 having the sequence of SEQ ID NO: 3.

14. A nucleic acid construct that encodes the isolated antibody of claim 1.

15. A recombinant cell comprising the nucleic acid construct of claim 14.

16. Use of the isolated antibody of claim 1 for treating Alzheimer's disease in a subject suffering from Alzheimer's disease.

17. The use of claim 16, wherein the antibody comprises H-CDR1 having the sequence of SEQ ID NO: 16, H-CDR2 having the sequence of SEQ ID NO: 19, H-CDR3 having the sequence of SEQ ID NO: 20, L-CDR1 having the sequence of SEQ ID NO: 14, L-CDR2 having the sequence of SEQ ID NO: 15, and L-CDR3 having the sequence of SEQ ID NO: 3.

18. The use claim 17, wherein the subject is identified by measuring a peripheral blood level of Aβ protein in the subject following administration of the isolated antibody of claim 1 to the subject, wherein the peripheral blood level positively correlates with the level of cerebral Aβ protein.

19. Use of the isolated antibody of claim 1 for detecting cerebral Aβ protein in a subject by measuring a peripheral blood level of Aβ protein in the subject following administration of the isolated antibody of claim 1 to the subject, wherein the peripheral blood level positively correlates with the level of cerebral Aβ protein.

20. The use of claim 19, wherein the antibody comprises H-CDR1 having the sequence of SEQ ID NO: 16, H-CDR2 having the sequence of SEQ ID NO: 19, H-CDR3 having the sequence of SEQ ID NO: 20, L-CDR1 having the sequence of SEQ ID NO: 14, L-CDR2 having the sequence of SEQ ID NO: 15, and L-CDR3 having the sequence of SEQ ID NO: 3.

21. Use of the isolated antibody of claim 1 for labeling an Aβ plaque in a subject by (i) labeling the isolated antibody of claim 1 with a detectable label, and (ii) detecting a location of the label in the subject following administration of the labeled antibody to the subject.

22. The use of claim 21, wherein the label is radioactive and the detection is carried out by positron emission tomography.

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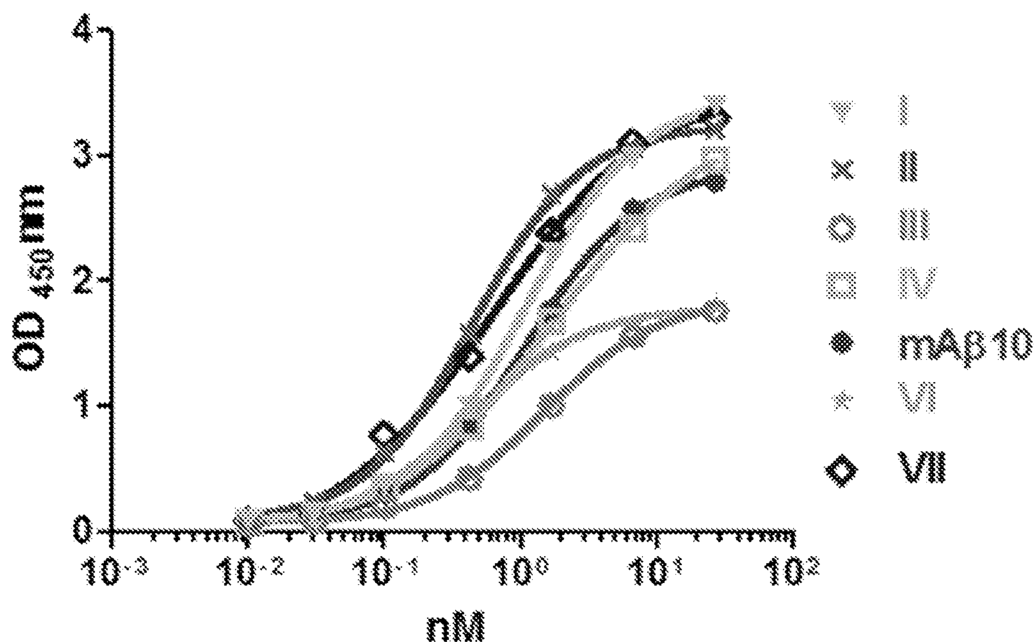
FIG. 1

A.



B.

		$A\beta_{1-42}$ DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO: 28)
SEQ ID NO: 29	1.	biotin- DAEFRHDSGYGSG
SEQ ID NO: 30	2.	biotin- SGSGEFRHDSGYEV
SEQ ID NO: 31	3.	biotin- SGSGRHDSGYEVHH
SEQ ID NO: 32	4.	biotin- SGSGDSGYEVHHQK
SEQ ID NO: 33	5.	biotin- SGSGGYEVHHQKLV
SEQ ID NO: 34	6.	biotin- SGSGEVHHQKLVFF
SEQ ID NO: 35	7.	biotin- SGSGHHQKLVFFAE
SEQ ID NO: 36	8.	biotin- SGSG QKLVFFAEDV
SEQ ID NO: 37	9.	biotin- SGSG LVFFAEDVGS
SEQ ID NO: 38	10.	biotin- SGSG FFAEDVGSNK
SEQ ID NO: 39	11.	biotin- SGSG AEDVGSNKGA
SEQ ID NO: 40	12.	biotin- SGSG DVGSNKGAIIG
SEQ ID NO: 41	13.	biotin- SGSG GSNKGAIIGLM
SEQ ID NO: 42	14.	biotin- SGSG NKGAIIGLMVG
SEQ ID NO: 43	15.	biotin- SGSG GAIIGLMVGGV
SEQ ID NO: 44	16	biotin- SGSG IIGLMVGGVV
SEQ ID NO: 45	17.	biotin- SGSGGLMVGGVVIA

Fig. 1 (continued)

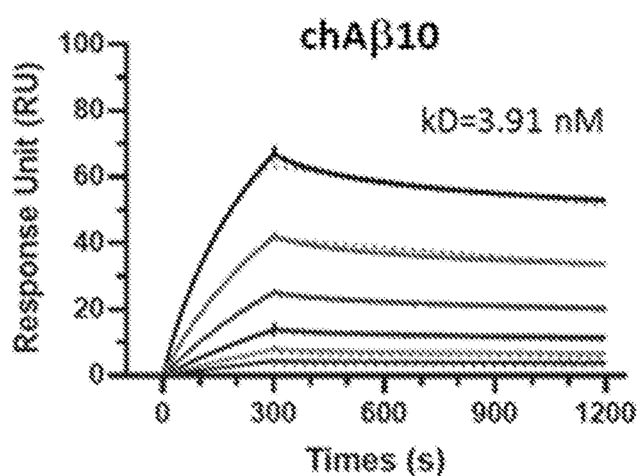
C.

Antibodies /isotype	CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
I/IgG2a	SEQ ID NO: 1 CRSSQTIVHSNGNTYLE	SEQ ID NO: 2 KVSNRFS	SEQ ID NO: 3 FQGSHVPLT	SEQ ID NO: 4 TSGMNVG	SEQ ID NO: 5 HIWWDDDKYYNPSLKS	SEQ ID NO: 6 RR**SIR--GS**DYF**D**Y
II/IgG1	SEQ ID NO: 7 CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 8 FQGSLVPLT	SEQ ID NO: 9 TSGMGVG	HIWWDDDKYYNPSLKS	SEQ ID NO: 10 RR**ALRNVVA**D**AMD**Y
III/IgG3	CRSSQSIVHSNGNTYLE	KVSNRFS	FQGSHVPLT	SEQ ID NO: 11 TSAVGVS	SEQ ID NO: 12 HIYWDDDKRYNPSLKS	SEQ ID NO: 13 RR**PYYRYDV**D**AMD**Y
IV/IgG2b	SEQ ID NO: 14 CRSSQNIVHSNGNTYLE	SEQ ID NO: 15 TVSNRFS	FQGSHVPLT	SEQ ID NO: 16 SSVLGVS	SEQ ID NO: 17 HIYWDDDRRYNPSLKS	SEQ ID NO: 18 RR**GKMGRGL**D**AMD**Y
V(mAβ-10)/IgG2a	CRSSQNIVHSNGNTYLE	TVSNRFS	FQGSHVPLT	SSVLGVS	SEQ ID NO: 19 HIYWDDDRRYNPSLRS	SEQ ID NO: 20 RR**GKMGRGL**D**ALDF**
VI/IgG2b	CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 21 FQGSRVPLT	TSGMGVG	SEQ ID NO: 22 HIWWDDDKYFNPSLKS	SEQ ID NO: 23 RR**SLK--WL**D**AMD**Y
VII/IgG1	CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 24 FQSSRVPLT	SEQ ID NO: 25 TSGMGVS	SEQ ID NO: 26 HIYWDDDKSYNPSLKS	SEQ ID NO: 27 RR**RNW**-**VIT**D**AME**Y

Fig. 2

A.

	ka(1/Ms)	Kd (1/s)	KD (nM)
I	1.7E+04	3.0E-04	17.25
II	6.3E+04	6.8E-04	10.87
III	9.8E+04	2.5E-04	2.56
IV	1.3E+05	4.9E-04	3.84
chAβ10	5.3E+04	2.1E-04	3.91
VI	5.4E+04	1.4E-04	2.63
VII	1.5E+05	8.4E-05	0.55



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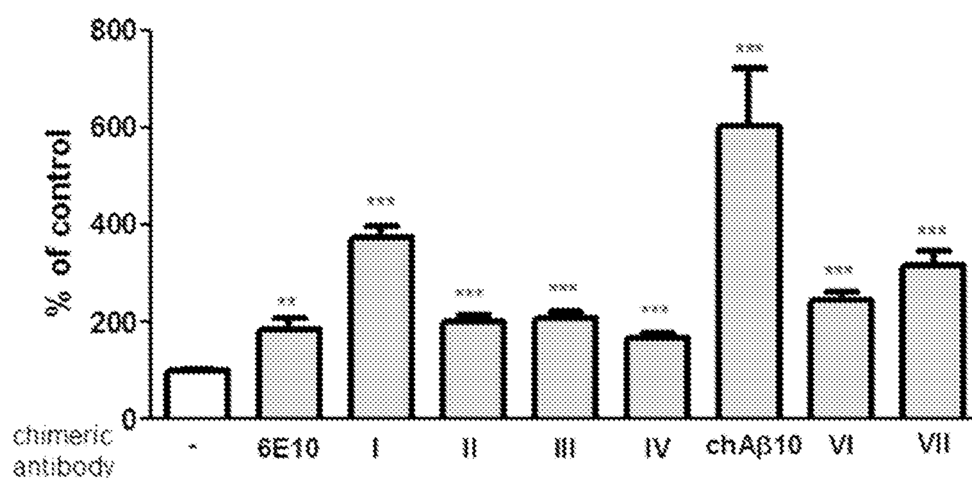
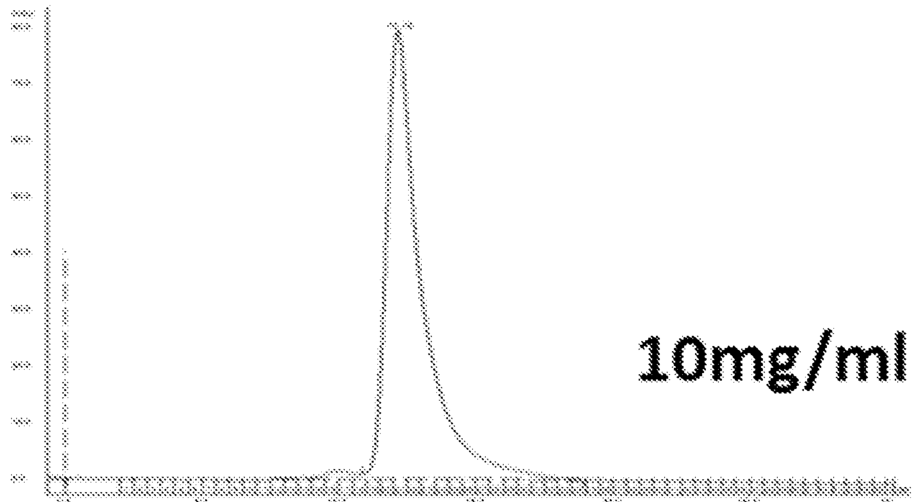


Fig. 3

A.



B.

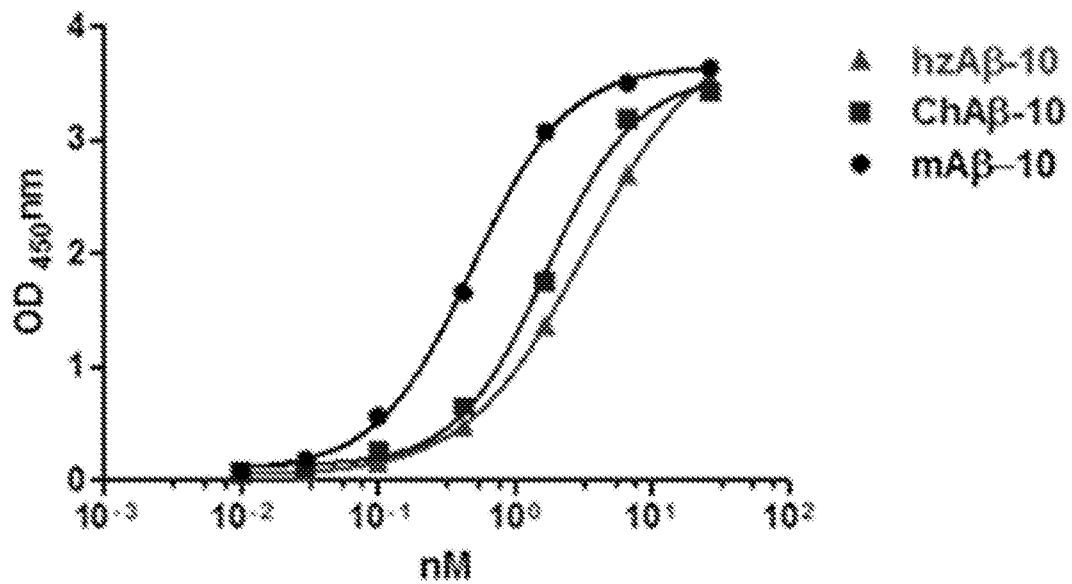


FIG. 3 (Continued)

C.

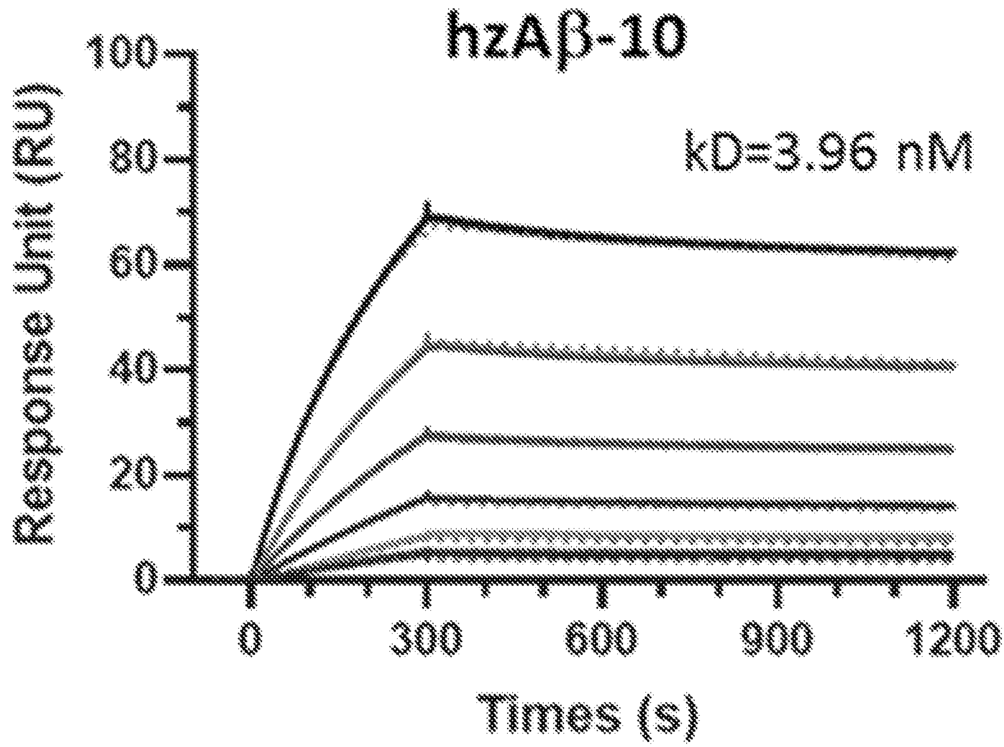


Fig. 4

A.

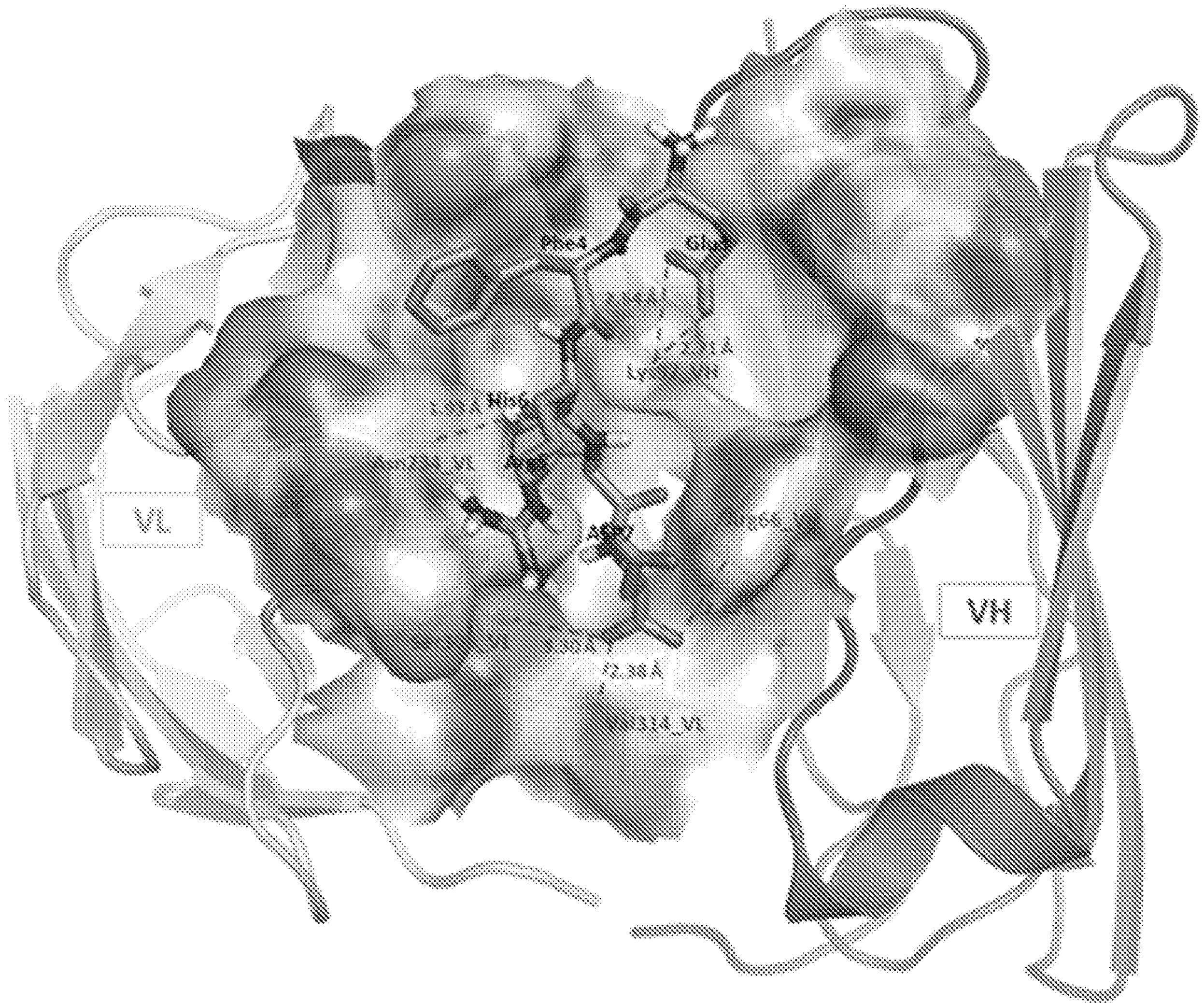


FIG. 4 (Continued)

B.

		Ka	kd	KD (nM)
pE-Aβ_{3-42}	mAβ-10	3.7E+04	5.2E-04	**14.22**
	chAβ-10	2.5E+04	8.3E-04	**32.59**
	hzAβ-10	1.7E+04	7.6E-04	**44.70**
Aβ_{1-42}	mAβ-10	8.7E+04	1.1E-04	**1.29**
	chAβ-10	5.3E+04	2.1E-04	**3.91**
	hzAβ-10	4.0E+04	1.6E-04	**3.96**

C.

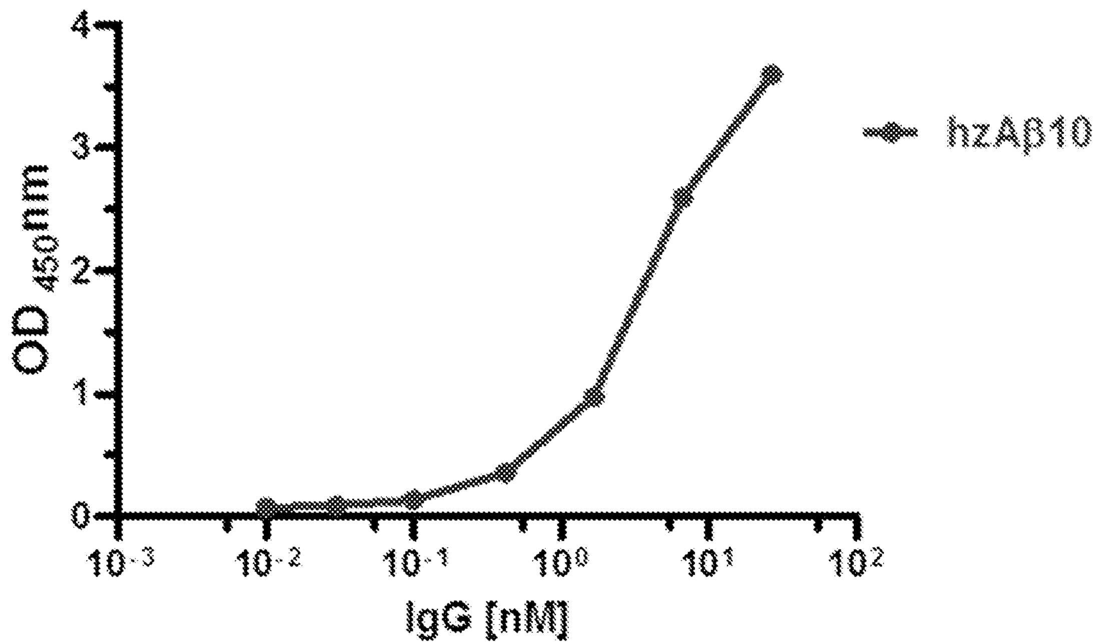


FIG. 5

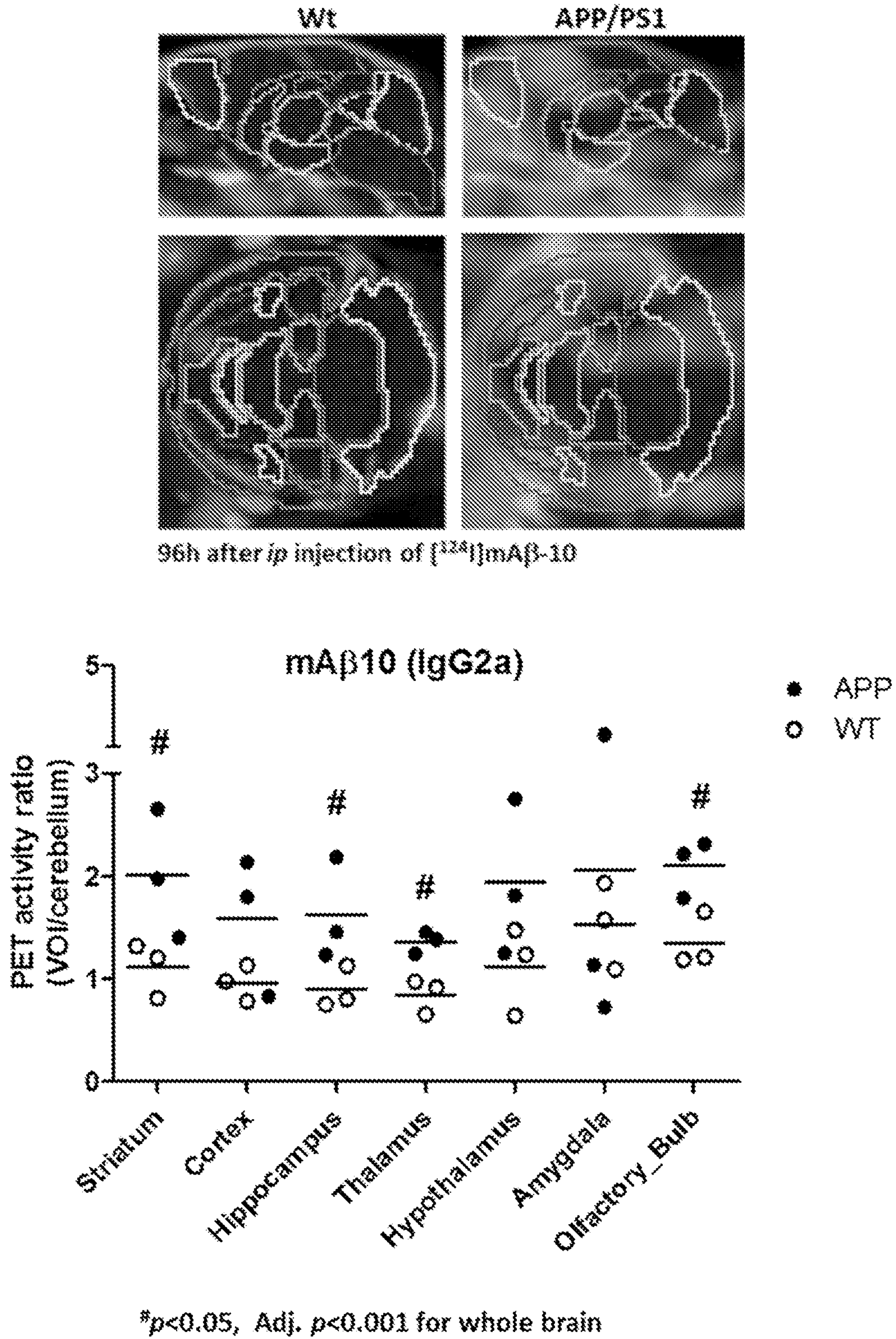


FIG. 6

serum Aβ1-42 (pg)

Total serum Aβ1-42 (pg)

serum Aβ1-40 (pg)

Total serum Aβ1-40 (pg)

Serum mAβ-10 IgG

Aβ plaque formation

Serum Aβ1-42 (log)

Brain Aβ1-42 (log)

$(R^2=0.7229, p<0.0001)$

Aβ plaque formation

Serum Aβ1-40 (log)

Brain Aβ1-40 (log)

$(R^2=0.5472, p<0.0001)$

FIG. 7

Gene expressions (FPKM ratio): mAβ-10 vs control	
Increased	Aβ-degradation enzymes
	Binding proteins for Aβ efflux
	Water channel
	Anti-aging proteins
	Wnt signaling activators
	Growth factors
Decreased	Proteins mediating Aβ toxicity
	Stress proteins
	Proteins inducing cognitive deficit
	Receptor inhibiting phagocytosis

FIG. 8

A.

CDR-H (average%)	CDR-H1	CDR-H2	CDR-H3	**CDR-L (average%)**	CDR-L1	CDR-L2	CDR-L3
27.4	28.6	25.0	28.6	**34.8**	31.3	28.6	44.4

B.

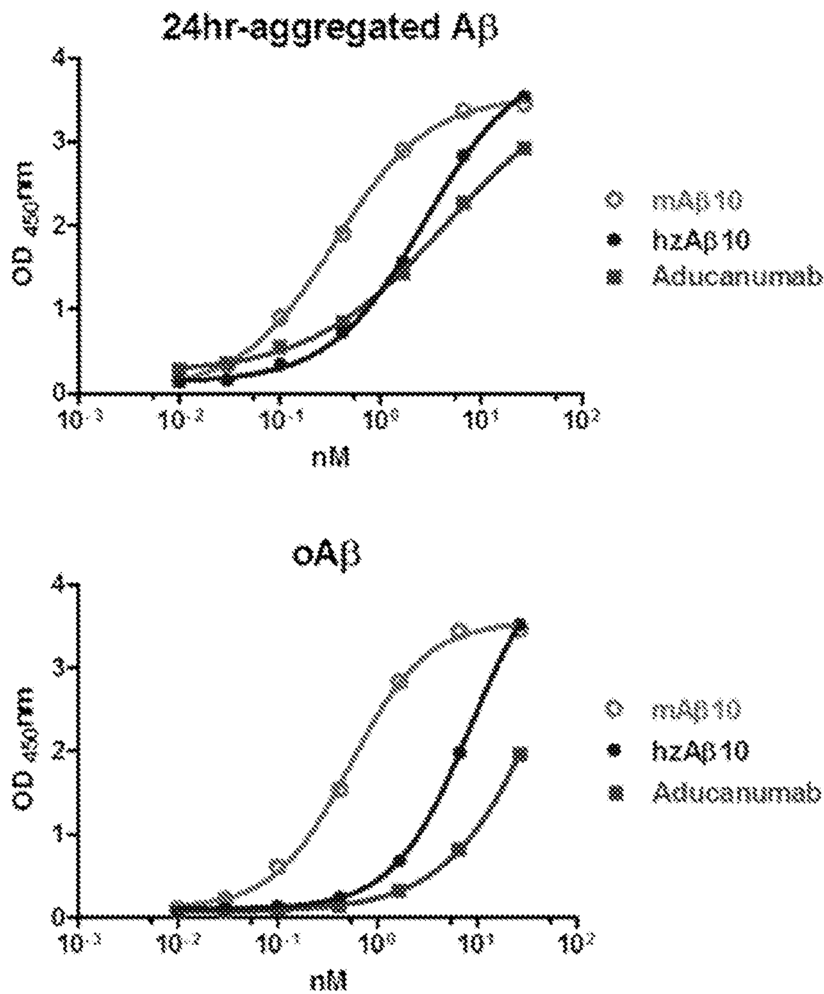


FIG. 8 (Continued)

C.

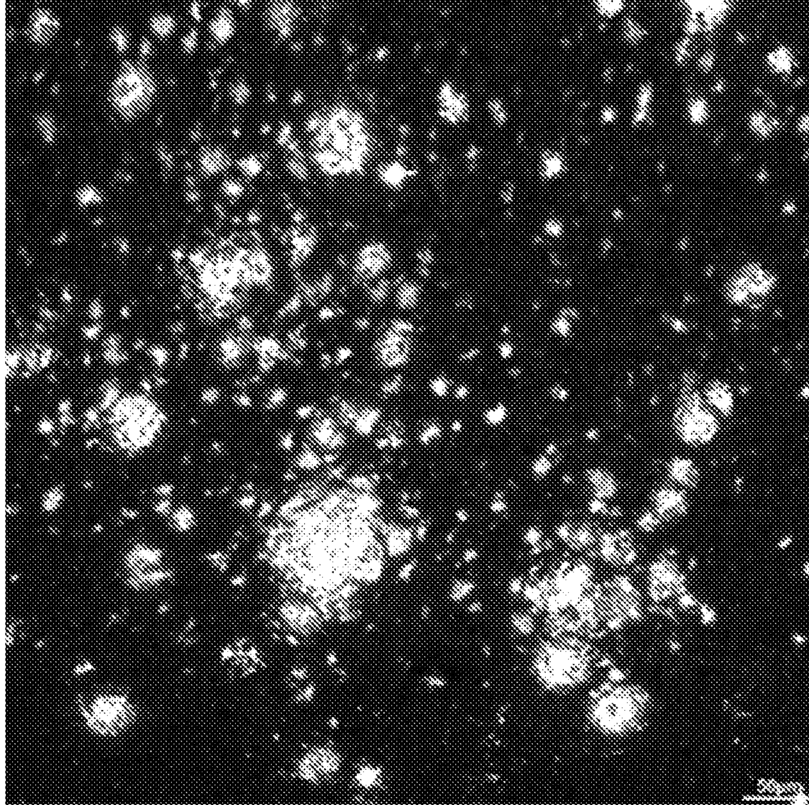
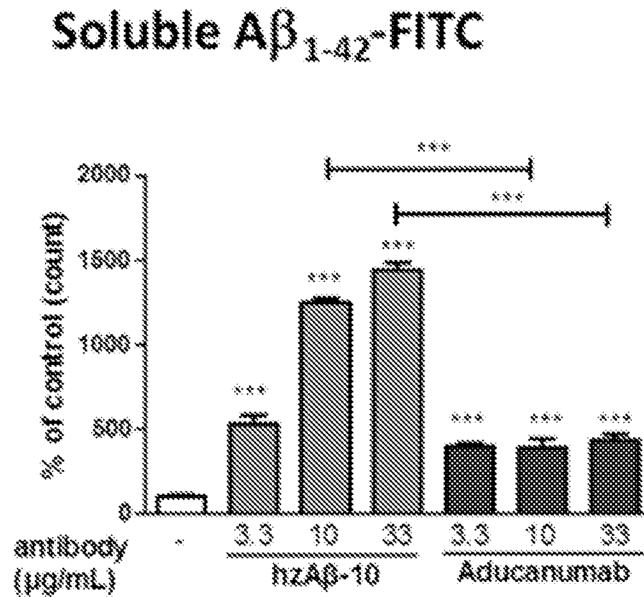
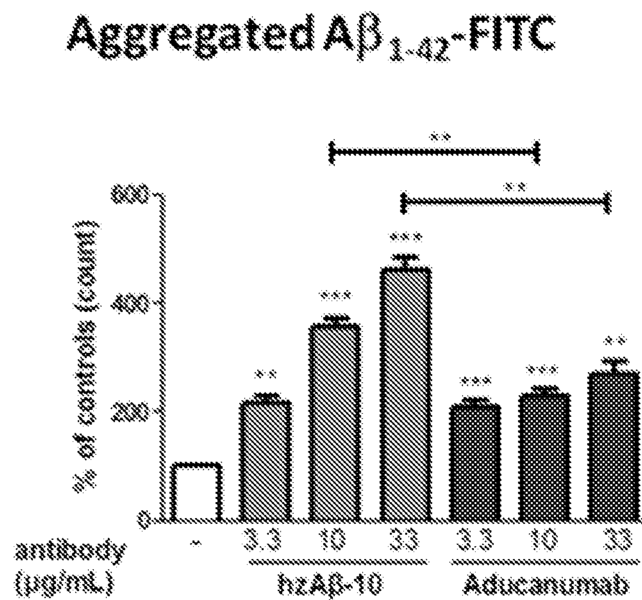


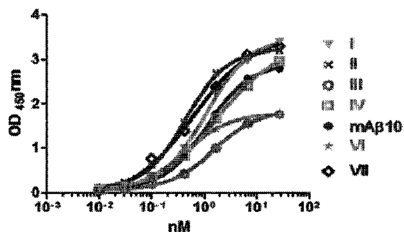
FIG. 8 (Continued)

D.





A.



B.

Aβ$_{1-42}$ DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO: 28)

SEQ ID NO: 29 1. biotin- DAEFRHDSGYGSG
SEQ ID NO: 30 2. biotin- SGSGEFRHDSGYEV
SEQ ID NO: 31 3. biotin- SGSGRHDSGYEVHH
SEQ ID NO: 32 4. biotin- SGSGDSGYEVHHQK
SEQ ID NO: 33 5. biotin- SGSGGYEVHHQKLV
SEQ ID NO: 34 6. biotin- SGSGEVHHQKLVFF
SEQ ID NO: 35 7. biotin- SGSGHHQKLVFFAE
SEQ ID NO: 36 8. biotin- SGSG QKLVFFAEDV
SEQ ID NO: 37 9. biotin- SGSG LVFFAEDVGS
SEQ ID NO: 38 10. biotin- SGSG FFAEDVGSNK
SEQ ID NO: 39 11. biotin- SGSG AEDVGSNKGA
SEQ ID NO: 40 12. biotin- SGSG DVGSNKGAIIG
SEQ ID NO: 41 13. biotin- SGSG GSNKGAIIGLM
SEQ ID NO: 42 14. biotin- SGSG NKGAIIGLMVG
SEQ ID NO: 43 15. biotin- SGSG GAIIGLMVGGV
SEQ ID NO: 44 16 biotin- SGSG IIGLMVGGVV
SEQ ID NO: 45 17. biotin- SGSGGLMVGGVVIA

C.

Antibodies /isotype	**CDR-L1**	**CDR-L2**	**CDR-L3**	**CDR-H1**	**CDR-H2**	**CDR-H3**
I/IgG2a	SEQ ID NO: 1 CRSSQTIVHSNGNTYLE	SEQ ID NO: 2 KVSNRFS	SEQ ID NO: 3 FQGSHVPLT	SEQ ID NO: 4 TSGMNVG	SEQ ID NO: 5 HIWWDDDKYYNPSLKS	SEQ ID NO: 6 RR**SIR--GS**DYFDY
II/IgG1	SEQ ID NO: 7 CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 8 FQGSLVPLT	SEQ ID NO: 9 TSGMGVG	HIWWDDDKYYNPSLKS	SEQ ID NO: 10 RR**ALRNVVADAMDY**
III/IgG3	CRSSQSIVHSNGNTYLE	KVSNRFS	FQGSHVPLT	SEQ ID NO: 11 TSAVGVS	SEQ ID NO: 12 HIYWDDDKRYNPSLKS	SEQ ID NO: 13 RR**PYYRYDVDAMDY**
IV/IgG2b	SEQ ID NO: 14 CRSSQNIVHSNGNTYLE	SEQ ID NO: 15 TVSNRFS	FQGSHVPLT	SEQ ID NO: 16 SSVLGVS	SEQ ID NO: 17 HIYWDDDRRYNPSLKS	SEQ ID NO: 18 RR**GKMGRGL**D**AMDY**
V(mAβ-10)/IgG2a	CRSSQNIVHSNGNTYLE	TVSNRFS	FQGSHVPLT	SSVLGVS	SEQ ID NO: 19 HIYWDDDRRYNPSLRS	SEQ ID NO: 20 RR**GKMGRGL**D**ALDF**
VI/IgG2b	CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 21 FQGSRVPLT	TSGMGVG	SEQ ID NO: 22 HIWWDDDKYFNPSLKS	SEQ ID NO: 23 RR**SLK--WL**D**AMDY**
VII/IgG1	CRSSQSIVHSNGNTYLE	KVSNRFS	SEQ ID NO: 24 FQSSRVPLT	SEQ ID NO: 25 TSGMGVS	SEQ ID NO: 26 HIYWDDDKSYNPSLKS	SEQ ID NO: 27 RR**RNW-VIT**D**AMEY**