

ANTIBODY WHICH BINDS TO ABETAPE3

Field of the invention

The present invention relates to an antibody or antigen-binding fragment thereof which binds to A β pE3, i.e. to an N-terminally truncated and
5 pyroglutamate-modified form of amyloid beta (A β), and to therapeutic and diagnostic uses thereof.

Background

Alzheimer's disease (AD) is a progressive neurodegenerative dementia
10 disorder which exists in a more common late-onset form and an early-onset familial form. AD is characterized by progressive loss of memory and cognitive function. At present, AD treatments are limited to symptomatic management and the prognosis is poor for AD patients. It is estimated that about 18 million people worldwide are presently suffering from AD, and the
15 number of people suffering from AD is expected to increase due to the aging population. The prevalence of AD doubles approximately every 5 years from the age of 60, from 10% of individuals at the age of 65 to 50% of individuals at the age of 85 or more (Solomon (2007), Expert Opin Investig Drugs 16(6):819-828).

20 Accumulation of A β peptide in the brain is thought to play an important role in the neuropathology of AD. A β is generated from the amyloid precursor protein (APP) by sequential proteolysis and secreted via major regulated as well as minor constitutive secretory pathways. A β is a normal product of cell metabolism, which is present in the plasma and cerebrospinal fluid in healthy
25 individuals. However, abnormal and excessive accumulation of A β in the brain leads to the formation of toxic A β aggregates that induce synaptic dysfunction and neuronal loss.

The main variants of A β detected in the human brain are A β 1-40 and A β 1-42. However, a significant proportion of AD brain A β also consists of N-
30 terminally truncated species (A β n-40/42 where n=2 to 11). Most such N-truncated A β peptides have been considered to be degradation products of

CLAIMS

(1) the VH-CDR1 comprises an amino acid sequence of:

wherein

X_2 is selected from L and M;

LINPYNGX₃TTYNX₄KFX₅G (SEQ ID NO:2)

wherein

X_3 is selected from I and V

X_4 is selected from P and Q ; and

25 X_5 is selected from M and K:

(3) the VH-CDR3 comprises the amino acid sequence of:

EGNWEGVY (SEQ ID NO:3);

30 (4) the VL-CDR1 comprises an amino acid sequence

of:X6SSQSLLDSNGKTYLH (SEQ ID NO:4)

wherein

X_6 is selected from K and R :

(5) the VL-CDR2 comprises an amino acid sequence of:

LVSX₇LDS (SEQ ID NO:5)

wherein

5 X₇ is selected from I and K; and

(6) the VL-CDR3 comprises the amino acid sequence of:

VQGTHFPFT (SEQ ID NO:6).

10 2. The anti-A β pE3 antibody or antigen-binding fragment thereof according to claim 1, wherein

(1) the VH-CDR1 comprises the amino acid sequence of:

GFTMN (SEQ ID NO:7);

(2) the VH-CDR2 comprises the amino acid sequence of:

15 LINPYNGVTTYNQKFKG (SEQ ID NO:8); and

(3) the VL-CDR2 comprises the amino acid sequence of:

LVSILDS (SEQ ID NO:9).

20 3. The anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of preceding claims, wherein the heavy chain variable domain comprises an amino acid sequence selected from

i) the group consisting of SEQ ID NOs:15-22; and

ii) an amino acid sequence having at least 80 % identity to any one of SEQ ID NOs:15-22, provided that the three VH-CDR regions
25 comprise amino acid sequence of SEQ ID NO:7, SEQ ID NO:8 and SEQ ID NO:3.

4. The anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of preceding claims, wherein the VL-CDR1 comprises
30 the amino acid sequence of:

RSSQSLLDSNGKTYLH (SEQ ID NO:10).

5. The anti-A β pE3 antibody or antigen-binding fragment thereof according to claim 5, wherein the light chain variable domain comprises an amino acid sequence selected from

- i) the group consisting of SEQ ID NOs:23-24; and
- 5 ii) an amino acid sequence having at least 80 % identity to any one of SEQ ID NOs:23-24, provided that the three VL-CDR regions comprise amino acid sequence of SEQ ID NO:10, SEQ ID NO:9 and SEQ ID NO:6.

10 6. The anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of preceding claims, wherein

- a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:15, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO:23;
- 15 b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:16, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO:23;
- c) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:17, and the light chain variable domain comprises
- 20 the amino acid sequence of SEQ ID NO:23;
- d) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:18, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO:23;
- e) the heavy chain variable domain comprises the amino acid
- 25 sequence of SEQ ID NO:19, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO:23;
- f) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:20, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO:23;
- 30 g) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:21, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO:24; or

h) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:22, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO:23.

- 5 7. An anti-A β pE3 antibody or antigen-binding fragment thereof comprising:
- (1) a VH-CDR1 comprising the amino acid sequence of SEQ ID NO:7;
 - (2) a VH-CDR2 comprising the amino acid sequence of SEQ ID NO:8;
 - (3) a VH-CDR3 comprising the amino acid sequence of SEQ ID NO:3;
 - 10 (4) a VL-CDR1 comprising the amino acid sequence of SEQ ID NO:10;
 - (5) a VL-CDR2 comprising the amino acid sequence of SEQ ID NO:9;
- and
- (6) a VL-CDR3 comprising the amino acid sequence of SEQ ID NO:6.
- 15 8. The anti-A β pE3 antibody or antigen-binding fragment thereof of according to claim 7, comprises a VH comprising an amino acid sequence at least 95% identical, or at least 98% identical, or 100% identical to the amino acid sequence of SEQ ID NO:18, and a VL comprising an amino acid sequence at least 95% identical, or at least 98% identical, or 100% identical
- 20 to the amino acid sequence of SEQ ID NO:23.
9. The anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of preceding claims, wherein the A β pE3 is in a form selected from the group consisting of monomers, protofibrils, fibrils and
- 25 plaques.
10. The anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of preceding claims, wherein the antibody or antigen-binding fragment thereof has a binding affinity for protofibrils comprising
- 30 A β pE3 that corresponds to a K_D value of no more than 1 nM, such as between 1 and 200 pM, such as between 10 and 100 pM, as determined by surface plasmon resonance.

11. The anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of preceding claims, wherein the antibody or antigen-binding fragment thereof has a binding affinity for A β pE3 monomers that corresponds to a K_D value of no more than 100 nM, such as between 0.1 and 50 nM, such as between 0.5 and 10 nM, as determined by surface plasmon resonance.

12. A pharmaceutical composition, comprising an anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of preceding claims, and a pharmaceutically acceptable carrier or excipient.

13. An anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of claims 1-11 or a composition according to claim 12 for use in treatment, such as for use in therapeutic treatment or for use in prophylactic treatment.

14. An anti-A β pE3 antibody or antigen-binding fragment thereof according to any one of claims 1-11 or composition according to claim 12 for use in diagnosis *in vivo* or prognosis *in vivo*.

15. The anti-A β pE3 antibody or antigen-binding fragment thereof or composition for use according to any one of claims 13-14, wherein the therapeutic treatment, prophylactic treatment, *in vivo* diagnosis or *in vivo* prognosis is with respect to a neurodegenerative disorder associated with amyloid beta peptide aggregation, for example a disorder selected from the group consisting of Alzheimer's disease (AD) (including familial AD and sporadic AD), mild cognitive impairment (MCI), Lewy body dementia, neurodegeneration in Down's syndrome, cerebral amyloid angiopathy (CAA), hereditary cerebral hemorrhage with amyloidosis (Dutch type), progressive supranuclear palsy, multiple sclerosis, Creutzfeld-Jacob disease, cerebral amyloid angiopathy, Parkinson's disease, amyotrophic lateral sclerosis, cataract due to A β deposition, traumatic brain injury with an accumulation of

A β , adult onset diabetes, senile cardiac amyloidosis and macular degeneration.

16. The anti-A β pE3 antibody or antigen-binding fragment thereof or
5 composition for use according to claim 15, wherein the neurodegenerative disorder is Alzheimer's disease.