ANTI-N3pGlu AMYLOID BETA PEPTIDE ANTIBODIES AND USES THEREOF

The present invention relates to antibodies that selectively bind N3pGlu Amyloid Beta peptide and their use in treating diseases related to Amyloid Beta (Aβ, also referred to as Abeta) peptide.

The Aβ peptide in circulating form is composed of 38-43 amino acids (mostly 38, 40 or 42 amino acids) resulting from the cleavage of a precursor protein, amyloid precursor protein (APP). Conversion of Aβ 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 angiopathy (CAA).

The deposits found in plaques are comprised mainly of a heterogeneous mixture of Aβ peptides. N3pGlu Aβ, also referred to as N3pE or $A\beta_{p3-42}$, is a truncated form of the Aβ peptide found only in plaques. N3pGlu Aβ lacks the first two amino acid residues at the N-terminus of Aβ and has a pyroglutamate which was derived from the glutamic acid at the third amino acid position. Although N3pGlu Aβ peptide is a minor component of the deposited Aβ in the brain, studies have demonstrated that N3pGlu Aβ peptide has aggressive aggregation properties and accumulates early in the deposition cascade.

While polyclonal and monoclonal antibodies that target the N3pGlu Aβ peptide have been previously described (US 7,122,374 and WO2010/009987), there is still a need for high affinity anti-N3pGlu Aβ monoclonal antibodies to engage the target *in vivo* (i.e. plaque binding) and subsequently lower plaque levels. In addition, given that amino-terminal and carboxyl-terminal anti-Aβ antibodies lead to an increase in cerebral amyloid angiopathy (CAA) related microhemorrhage, there is a need for anti-N3pGlu Aβ antibodies that do not result in an increase in microhemorrhage even though chronic treatment results in a significant reduction of deposited plaque.

Summary

In a first aspect, there is provided a human engineered anti-N3pGlu Aβ monoclonal antibody or antigen-binding fragment thereof, comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR comprises LCDR1, LCDR2, and LCDR3 polypeptides and HCVR comprises HCDR1, HCDR2, and HCDR3 polypeptides which are selected from the group consisting of:

a) LCDR1 is KSSQSLLYSRGKTYLN (SEQ ID NO: 3), LCDR2 is AVSKLDS (SEQ ID NO: 4), LCDR3 is VQGTHYPFT (SEQ ID NO: 5), HCDR1 is GYDFTRYYIN (SEQ ID NO: 6), HCDR2 is WINPGSGNTKYNEKFKG (SEQ ID NO: 8), and HCDR3 is EGITVY (SEQ ID NO: 9);

b) LCDR1 is KSSQSLLYSRGKTYLN (SEQ ID NO: 3), LCDR2 is AVSKLDS (SEQ ID NO: 4), LCDR3 is VQGTHYPFT (SEQ ID NO: 5), HCDR1 is GYTFTRYYIN (SEQ ID NO: 7), HCDR2 is WINPGSGNTKYNEKFKG (SEQ ID NO: 8), and HCDR3 is EGTTVY (SEQ ID NO: 10);

c) LCDR1 is KSSQSLLYSRGKTYLN (SEQ ID NO: 3), LCDR2 is AVSKLDS (SEQ ID NO: 4), LCDR3 is VQGTHYPFT (SEQ ID NO: 5), HCDR1 is GYTFTDYYIN (SEQ ID NO: 40), HCDR2 is WINPGSGNTKYNEKFKG (SEQ ID NO: 8), and HCDR3 is EGETVY (SEQ ID NO: 41);

d) LCDR1 is KSSQSLLYSRGKTYLN (SEQ ID NO: 3), LCDR2 is AVSKLGS (SEQ ID NO: 35), LCDR3 is VQGTHYPFT (SEQ ID NO: 5), HCDR1 is GYTFTRYYIN (SEQ ID NO: 7), HCDR2 is WINPGSGNTKYNEKFKG (SEQ ID NO: 8), and HCDR3 is EGTTVY (SEQ ID NO: 10); and

e) LCDR1 is KSTRSLLYSRSKTYLN (SEQ ID NO: 45), LCDR2 is AVSKLDS (SEQ ID NO: 4), LCDR3 is VQGTHYPFT (SEQ ID NO: 5), HCDR1 is GYTFTDYYIN (SEQ ID NO: 40), HCDR2 is WINPGSGNTKYNEKFKG (SEQ ID NO: 8), and HCDR3 is EGVTVY (SEQ ID NO: 46).

In a second aspect, there is provided a pharmaceutical composition comprising the human engineered antibody or antigen-binding fragment thereof as defined herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

In a third aspect, there is provided a pharmaceutical composition comprising the human engineered antibody or antigen-binding fragment thereof as defined herein, and a pharmaceutically acceptable carrier diluent, or excipient, for use in therapy.

In a fourth aspect, there is provided a pharmaceutical composition comprising the human engineered antibody or antigen-binding fragment thereof as defined herein and a pharmaceutically acceptable carrier diluent, or excipient, for use in the treatment of a condition selected from clinical or pre-clinical Alzheimer's disease, prodromal Alzheimer's disease, Down's syndrome, or clinical or pre-clinical CAA.

In a fifth aspect, there is provided a human engineered antibody or antigen-binding fragment thereof, as defined herein, for use in therapy.

In a sixth aspect, there is provided a human engineered antibody or antigen-binding fragment thereof, as defined herein, for use in the treatment of a condition selected from clinical or pre-clinical Alzheimer's disease, prodromal Alzheimer's disease, Down's syndrome, or clinical or pre-clinical CAA.

Detailed Disclosure

The antibodies within the scope of the present invention are therapeutically useful N3pGlu Aβ peptide antagonists possessing a number of desirable properties. The present antibodies bind human N3pGlu Aβ peptide with high affinity and exhibit dose-dependent *in vivo* plaque lowering without an increase in cerebral amyloid angiopathy (CAA) related microhemorrhage.

The present invention provides a human engineered anti-N3pGlu Aβ antibody, or antigen-binding fragment thereof that has a Kd at 25°C of less than 1×10^{-9} M for human N3pGlu Aβ peptide. In a preferred embodiment, the present invention provides a human engineered anti-N3pGlu Aβ