transmembrane glycoprotein termed amyloid precursor protein (APP). As a result of proteolytic processing of APP by different secretase enzymes, Aβ is primarily found in both a short form, 40 amino acids in length, and a long form, ranging from 42-43 amino acids in length. Part of the hydrophobic transmembrane domain of APP is found at the carboxy end of Aβ, and may account for the ability of Aβ to aggregate into plaques, particularly in the case of the long form. Accumulation of amyloid plaques in the brain eventually leads to neuronal cell death. The physical symptoms associated with this type of neural deterioration characterize Alzheimer's disease.

SUMMARY

[006] The present disclosure relates to antibodies (and antibody fragments) that specifically bind to Aβ, methods of producing such antibodies and antibody fragments and associated nucleic acids, methods of treatment of patients with Aβ-related neurological disorders, pharmaceutical formulations and compositions of antibodies that show high affinity binding to Aβ for prophylactic and/or therapeutic use to, for example, treat, reduce the risk of or delay the outset of amyloidogenic disease, prevent, reduce or inhibit markers of amyloidogenic disease, e.g., Aβ plaques, and improve cognition. The present disclosure further relates to methods of detecting amyloid plaques and measuring the efficacy of treatment in patients being treated for amyloidogenic disease. The disclosure is based, at least in part, on the identification and characterization of monoclonal antibodies that specifically bind to Aβ peptide and are effective at reducing plaque burden and neutralizing soluble Aβ species associated with amyloidogenic disorders.

[006a] In one aspect, there is provided an antibody or fragment thereof that that specifically binds to Aβ peptide, comprising a heavy chain variable region comprising heavy chain CDR1, CDR2 and CDR3 and a light chain variable region comprising light chain CDR1, CDR2 and CDR3, wherein the heavy chain CDR1, CDR2 and CDR3 and the light chain CDR1, CDR2 and CDR3 are as shown for one of the antibodies in Table 1A and Table 1B.

[006b] In one aspect, there is provided an antibody or fragment thereof that that specifically binds to Aβ peptide, comprising a heavy chain variable region comprising heavy chain CDR1, CDR2 and CDR3 and a light chain variable region comprising light chain CDR1, CDR2 and CDR3, wherein heavy chain CDR1 comprises one of SEQ ID NO: 16, 19, or 20, heavy chain CDR2 comprises one of SEQ ID NO: 20, 21, 22 or 23, heavy chain CDR3

comprises one of SEQ ID NO: 18, 24, or 25, light chain CDR1 comprises one of SEQ ID NO: 26, 29, 31, or 32, light chain CDR2 comprises one of SEQ ID NO: 33, 34, 35 or 36, and light chain CDR3 comprises one of SEQ ID NO: 28, 38 or 39.

[007] In various aspects, the disclosure are directed to antibodies or fragments thereof that that specifically binds to Aβ peptide. The antibodies and fragments include a heavy chain variable region including heavy chain CDR1, CDR2 and CDR3 and a light chain ariable region including light chain CDR1, CDR2 and CDR3, wherein the heavy chain CDR1, CDR2 and CDR3 and the light chain CDR1, CDR2 and CDR3 are as shown for one of the antibodies in Table 1. In addition, the antibodies or fragments or fragments of the disclosure may have a heavy chain variable region that is as shown for one of the antibodies in Table 1 and may have a light chain variable region that is shown for one of the antibodies in Table 1.

disease. Such methods include administering to the subject an effective regime of the antibody or fragment thereof as described herein.

[0030] The methods of the disclosure also include inhibiting or reducing Aβ accumulation or aggregation in brain tissue of a subject having or at risk of developing an amyloidogenic disease. Such methods include administering to the subject an effective regime of the antibody or fragment thereof as described herein. .

[0031] A method of inhibiting Aβ accumulation or aggregation in brain tissue of a subject having or at risk of developing an amyloidogenic disease, including administering to the subject an effective regime of the antibody of any one of claims 1 to 18, thereby inhibiting Aβ accumulation or aggregation in brain tissue in the subject. The amyloidogenic disease may be systemic amyloidosis, Alzheimer's disease, mature onset diabetes, Parkinson's disease, Huntington's disease, fronto-temporal dementia, Down's syndrome, or mild cognitive impairment. The Aβ may be $A\beta_{1-42}$, pyroglutamate species of Aβ (e.g., $A\beta_{pE3-42}$), or a combination thereof.

[0032] In each of the foregoing methods of the disclosure, the antibody is administered by peripheral administration, which may be intravenous or subcutaneous administration.

[0032a] In one aspect, provided herein is a use of the antibody or fragment thereof as described herein in the manufacture of a medicament for treating a patient diagnosed with Alzheimer's disease, wherein the medicament is to be administered to the having the disease in a regime effective to treat the disease.

[0032b] In one aspect, provided herein is a use of an antibody or fragment thereof as described herein in the manufacture of a medicament for reducing the risk or delaying the outset of Alzheimer's disease in a patient whose risk of the disease has been determined from a genetic or biochemical marker, wherein the medicament is to be administered to the patient in a regime effective to reduce the risk or delay the outset of the disease.

[0032c] In one aspect, provided herein is a use of the antibody or fragment thereof as described herein in the manufacture of a medicament for effecting improvement of cognition in a subject having a condition or disease related amyloidogenic disease.

[0032d] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for treating Down's syndrome or clinical or pre-clinical Alzheimer's disease in a human subject.

[0032e] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for inhibiting the formation of amyloid plaque in a human subject.

[0032f] In one aspect, provided herein is a use of a humanized antibody or fragment of as described herein in the manufacture of a medicament for reducing amyloid plaque in the brain of a human subject.

[0032g] In one aspect, provided herein is a use of the antibody as described herein in the manufacture of a medicament for inhibiting or reducing amyloid plaque in a subject having or at risk of developing an amyloidogenic disease, wherein the medicament is to be administered to the subject an effective regime thereby inhibiting or reducing amyloid plaque in the subject.

[0032h] In one aspect, provided herein is a use of an antibody or fragment thereof as described herein in the manufacture of a medicament for detecting amyloid plaques in a subject having or at risk of an amyloidogenic disease, wherein the medicament is to be administered to the subject and the antibody or fragment thereof bound to Aβ in the subject is to be detected.

[0032i] In one aspect, provide herein is a method of measuring efficacy of treatment in a subject being treated for an amyloidogenic disease, comprising: (a) measuring a first level of amyloid plaque in the subject prior to treatment by administration to a subject an antibody or fragment thereof as described herein, and detecting a first amount of the antibody or fragment thereof bound to Aβ in the subject, (b) measuring a second level of amyloid plaque in the subject after treatment by administration to a subject the antibody or fragment thereof, and detecting the antibody or fragment thereof bound to Aβ in the subject, wherein the treatment is to be administered to the subject after step (a) and prior to step (b), wherein a decrease in the level of amyloid plaque indicates a positive response to treatment.

[0032j] In one aspect, provided herein is a method of measuring efficacy of treatment in a subject being treated for an amyloidogenic disease, comprising: (a) measuring a first level of amyloid plaque in the subject prior to treatment by administration to a subject an antibody or fragment thereof of as described herein, and detecting a first amount of antibody or fragment thereof bound to Aβ in the subject, (b) measuring a second level of amyloid plaque in the subject after treatment by administration to a subject the antibody or fragment thereof, and detecting a second amount of antibody or fragment thereof bound to Aβ in the subject, wherein the treatment is to be administered to the subject after step (a) and prior to step (b), wherein no change in the level of amyloid plaque or a small increase in amyloid plaque indicates a positive response to treatment.

[0032k] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for promoting clearance of Aβ in a human subject, wherein the medicament is to be administered to the subject in an effective regime.

[0032l] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for clearing Aβ in a human subject, wherein the medicament is to be administered to the subject in an effective regime.

[0032m] In one aspect, provided herein is a use of the antibody or as described herein in the manufacture of a medicament for reducing Aβ in a human subject, wherein the medicament is to be administered to the subject in an effective regime.

[0032n] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for reducing Aβ accumulation or aggregation in a human subject, wherein the medicament is to be administered to the subject in an effective regime.

[0032o] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for inhibiting Aβ accumulation or aggregation in a human subject, wherein the medicament is to be administered to the subject in an effective regime.

[0032p] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for promoting clearance of Aβ in brain tissue of a subject having or at risk of developing an amyloidogenic disease, wherein the medicament is to be administered to the subject in an effective regime, thereby promoting clearance of Aβ in brain tissue in the subject.

[0032q] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for clearing Aβ in brain tissue of a subject having or at risk of developing an amyloidogenic disease, wherein the medicament is to be administered to the subject in an effective regime, thereby clearing Aβ in brain tissue in the subject.

[0032r] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for reducing Aβ in brain tissue of a subject having or at risk of developing an amyloidogenic disease, wherein the medicament is to be administered to the subject in an effective regime, thereby reducing Aβ in brain tissue in the subject.

[0032s] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for reducing Aβ accumulation or aggregation in brain tissue of a subject having or at risk of developing an amyloidogenic disease, wherein the medicament is to be administered to the subject in an effective regime, thereby reducing Aβ accumulation or aggregation in brain tissue in the subject.

[0032t] In one aspect, provided herein is a use of the antibody or fragment as described herein in the manufacture of a medicament for inhibiting Aβ accumulation or aggregation in brain tissue of a subject having or at risk of developing an amyloidogenic disease, wherein the medicament is to be administered to the subject in an effective regime, thereby inhibiting Aβ accumulation or aggregation in brain tissue in the subject.

[0032u] In one aspect, provided herein is an antibody or fragment as described herein for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] **FIG. 1** shows an alignment of three different versions of VL that were designed by incorporating human germline framework residues into bapineuzumab (hBP) VL sequence. Canonical or interface residues were not changed.

[0034] **FIG. 2** shows competitive ELISA assay graphs for 4918, 4917, 4921, 3818, 49human3, 2931 and bapineuzumab control for IC_{50} ratio determination relative to bapineuzumab (hBP).

[0035] **FIG. 3** shows competitive ELISA assay graphs for 2926, 2831, 2927, 2726, 2731, 2826 and bapineuzumab control for IC_{50} ratio determination relative to bapineuzumab (hBP).

[0036] **FIG. 4** shows competitive ELISA assay graphs for 2727, 2931 and bapineuzumab control for IC_{50} ratio determination relative to bapineuzumab (hBP).

[0037] **FIG. 5A** and **FIG. 5B** show competitive ELISA assay graphs for 2931, 2731 and bapineuzumab (FIG. 5A) and 2726, 2831 and bapineuzumab (FIG. 5B).

[0038] **FIGS. 6A-6D** shows BIAcore sensorgrams of binding of h2726 (**FIG. 6A**), h2731 (**FIG. 6B**), h2831 (**FIG. 6C**) and 2931 (**FIG. 6D**) to $A\beta_{1-28}$ at analyte concentrations from 100 nM to 0.39 nM (2-fold serial dilutions).

[0039] **FIG. 7** shows a BIAcore sensorgram comparing binding characteristics of humanized antibodies (PB-0569 (aducanumab), PB-0573 (h2726), PB-0574 (h2731), PB-0575 (h2831), PB-0576 (h2931)) to recombinant Abeta 1-42 ($A\beta_{1-42}$) fibrils.

[0040] **FIG. 8** shows h2931 binds soluble Aβ oligomers with high relative affinity.

[0041] **FIG. 9** shows graphs evaluating Aβ fibril binding activity of 2726, 2731, 2831, 2931 versus aducanumab control. Antibody was titrated in a constant concentration of Aβ fibrils (left panel) or Aβ fibrils were titrated in a constant concentration of antibody (right panel), both indicating substantially better binding for 2726, 2731, 2831 and 2931 than for aducanumab.

[0042] **FIG. 10** shows Aβ binding in AD brain. Binding to tissue Aβ pathology appears similar among h2726, h2731, h2831 and h2931 antibodies. Examples of images stained with the four antibodies, h2726, h2731, h2831, h2931, at 0.3 µg/ml show their pattern of staining in two AD brains with different amounts of Aβ pathology (AD 11-97 and AD 13-75). For each brain, the images are from the same area of the section and show comparatively similar intensity and distribution of pathology with all four antibodies. Staining with aducanumab was always the weakest (Scale bar: 500 µm).

[0043] **FIG. 11** shows Aβ binding in AD brain of controls. Human IgG isotype control antibody produced no staining in AD brains. As shown in these examples, AD sections incubated with human IgG isotype at 1 µg/ml were devoid of any staining (Scale bar: 500 µm).

[0044] **FIG. 12** shows quantification of Aβ binding in AD brain. Quantification of Aβ pathology staining in AD tissues revealed similar binding between h2726, h2731, h2831 and h2931 antibodies. Section from four AD brains were incubated with the antibodies h2726, h2731, h2831, h2931 as well as aducanumab at the following concentrations: 0.03, 0.1, 0.3, 1, 3 and 9 µg/ml. After imaging of sections, the percent of stained tissue area was determined morphometrically using Halo® imaging analysis software. Each graph compares measurements in an AD brain obtained with the five antibodies. The four graphs consistently

show that the binding profiles of h2726, h2731, h2831, h2931 antibodies are similar. Measurements obtained with aducanumab were significantly lower.

[0045] **FIG. 13** shows Aβ binding in AD brain. hBP binds to tissue Aβ pathology strongly and in a dose-dependent manner. Images from relatively the same area of the section (Brain AD 13-75) with similar pathology distribution. hBP shows an increase in the amount of staining with concentration, and its binding to Aβ pathology was stronger than that of BAN2401 or aducanumab at each concentration (Scale bar: 500 µm).

[0046] **FIGS. 14A and 14B** show~~s~~ individual (**FIG. 14A**) and pooled (**FIG. 14B**) results from an ex vivo phagocytosis study of h2931 and aducanumab in APP.PS1 Tg mouse tissue with primary murine microglia. h2931 and aducanumab both demonstrate highly significant reductions in $A\beta_{1-42}$ over isotype control. ~~FIG. 14B~~

[0047] **FIGS. 15A and 15B** show~~s~~ graphs indicating a reduction of soluble oligomer binding to neurites on rat hippocampal neurons with increasing concentration of h2726, h2731, h2831 and h2931 compared to isotype control, and normalized by +/- Aβ addition. **FIG. 15A** shows spots per neuron and **FIG. 15B** shows total spot counts (at 40 fields per well).

[0048] **FIG. 16** shows a graph representing the percentage of Aβ spots per neuron with increasing concentration of 2726, 2731, 2831 and 2931 normalized by +/- Aβ addition.

[0049] **FIG. 17** shows an alignment of bapineuzumab variable heavy chain sequence and four sequences of the disclosure, 2726, 2731, 2831 and 2931. CDRs are in bold.

[0050] **FIG. 18** shows an alignment of bapineuzumab light chain sequence and four (variable light chain) sequences of the disclosure, 2726, 2731, 2831 and 2931. CDRs are in bold.

[0051] **FIGS. 19A and 19B** show~~s~~ a CDR table listing the variable heavy and light chain CDR sequences for antibodies of the disclosure. **FIG. 19A** refers to heavy chain CDRs and **FIG. 19B** refers to light chain CDRs.

[0052] **FIGS. 20A and 20B** show~~s~~ graphs measuring antibody potency for binding heterogenous aggregated Aβ42 species by competition ELISA. **FIG. 20A** shows h2931, h2731 and bapineuzumab control, and **FIG. 20BA** shows h2831, h2726 and bapineuzumab control.

NOS: 17, 20, 21 22, and 23 and wherein CDR3 may be selected from any one of SEQ ID NOS: 18, 24, 25. In addition, the antibody or fragment thereof includes a light chain CDR1, CDR2, and CDR3, wherein CDR1 may be selected from any one of SEQ ID NOS: 26, 29, 31, and 32, wherein CDR2 may be selected from any one of SEQ ID NOS: 27, 33, 34 and 35, and wherein CDR3 may be selected from any one of SEQ ID NOS: 28, 38 and 39. In each of these embodiments, the heavy chain CDRs and the light chain CDRs are not, in combination, simultaneously SEQ ID NOS: 16, 17, 18, 26, 27 and 28.

[00105] Analysis of protein modeling information for the antibodies described above identified two changes in the CDRs that, among others, were the contributors to increased avidity/affinity characteristics of the antibodies of the disclosure:

CDR-L1: S32Y (Ser to Tyr at position 32), and

CDR-H2: G55S (Gly to Ser at position ~~54~~55)

[00106] Anti-Aβ antibodies with Tyr at position 32 in CDR-L1 and Ser at position ~~54~~ 55 in CDR-H2 that bind the same epitope bound by antibodies listed herein are expected to have the same properties as the listed identified antibodies (*See* Table 1A and Figure 19A and Figure 19B). Antibodies disclosed that do not have Tyr at position 32 in CDR-L1 and Ser at position 55 in CDR-H2 can be modified to possess Tyr at position 32 in CDR-L1 and Ser at position 55 in CDR-H2 and can be expected to confer similar binding properties to such antibodies identified herein.

[00107] Examples of a CDR-L1 with Tyr at position 32 include SEQ NOs: 29 and 31. Examples of a CDR-H2 with Ser at position 55 include SEQ Nos: 20 and 21.

[00108] As examples, antibodies comprising a CDR-L1 with Tyr at position 32 and a CDR-H2 with Ser at position 55 include antibodies with the CDRs of h2726, h2731, h2727, h2826, h2831, h2926, h2927, h2931, h2929 (See Table 1A). Additional such antibodies include antibodies comprising LC CDRs 1, 2, 3 and HC CDRs 1, 2, 3 as set forth in the table below in Table 1B.

Table 1B

Antibody	**HC/LC**	**CDR Sequences (HC 1, 2, 3; LC 1, 2, 3)**		**SEQ ID**
h2729	HC	1	GFTFS NYGMS	16
		2	SIRSG SGRTY YSDNV KG	20

sequence variation in the VH and VL may be present outside the CDRs so that the VH and VL sequences of the disclosure include the CDRs identified in Table 1A, but the regions of the VH and VL sequences outside of the CDRs may be at least 75% identical to the regions outside the CDRs of the VH and VL sequences in Table 1A.

[00114] For example, the antibody or fragment of the disclosure may include a heavy chain variable region, excluding the CDRS, that is at least 95% identical to one of SEQ ID NOS: 3, 4, 5, 6 and 7, and the light chain variable region, excluding the CDRs, that is at least 95% identical to one of SEQ ID NOS: 8, 9, 10, 11, 12, 13, 14 and 15.

[00115] The antibodies and fragments of the disclosure may also include a heavy chain constant region that is at least 75% identical to SEQ ID NO: 40. For example, the heavy chain constant region may be 75% identical, 80%, identical, 85% identical, 90% identical, 95% identical, 96% identical, 97% identical, 98% identical, 99% identical, of 100% identical to SEQ ID NO: 40.

[00116] The antibodies and fragments of the disclosure may also include a light chain constant region that is at least 75% identical to SEQ ID NO: 41. For example, the ~~heavy~~ light chain constant region may be 75% identical, 80%, identical, 85% identical, 90% identical, 95% identical, 96% identical, 97% identical, 98% identical, 99% identical, of 100% identical to SEQ ID NO: 41.

[00117] A variant antibodies or fragments that are less than 100% identical to the sequences described in Table 1A (plus any constant region) can differ from an anti-Aβ antibody of Table 1A by as few as 1 to 15 amino acid residues, as few as 1 to 10 amino acid residues, such as 6-10, as few as 5, as few as 4, 3, 2, or even 1 amino acid residue. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly