

ANTI-N3pGlu AMYLOID BETA PEPTIDE ANTIBODIES AND USES THEREOF

The present invention relates to antibodies that bind human N3pGlu Amyloid Beta peptide and their use in treating diseases related to Amyloid Beta (herein referred to as A β or Abeta) peptide.

5 The cleavage of the amyloid precursor protein results in A β peptides ranging in size from 38 to 43 amino acids. Conversion of A β from soluble to insoluble forms having high β -sheet content and the deposition of these insoluble forms as neuritic and cerebrovascular plaques in the brain has been associated with a number of conditions and diseases, including Alzheimer's disease (AD), Down's syndrome, and cerebral amyloid
10 angiopathy (CAA).

 The deposits found in plaques are comprised of a heterogeneous mixture of A β peptides. N3pGlu A β , also referred to as N3pE, pE3-X, or A β_{p3-X} , is an N-terminal truncated form of A β peptide and is primarily found in plaque. N3pGlu A β lacks the first two amino acid residues at the N-terminus of human A β and has a pyroglutamate which
15 was derived from the glutamic acid at the third amino acid position. Although N3pGlu A β peptide is a minor component of the deposited A β in the brain, studies have demonstrated that N3pGlu A β peptide has aggressive aggregation properties and accumulates early in the deposition cascade.

 Antibodies to N3pGlu A β are known in the art. For example, U.S. Patent Number
20 8,679,498 discloses human N3pGlu A β antibodies (e.g. B12L; also known as LY3002813) and methods of treating diseases, such as Alzheimer's disease, with said antibodies. A clinical trial has demonstrated concerns with anti-drug antibodies against an anti- N3pGlu A β antibody (LY3002813). Anti-drug antibodies were present in the plasma of almost everyone treated in this trial, and an associated problem with the
25 immune reaction was a shortened half-life of LY3002813. Therefore, there still remains a need for alternative anti-N3pGlu A β antibodies.

Summary

In one aspect of the present disclosure, there is provided an antibody that binds human N3pGlu A β , comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises:

- 5 i) LCDR1 having the amino acid sequence of SEQ ID NO: 4, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 8; or
- ii) LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 7, and LCDR3 having the amino acid sequence of SEQ ID NO: 8, and
- 10 iii) LCDR3 having the amino acid sequence of SEQ ID NO: 8, and wherein the HCVR comprises HCDR1 having the amino acid sequence of SEQ ID NO: 1, HCDR2 having the amino acid sequence of SEQ ID NO: 2, and HCDR3 having the amino acid sequence of SEQ ID NO: 3.

In another aspect, the present disclosure refers to a pharmaceutical composition
15 comprising the antibody disclosed herein and one or more pharmaceutically acceptable carriers, diluents or excipients.

In a further aspect, the present disclosure refers to the antibody disclosed herein for use in therapy.

In another aspect, the present disclosure refers to the disclosed herein for use in
20 the treatment of a condition characterized by amyloid deposits (A β deposits).

In a further aspect, the present disclosure refers to the antibody disclosed herein for use in the treatment of a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA.

In another aspect, the present disclosure refers to the disclosed herein for use in the treatment of a condition selected from prodromal AD, mild AD, moderate AD, and severe AD.

5 In a further aspect, the present disclosure refers to the antibody disclosed herein for use in slowing cognitive or functional decline in a patient diagnosed with a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA.

10 In another aspect, the present disclosure refers to the antibody disclosed herein for use in slowing cognitive or functional decline in a patient diagnosed with a condition selected from prodromal AD, mild AD, moderate AD, and severe AD.

In a further aspect, the present disclosure refers to the antibody disclosed herein in reducing brain A β amyloid plaque load.

15 In another aspect, the present disclosure refers to the antibody disclosed herein for use in treating a condition characterized by amyloid deposits (A β deposits) in a patient having the PSEN1 E280A genetic mutation.

In a further aspect, the present disclosure refers to the antibody disclosed herein for use in treating a condition characterized by amyloid deposits (A β deposits) in a patient having a genetic mutation that causes autosomal-dominant Alzheimer's disease.

5 In another aspect, the present disclosure refers to the antibody disclosed herein for use in treating memory loss or cognitive decline in a patient having the PSEN1 E280A genetic mutation.

In a further aspect, the present disclosure refers to the antibody disclosed herein for use in treating memory loss or cognitive decline in a patient having a genetic mutation that causes autosomal-dominant Alzheimer's disease.

10 In another aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for the treatment of a condition characterized by amyloid deposits (A β deposits).

15 In a further aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for the treatment of a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA.

In another aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for the treatment of a condition selected from prodromal AD, mild AD, moderate AD, and severe AD.

In a further aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for slowing cognitive or functional decline in a patient diagnosed with a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA.

5 In another aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for slowing cognitive or functional decline in a patient diagnosed with a condition selected from prodromal AD, mild AD, moderate AD, and severe AD.

10 In a further aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for reducing brain A β amyloid plaque load.

 In another aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for treating a condition characterized by deposition of A β in a patient having the PSEN1 E280A genetic mutation.

15 In a further aspect, the present disclosure refers to a use of the disclosed herein in the manufacture of a medicament for treating a condition characterized by deposition of A β in a patient having a genetic mutation that causes autosomal-dominant Alzheimer's disease.

20 In another aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for treating memory loss or cognitive decline in a patient having the PSEN1 E280A genetic mutation.

 In a further aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for treating memory loss or cognitive decline in a patient having a genetic mutation that causes autosomal-dominant Alzheimer's disease.

In another aspect, the present disclosure refers to a pharmaceutical composition for use in treating a condition characterized by amyloid deposits (A β deposits), comprising an effective amount of the antibody disclosed herein.

5 In a further aspect, the present disclosure refers to a pharmaceutical composition for use in treating a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA, comprising an effective amount of the antibody disclosed herein.

10 In another aspect, the present disclosure refers to a pharmaceutical composition for use in treating a condition selected from prodromal AD, mild AD, moderate AD, and severe AD, comprising an effective amount of the antibody disclosed herein.

Description

15 The antibodies of the present invention seek to provide anti-N3pGlu A β antibodies that bind N3pGlu A β , lower plaque (A β ₁₋₄₂) *in vivo*, but which also demonstrate reduced immunogenicity. Such anti-N3pGlu A β antibodies may also demonstrate reduced non-specific binding to plasma proteins. In addition, such anti-

WE CLAIM:

1. An antibody that binds human N3pGlu A β , comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR),
5 wherein the LCVR comprises:
 - i) LCDR1 having the amino acid sequence of SEQ ID NO: 4, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 8; or
 - 10 ii) LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 7, and LCDR3 having the amino acid sequence of SEQ ID NO: 8, and
 - iii) LCDR3 having the amino acid sequence of SEQ ID NO: 8, and wherein the HCVR comprises HCDR1 having the amino acid sequence of SEQ ID NO: 1, HCDR2 having the amino acid sequence of SEQ ID NO:
15 2, and HCDR3 having the amino acid sequence of SEQ ID NO: 3.
2. The antibody of Claim 1, wherein LCDR1 has the amino acid sequence of SEQ ID NO: 4, LCDR2 has the amino acid sequence of SEQ ID NO: 6, LCDR3 has the amino acid sequence of SEQ ID NO: 8, HCDR1 having
20 the amino acid sequence of SEQ ID NO: 1, HCDR2 having the amino acid sequence of SEQ ID NO: 2, and HCDR3 having the amino acid sequence of SEQ ID NO: 3.
3. The antibody of Claim 1, wherein LCDR1 has the amino acid sequence of SEQ ID NO: 5, LCDR2 has the amino acid sequence of SEQ ID NO: 7, LCDR3 has the amino acid sequence of SEQ ID NO: 8, HCDR1 having
25 the amino acid sequence of SEQ ID NO: 1, HCDR2 having the amino acid sequence of SEQ ID NO: 2, and HCDR3 having the amino acid sequence of SEQ ID NO: 3.
4. The antibody of any one of Claims 1-3, wherein the LCVR has the amino acid sequence of SEQ ID NO: 10 or 11, and the HCVR has the amino acid
30 sequence of SEQ ID NO: 9.

5. The antibody of Claim 4, comprising a LCVR having the amino acid sequence of SEQ ID NO: 10, and a HCVR having the amino acid sequence of SEQ ID NO:9.
- 5 6. The antibody of Claim 4, comprising a LCVR having the amino acid sequence of SEQ ID NO: 11, and a HCVR having the amino acid sequence of SEQ ID NO:9.
7. The antibody of any one of Claims 1-6, comprising a light chain (LC) having the amino acid sequence of SEQ ID NO: 13 or 14, and a heavy chain (HC) having the amino acid sequence of SEQ ID NO: 12.
- 10 8. The antibody of Claim 7, comprising a LC having the amino acid sequence of SEQ ID NO: 13 and a HC having the amino acid sequence of SEQ ID NO: 12.
9. The antibody of Claim 7, comprising a LC having the amino acid sequence of SEQ ID NO: 14 and a HC having the amino acid sequence of SEQ ID NO: 12.
- 15 10. The antibody of any one of Claims 1-9, comprising two LCs and two HCs, wherein the amino acid sequence of each LC is SEQ ID NO: 13 or 14, and the amino acid sequence of each HC is SEQ ID NO: 12.
11. The antibody of Claim 10, wherein the amino acid sequence of each LC is SEQ ID NO:13, and the amino acid sequence of each HC is SEQ ID NO: 12.
- 20 12. The antibody of Claim 10, wherein the amino acid sequence of each LC is SEQ ID NO:14, and the amino acid sequence of each HC is SEQ ID NO: 12.
- 25 13. A pharmaceutical composition comprising the antibody of any one of Claims 1 to 12 and one or more pharmaceutically acceptable carriers, diluents or excipients.

14. The antibody of any one of Claims 1 to 12 for use in therapy.
15. The antibody of any one of Claims 1 to 12 for use in the treatment of a condition characterized by amyloid deposits (A β deposits).
- 5 16. The antibody of any one of Claims 1 to 12 for use in the treatment of a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA.
17. The antibody of any one of Claims 1 to 12 for use in the treatment of a condition selected from prodromal AD, mild AD, moderate AD, and severe AD.
- 10 18. The antibody of any one of Claims 1 to 12 for use in slowing cognitive or functional decline in a patient diagnosed with a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA.
- 15 19. The antibody of any one of Claims 1 to 12 for use in slowing cognitive or functional decline in a patient diagnosed with a condition selected from prodromal AD, mild AD, moderate AD, and severe AD.

20. The antibody of any one of Claims 1 to 12 for use in reducing brain A β amyloid plaque load.
21. The antibody of any one of Claims 1 to 12 for use in treating a condition characterized by amyloid deposits (A β deposits) in a patient having the PSEN1 E280A genetic mutation.
22. The antibody of any one of Claims 1 to 12 for use in treating a condition characterized by amyloid deposits (A β deposits) in a patient having a genetic mutation that causes autosomal-dominant Alzheimer's disease.
23. The antibody of any one of Claims 1 to 12 for use in treating memory loss or cognitive decline in a patient having the PSEN1 E280A genetic mutation.
24. The antibody of any one of Claims 1 to 12 for use in treating memory loss or cognitive decline in a patient having a genetic mutation that causes autosomal-dominant Alzheimer's disease.
25. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for the treatment of a condition characterized by amyloid deposits (A β deposits).
26. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for the treatment of a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA.

27. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for the treatment of a condition selected from prodromal AD, mild AD, moderate AD, and severe AD.
- 5 28. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for slowing cognitive or functional decline in a patient diagnosed with a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA.
- 10 29. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for slowing cognitive or functional decline in a patient diagnosed with a condition selected from prodromal AD, mild AD, moderate AD, and severe AD.
30. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for reducing brain A β amyloid plaque load.
- 15 31. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for treating a condition characterized by deposition of A β in a patient having the PSEN1 E280A genetic mutation.
- 20 32. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for treating a condition characterized by deposition of A β in a patient having a genetic mutation that causes autosomal-dominant Alzheimer's disease.
- 25 33. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for treating memory loss or cognitive decline in a patient having the PSEN1 E280A genetic mutation.
- 30 34. Use of the antibody of any one of Claims 1 to 12 in the manufacture of a medicament for treating memory loss or cognitive decline in a patient having a genetic mutation that causes autosomal-dominant Alzheimer's disease.
35. A pharmaceutical composition for use in treating a condition characterized by amyloid deposits (A β deposits), comprising an effective amount of the antibody of any one of Claims 1 to 12.

36. A pharmaceutical composition for use in treating a condition selected from clinical or pre-clinical AD, Down's syndrome, and clinical or pre-clinical CAA, comprising an effective amount of the antibody of any one of Claims 1 to 12.
- 5 37. A pharmaceutical composition for use in treating a condition selected from prodromal AD, mild AD, moderate AD, and severe AD, comprising an effective amount of the antibody of any one of Claims 1 to 12.