Claims

1. An isolated human antibody or antigen-binding fragment thereof which is capable of binding a beta-amyloid plaque, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (V_H) and a light chain variable region (V_L) each comprising three complementarity determining regions (CDRs), wherein the CDRs comprise the heavy chain CDR1 of SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 26, or SEQ ID NO: 32, the heavy chain CDR2 of SEQ ID NO: 18, SEQ ID NO: 21, SEQ ID NO: 27 or SEQ ID NO: 33, the heavy chain CDR3 of SEQ ID NO: 19, SEQ ID NO: 22, SEQ ID NO: 28 or SEQ ID NO: 34, the light chain CDR1 of SEQ ID NO: 23, SEQ ID NO: 29, SEQ ID NO: 35, SEQ ID NO: 46, or SEQ ID NO: 49, the light chain CDR2 of SEQ ID NO: 24, SEQ ID NO: 30, SEQ ID NO: 36, SEQ ID NO: 47, or SEQ ID NO: 50, and the light chain CDR3 of SEQ ID NO: 25, SEQ ID NO: 31, SEQ ID NO: 37, SEQ ID NO: 48, or SEQ ID NO: 51, or the V_H region is selected from the group consisting of: SEQ ID NO:4; SEQ ID NO:6; SEQ ID NO: 10; SEQ ID NO: 14; SEQ ID NO: 39; SEQ ID NO: 42; and SEQ ID NO: 43, or the V_L region is selected from the group consisting of: SEQ ID NO:8; SEQ ID NO: 12; SEQ ID NO: 16; SEQ ID NO: 41; SEQ ID NO: 44; and SEQ ID NO: 45.

2. The isolated human antibody or antigen-binding fragment thereof of claim 1, comprising a V_H region and a V_L region each comprising three CDRs, wherein the CDRs are: the heavy chain CDR1 of SEQ ID NO: 20; the heavy chain CDR2 of SEQ ID NO: 21; and the heavy chain CDR3 of SEQ ID NO: 22; and the light chain CDR1 of SEQ ID NO: 23; the light chain CDR2 of SEQ ID NO: 24; and the light chain CDR3 of SEQ ID NO: 25.

3. An isolated antibody or antigen-binding fragment thereof which:

(a) specifically binds to the same beta-amyloid neoepitope as a reference antibody, wherein the reference antibody comprises a V_H region and a V_L region selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:8; SEQ ID NO:6 and SEQ ID NO: 8; SEQ ID NO: 10 and SEQ ID NO: 12; SEQ ID NO: 14 and SEQ ID NO: 16; SEQ ID NO: 39 and SEQ ID NO: 41; SEQ ID NO: 42 and SEQ ID NO: 44; and SEQ ID NO: 43 and SEQ ID NO: 45;

(b) competitively inhibits a reference antibody from binding to the beta-amyloid neoepitope, wherein the reference antibody comprises a V_H region and a V_L region

selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:8; SEQ ID NO:6 and SEQ ID NO: 8; SEQ ID NO: 10 and SEQ ID NO: 12; SEQ ID NO: 14 and SEQ ID NO: 16; SEQ ID NO: 39 and SEQ ID NO: 41; SEQ ID NO: 42 and SEQ ID NO: 44; and SEQ ID NO: 43 and SEQ ID NO: 45; or

(c) comprises an antigen binding domain identical to that of an antibody, wherein the antibody comprises a V_H region and a V_L region selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:8; SEQ ID NO:6 and SEQ ID NO: 8; SEQ ID NO: 10 and SEQ ID NO: 12; SEQ ID NO: 14 and SEQ ID NO: 16; SEQ ID NO: 39 and SEQ ID NO: 41; SEQ ID NO: 42 and SEQ ID NO: 44; and SEQ ID NO: 43 and SEQ ID NO: 45.

4. An isolated human antibody which is capable of selectively recognizing a neoepitope of a disorder-associated protein and which does not substantially recognize said protein in its non-disorder associated form, wherein said disorder is a neurological disorder and the antibody is capable of binding a beta-amyloid plaque, a cerebrovascular amyloid, a diffuse Abeta deposit, a neurofibrillary tangle, a hyperphosphorylated tau, an alpha-synuclein positive Lewy-bodies or an Abeta protein aggregate associated with dystrophic neuritis; wherein the antibody or its encoding cDNA is derived from B-cells or memory B-cells obtained from a human patient who is symptom-free but affected with or at risk of developing a disorder, or a human patient with an unusually stable disease course, and wherein the antibody has been identified by binding to a specimen of pathologically altered cells or tissue of predetermined clinical characteristics.

5. The antibody or fragment thereof of any one of claims 1-4, which is selected from the group consisting of a single chain Fv fragment (scFv), a F(ab') fragment, a F(ab) fragment, and an $F(ab')_2$ fragment.

6. A polynucleotide encoding the antibody or antigen-binding fragment thereof of any one of claims 1-5.

7. A vector comprising the polynucleotide of claim 6.

8. A host cell comprising the polynucleotide of claim 6, or the vector of claim 7.

9. A method for preparing a beta-amyloid specific antibody or antigen-binding fragment or immunoglobulin chain(s) thereof, comprising
   (a) culturing the host cell of claim 8; and
   (b) isolating said antibody or antigen-binding fragment thereof from the culture.

10. An isolated human antibody or antigen-binding fragment thereof encoded by the polynucleotide of claim 6, or obtained by the method of claim 9.

11. The antibody or antigen-binding fragment thereof of any one of claims 1-5 or 10, which is detectably labelled or is attached to a drug.

12. The antibody or antigen-binding fragment thereof of claim 11 wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore, and a heavy metal.

13. A composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-5 or 10-11, the polynucleotide of claim 6, the vector of claim 7, the host cell of claim 8, or any combination thereof, and a pharmaceutically-acceptable carrier.

14. The composition of claim 13, for the treatment of a neurological disorder characterized by abnormal accumulation and/or deposition of a protein in the central nervous system.

15. The composition of claim 14, wherein the disorder is selected from the group consisting of Alzheimer's disease, Down's syndrome, mild cognitive impairment, cerebral amyloid angiopathy, vascular dementia, multi-infarct dementia, Parkinson's disease, Huntington's disease, Creutzfeldt-Jakob disease, cystic fibrosis, and Gaucher's disease.

16. The composition of any one of claims 13-15, wherein the composition is designed to be administered intravenously, intramuscularly, subcutaneously, intraperitoneally, intranasally, parenterally or as an aerosol.

17. The composition of any one of claims 14-16, further comprising an additional agent useful for treating Alzheimer's disease, selected from the group consisting of a small organic molecules, an anti-Abeta antibody, and a combination thereof.

18. Use of the composition of any one of claims 13-17, in the preparation of a medicament for the treatment of a neurological disorder characterized by abnormal accumulation and/or deposition of a protein in the central nervous system.

19. The use of claim 18, wherein said disorder is selected from the group consisting of Down's syndrome, mild cognitive impairment, cerebral amyloid angiopathy, vascular dementia, multi-infarct dementia, Parkinson's disease, Dementia with Lewy Bodies, Huntington's disease, Creutzfeldt-Jakob disease, cystic fibrosis, and Gaucher's disease.

20. Use of the composition of any one of claims 13-17, in the preparation of a medicament or a diagnostic composition for treating or preventing the progression of Alzheimer's disease; for the amelioration of symptoms associated with Alzheimer's disease; for diagnosing or screening a subject for the presence of Alzheimer's disease or for determining a subject's risk for developing Alzheimer's disease.

21. The use of any one of claims 18-20, wherein said medicament is formulated for intravenous, intramuscular, sub-cutaneous, intraperitoneal, intranasal or parenteral administration, or is formulated as an aerosol.

22. A diagnostic kit comprising the antibody or antigen-binding fragment thereof of any one of claims 1-5 and 10-11, the polynucleotide of claim 6, the vector of claim 7, the host cell of claim 8, or any combination thereof, and reagents conventionally used in immuno or nucleic acid based diagnostic methods.

CLAIMS

1. An isolated human antibody or antigen-binding fragment thereof which is capable of binding a beta-amyloid plaque, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (V_H) and a light chain variable region (V_L) each comprising three complementarity determining regions (CDRs), wherein the CDRs comprise

(a) the heavy chain CDR1 of SEQ ID NO: 17, the heavy chain CDR2 of SEQ ID NO: 18, the heavy chain CDR3 of SEQ ID NO: 19, the light chain CDR1 of SEQ ID NO: 23, the light chain CDR2 of SEQ ID NO: 24, and the light chain CDR3 of SEQ ID NO: 25;

(b) the heavy chain CDR1 of SEQ ID NO: 20, the heavy chain CDR2 of SEQ ID NO: 21, the heavy chain CDR3 of SEQ ID NO: 22, the light chain CDR1 of SEQ ID NO: 23, the light chain CDR2 of SEQ ID NO: 24, and the light chain CDR3 of SEQ ID NO: 25;

(c) the heavy chain CDR1 of SEQ ID NO: 26, the heavy chain CDR2 of SEQ ID NO: 27, the heavy chain CDR3 of SEQ ID NO: 28, the light chain CDR1 of SEQ ID NO: 29, the light chain CDR2 of SEQ ID NO: 30, and the light chain CDR3 of SEQ ID NO: 31;

(d) the heavy chain CDR1 of SEQ ID NO: 32, the heavy chain CDR2 of SEQ ID NO: 33, the heavy chain CDR3 of SEQ ID NO: 34, the light chain CDR1 of SEQ ID NO: 35, the light chain CDR2 of SEQ ID NO: 36, and the light chain CDR3 of SEQ ID NO: 37;

(e) the heavy chain CDR1 of SEQ ID NO: 32, the heavy chain CDR2 of SEQ ID NO: 33, the heavy chain CDR3 of SEQ ID NO: 34, the light chain CDR1 of SEQ ID NO: 46, the light chain CDR2 of SEQ ID NO: 47, and the light chain CDR3 of SEQ ID NO: 48; or

(f) the heavy chain CDR1 of SEQ ID NO: 32, the heavy chain CDR2 of SEQ ID NO: 33, the heavy chain CDR3 of SEQ ID NO: 34, the light chain CDR1 of SEQ ID NO: 49, the light chain CDR2 of SEQ ID NO: 50, and the light chain CDR3 of SEQ ID NO: 51.

2. The isolated human antibody or antigen-binding fragment thereof of claim 1, comprising a V_H region and a V_L region each comprising three CDRs, wherein the CDRs are: the heavy chain CDR1 of SEQ ID NO: 20; the heavy chain CDR2 of SEQ ID NO: 21; and the heavy chain

CDR3 of SEQ ID NO: 22; and the light chain CDR1 of SEQ ID NO: 23; the light chain CDR2 of SEQ ID NO: 24; and the light chain CDR3 of SEQ ID NO: 25.

3. An isolated antibody or antigen-binding fragment thereof which comprises:

(a) a V_H region and a V_L region of SEQ ID NO:4 and SEQ ID NO:8, respectively;

(b) a V_H region and a V_L region SEQ ID NO:6 and SEQ ID NO: 8, respectively;

(c) a V_H region and a V_L region SEQ ID NO: 10 and SEQ ID NO: 12, respectively;

(d) a V_H region and a V_L region SEQ ID NO: 14 and SEQ ID NO: 16, respectively;

(e) a V_H region and a V_L region SEQ ID NO: 39 and SEQ ID NO: 41, respectively;

(f) a V_H region and a V_L region SEQ ID NO: 42 and SEQ ID NO: 44, respectively; or

(g) a V_H region and a V_L region SEQ ID NO: 43 and SEQ ID NO: 45, respectively.

4. The antibody or fragment thereof of claim 2, which comprises an antibody VH region and an antibody VL region, and wherein the V_H and V_L regions are SEQ ID NO:6 and SEQ ID NO:8, respectively.

5. The antibody or fragment thereof of claim 2, which comprises an antibody V_H region and an antibody V_L region, and wherein the V_H and V_L regions are SEQ ID NO:39 and SEQ ID NO:41, respectively.

6. An isolated antibody or antigen-binding fragment thereof which binds to beta amyloid and comprises a heavy chain variable region (V_H) and a light chain variable region (V_L),

wherein the V_H comprises a first complementarity determining region (VHCDR1) with the amino acid sequences SEQ ID NO:20, a VHCDR2 with the amino acid sequence SEQ ID NO:21, and a VHCDR3 with the amino acid sequences SEQ ID NO:22,

wherein the V_L comprises a VLCDR1 with the amino acid sequence SEQ ID NO:23, a VLCDR2 with the amino acid sequence SEQ ID NO:24, and a VLCDR3 with the amino acid sequence SEQ ID NO:25, and

wherein the antibody or fragment thereof further comprises a human IgG1 constant region or fragment thereof.

7. The antibody or fragment thereof of claim 6, which comprises an antibody V_H region and an antibody V_L region, and wherein the V_H and V_L regions are SEQ ID NO:6 and SEQ ID NO:8, respectively.

8 The antibody or fragment thereof of claim 6, which comprises an antibody V_H region and an antibody V_L region, and wherein the V_H and V_L regions are SEQ ID NO:39 and SEQ ID NO:41, respectively.

9. The antibody or fragment thereof of any one of claims 1-8, which is selected from the group consisting of a single chain Fv fragment (scFv), a F(ab') fragment, a F(ab) fragment, and an F(ab')2 fragment.

10. A polynucleotide encoding the antibody or antigen-binding fragment thereof of any one of claims 1-9.

11. A vector comprising the polynucleotide of claim 10.

12. A host cell comprising the polynucleotide of claim 10, or the vector of claim 11.

13. A method for preparing a beta-amyloid specific antibody or antigen-binding fragment or immunoglobulin chain(s) thereof, comprising

(a) culturing the host cell of claim 12; and

(b) isolating said antibody or antigen-binding fragment thereof from the culture.

14. An isolated human antibody or antigen-binding fragment thereof encoded by the polynucleotide of claim 10, or obtained by the method of claim 13.

15. The antibody or antigen-binding fragment thereof of any one of claims 1-9 or 14, which is detectably labelled or is attached to a drug.

16. The antibody or antigen-binding fragment thereof of claim 15 wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore, and a heavy metal.

17. A composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-9 or 14-15, the polynucleotide of claim 10, the vector of claim 11, the host cell of claim 12, or any combination thereof, and a pharmaceutically-acceptable carrier.

18. The composition of claim 17, for the treatment of a neurological disorder characterized by abnormal accumulation and/or deposition of a protein in the central nervous system.

19. The composition of claim 18, wherein the disorder is selected from the group consisting of Alzheimer's disease, Down's syndrome, mild cognitive impairment, cerebral amyloid angiopathy, vascular dementia, multi-infarct dementia, Parkinson's disease, Huntington's disease, Creutzfeldt-Jakob disease, cystic fibrosis, and Gaucher's disease.

20. The composition of any one of claims 17-19, wherein the composition is designed to be administered intravenously, intramuscularly, subcutaneously, intraperitoneally, intranasally, parenterally or as an aerosol.

21. The composition of any one of claims 18-20, further comprising an additional agent useful for treating Alzheimer's disease, selected from the group consisting of a small organic molecules, an anti-Abeta antibody, and a combination thereof.

22. Use of the composition of any one of claims 17-21, in the preparation of a medicament for the treatment of a neurological disorder characterized by abnormal accumulation and/or deposition of a protein in the central nervous system.

23. The use of claim 22, wherein said disorder is selected from the group consisting of Down's syndrome, mild cognitive impairment, cerebral amyloid angiopathy, vascular dementia, multi-infarct dementia, Parkinson's disease, Dementia with Lewy Bodies, Huntington's disease, Creutzfeldt-Jakob disease, cystic fibrosis, and Gaucher's disease.

24. Use of the composition of any one of claims 17-21, in the preparation of a medicament or a diagnostic composition for treating or preventing the progression of Alzheimer's disease; for the amelioration of symptoms associated with Alzheimer's disease; for diagnosing or screening a subject for the presence of Alzheimer's disease or for determining a subject's risk for developing Alzheimer's disease.

25. The use of any one of claims 22-24, wherein said medicament is formulated for intravenous, intramuscular, sub-cutaneous, intraperitoneal, intranasal or parenteral administration, or is formulated as an aerosol.

26. A diagnostic kit comprising one or more containers filled with the antibody or antigen-binding fragment thereof of any one of claims 1-9 and 14-15, the polynucleotide of claim 10, the vector of claim 11, the host cell of claim 12, or any combination thereof, and reagents conventionally used in immuno or nucleic acid based diagnostic methods.