Claims:

1. A polypeptide comprising a first immunoglobulin single variable domain specifically binding to a first epitope of A-beta and a second immunoglobulin single variable domain specifically binding to a second epitope of A-beta, wherein said first and said second epitopes of A-beta are not identical epitopes.

2. The polypeptide according to claim 1, wherein said first and said second immunoglobulin single variable domains each essentially consist of four framework regions (FR1 to FR4, respectively) and three complementarity determining regions (CDR1 to CDR3, respectively), wherein said first and said second immunoglobulin single variable domains are covalently linked by a linker peptide, wherein said linker peptide optionally comprises or consists of a third immunoglobulin domain.

3. The polypeptide according to claim 1 or claim 2, wherein said first and said second immunoglobulin single variable domains are antibody domains, preferably VHH domains, and more preferably humanized VHH domains.

4. The polypeptide according to any of the preceding claims, wherein said first epitope of A-beta is the epitope defined by SEQ ID NO:3 and said second epitope of A-beta is the epitope defined by SEQ ID NO:4, or wherein said first epitope of A-beta is the epitope defined by SEQ ID NO:4 and said second epitope of A-beta is the epitope defined by SEQ ID NO:3.

5. The polypeptide according to any of the preceding claims, wherein said polypeptide forms contacts to at least amino acids 1 (aspartate), 3 (glutamate), 19 (phenylalanine), 20 (phenylalanine), and 23 (aspartate) of the human A-beta peptide (SEQ ID NO:1)

6. The polypeptide according to any of the preceding claims, wherein the IC50 value as measured in a TR-FRET binding assay (using ABII002 = SEQ ID

NO:62 and ABII050 = SEQ ID NO:100 as competitors) is in the range of 10^{-9} moles/litre or less, and preferably in the range of from 5×10^{-10} moles/litre to 10^{-12} moles/litre.

7. The polypeptide according to any of claims 2 to 6, wherein said polypeptide comprises two A-beta binding immunoglobulin single variable domains, said immunoglobulin single variable domains having the structure FR(1)1 - CDR(1)1 - FR(1)2 - CDR(1)2 - FR(1)3 - CDR(1)3 - FR(1)4, and FR(2)1 - CDR(2)1 - FR(2)2 - CDR(2)2 - FR(2)3 - CDR(2)3 - FR(2)4, respectively, and wherein

CDR(1)3 is selected from the group consisting of:
- the amino acid sequences according to SEQ ID NO:13 and SEQ ID NO:16; and
- amino acid sequences which have up to three, preferably up to two, and more preferably one amino acid difference as compared to said amino acid sequences according to SEQ ID NO:13 or SEQ ID NO:16, respectively; and
CDR(2)3 is selected from the group consisting of:
- the amino acid sequence according to SEQ ID NO:19; and
- amino acid sequences which have up to three, preferably up to two, and more preferably one amino acid difference as compared to said amino acid sequence according to SEQ ID NO:19;

or wherein

CDR(1)3 is selected from the group consisting of:
- the amino acid sequence according to SEQ ID NO:19; and
- amino acid sequences which have up to three, preferably up to two, and more preferably one amino acid difference as compared to said amino acid sequence according to SEQ ID NO:19; and
CDR(2)3 is selected from the group consisting of:
- the amino acid sequences according to SEQ ID NO:13 and SEQ ID NO:16; and

amino acid sequences which have up to three, preferably up to two, and more preferably one amino acid difference as compared to said amino acid sequences according to SEQ ID NO:13 or SEQ ID NO:16, respectively.

8. The polypeptide according to any of claims 2 to 7, wherein the CDR sequences of said first immunoglobulin variable domain (CDR(1) sequences) and the CDR sequences of said second immunoglobulin variable domain (CDR(2) sequences) are defined as follows:

- CDR(1)1: SEQ ID NO:11
- CDR(1)2: SEQ ID NO:12
- CDR(1)3: SEQ ID NO:13
- CDR(2)1: SEQ ID NO:17
- CDR(2)2: SEQ ID NO:18
- CDR(2)3: SEQ ID NO:19

or:

- CDR(1)1: SEQ ID NO:14
- CDR(1)2: SEQ ID NO:15
- CDR(1)3: SEQ ID NO:16
- CDR(2)1: SEQ ID NO:17
- CDR(2)2: SEQ ID NO:18
- CDR(2)3: SEQ ID NO:19

or:

- CDR(1)1: SEQ ID NO:17
- CDR(1)2: SEQ ID NO:18
- CDR(1)3: SEQ ID NO:19
- CDR(2)1: SEQ ID NO:11
- CDR(2)2: SEQ ID NO:12
- CDR(2)3: SEQ ID NO:13

or:

- CDR(1)1: SEQ ID NO:17
- CDR(1)2: SEQ ID NO:18
- CDR(1)3: SEQ ID NO:19
- CDR(2)1: SEQ ID NO:14

- CDR(2)2: SEQ ID NO:15
- CDR(2)3: SEQ ID NO:16.

9. The polypeptide according to any of the preceding claims, wherein the polypeptide comprises a first immunoglobulin single variable domain and a second immunoglobulin single variable domain, wherein said first immunoglobulin single variable domain is VHH domain ABII035 (SEQ ID NO:44), and said second immunoglobulin single variable domain is VHH domain ABII059 (SEQ ID NO:45), or wherein said first immunoglobulin single variable domain is VHH domain ABII059 (SEQ ID NO:45), and said second immunoglobulin single variable domain is VHH domain ABII035 (SEQ ID NO:44).

10. The polypeptide according to any of claims 1 to 9, wherein the polypeptide additionally includes a half-life extending moiety.

11. The polypeptide according to claim 10, wherein said half-life extending moiety is covalently linked to said polypeptide and is selected from the group consisting of an albumin binding moiety, such as an anti-albumin immunoglobulin domain, a transferrin binding moiety, such as an anti-transferrin immunoglobulin domain, a polyethylene glycol molecule, a recombinant polyethylene glycol molecule, human serum albumin, a fragment of human serum albumin, and an albumin binding peptide.

12. The polypeptide according to any of claims 10 and 11, wherein the polypeptide is selected from the group consisting of polypeptides having SEQ ID NOs: 26 to 32, 34 to 43, 142, 143, and 145 to 152.

13. A polypeptide comprising or consisting of an immunoglobulin single variable domain essentially consisting of four framework regions (FR1 to FR4, respectively) and three complementarity determining regions (CDR1 to CDR3, respectively), wherein said CDR sequences are defined as follows:
- CDR1: SEQ ID NO:11

- CDR2: SEQ ID NO:12
- CDR3: SEQ ID NO:13

or

- CDR1: SEQ ID NO:14
- CDR2: SEQ ID NO:15
- CDR3: SEQ ID NO:16

or

- CDR1: SEQ ID NO:17
- CDR2: SEQ ID NO:18
- CDR3: SEQ ID NO:19.

14. A polypeptide comprising or consisting of a VHH domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 47 to 111.

15. The polypeptide according to claim 13 or claim 14 for use in the construction of a biparatopic A-beta binding polypeptide according to any of claims 1 to 12.

16. A nucleic acid molecule, preferably in isolated form, comprising a region encoding a polypeptide according to any of claims 1 to 15.

17. An expression vector comprising a nucleic acid molecule according to claim 16.

18. A host cell carrying an expression vector according to claim 17, wherein said host cell is capable of expressing a polypeptide according to any of claims 1 to 15, and wherein said host cell is a prokaryotic or a eukaryotic cell.

19. A pharmaceutical composition comprising (i) as the active ingredient, one or more polypeptides according to any of claims 1 to 15, and (ii) a pharmaceutically acceptable carrier, and optionally (iii) a diluent, excipient, adjuvant and/or stabilizer.

20. A method of manufacturing a polypeptide according to any of claims 1 to 15, comprising the steps of

- culturing a host cell according to claim 18 under conditions that allow expression of a polypeptide according to any of claims 1 to 15;
- recovering said polypeptide; and
- purifying said polypeptide.

21. A polypeptide according to any of claims 1 to 15 or a pharmaceutical composition according to claim 19 for use as a medicament for the treatment, prevention or alleviation of a disease, disorder or condition in a human being.

22. A polypeptide according to any of claims 1 to 15 or a pharmaceutical composition according to claim 19 for use as a medicament for the therapeutical treatment, prevention or alleviation of a disease, disorder or condition in a human being, wherein said disease, disorder or condition is selected from the group consisting of neurodegenerative diseases or disorders, Alzheimer's disease, dementia of the Alzheimer type, dry AMD, glaucoma, cerebral amyloid angiopathy, trisomy 21 (Down's Syndrome), adult Down syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch-type (HCHWA-D), dementia with Lewy Bodies, frontotemporal lobar degeneration, glaucoma, amyotrophic lateral sclerosis, sporadic inclusion body myositis, and anxiety disorder in an elderly human subject.

23. A polypeptide according to any of claims 1 to 15 or a pharmaceutical composition according to claim 19 prepared for being administered to a human being in need thereof by intravenous or subcutaneous injection.

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24. Use of a polypeptide according to any of claims 1 to 15 or a pharmaceutical composition according to claim 19 in the manufacture of a medicament for the prevention and/or treatment of a disease or disorder that is associated with A-beta deposition.

25. A polypeptide according to any of claims 1 to 15 or a pharmaceutical composition according to claim 19 prepared for the administration in combination with a therapeutic agent selected from the group consisting of ELND-005, Caprospinol, NRM-8499, PBT-2, Posiphen, EHT-0202, CTS-21166, Semagacest, BMS-708163, BMS-299897, BMS-433796, ELND-006, ELN-475516, ELN-318463, ELN-475513,Begacestat, E-2012, CHF-5074, Dimebolin, and PF-4494700.

26. A therapeutic agent selected from the group consisting of ELND-005, Caprospinol, NRM-8499, PBT-2, Posiphen, EHT-0202, CTS-21166, Semagacest, BMS-708163, BMS-299897, BMS-433796, ELND-006, ELN-475516, ELN-318463, ELN-475513,Begacestat, E-2012, CHF-5074, Dimebolin, and PF-4494700, prepared for the administration in combination with a polypeptide according to any of claims 1 to 15 or a pharmaceutical composition according to claim 19 to a patient in need thereof.

27. A pharmaceutical composition comprising (i) one of more polypeptides according to any of claims 1 to 15, and (ii) one or more additional therapeutic agents, preferably selected from the group consisting of ELND-005, Caprospinol, NRM-8499, PBT-2, Posiphen, EHT-0202, CTS-21166, Semagacest, BMS-708163, BMS-299897, BMS-433796, ELND-006, ELN-475516, ELN-318463, ELN-475513,Begacestat, E-2012, CHF-5074, Dimebolin, and PF-4494700, and (iii) a pharmaceutically acceptable carrier, and optionally (iv) a diluent, excipient, adjuvant and/or stabilizer.

28. A polypeptide according to any of claims 1 to 15 for the reduction of A-beta levels in a body fluid, and preferably for the reduction of the level of soluble A-beta in blood.

Claims:

~~291~~.A polypeptide comprising a first immunoglobulin single variable domain and a second immunoglobulin single variable domain, wherein the CDR sequences of said first immunoglobulin variable domain (CDR(1) sequences) and the CDR sequences of said second immunoglobulin variable domain (CDR(2) sequences) are defined as follows:

~~- CDR(1)1: SEQ ID NO:11~~
~~- CDR(1)2: SEQ ID NO:12~~
~~- CDR(1)3: SEQ ID NO:13~~
~~- CDR(2)1: SEQ ID NO:17~~
~~- CDR(2)2: SEQ ID NO:18~~
~~- CDR(2)3: SEQ ID NO:19~~

~~or:~~

- CDR(1)1: SEQ ID NO:14
- CDR(1)2: SEQ ID NO:15
- CDR(1)3: SEQ ID NO:16
- CDR(2)1: SEQ ID NO:17
- CDR(2)2: SEQ ID NO:18
- CDR(2)3: SEQ ID NO:19

~~or:~~

~~- CDR(1)1: SEQ ID NO:17~~
~~- CDR(1)2: SEQ ID NO:18~~
~~- CDR(1)3: SEQ ID NO:19~~
~~- CDR(2)1: SEQ ID NO:11~~
~~- CDR(2)2: SEQ ID NO:12~~
~~- CDR(2)3: SEQ ID NO:13~~

or:

- CDR(1)1: SEQ ID NO:17
- CDR(1)2: SEQ ID NO:18
- CDR(1)3: SEQ ID NO:19
- CDR(2)1: SEQ ID NO:14
- CDR(2)2: SEQ ID NO:15
- CDR(2)3: SEQ ID NO:16.

~~302~~. A polypeptide comprising a first immunoglobulin single variable domain and a second immunoglobulin single variable domain, wherein said first immunoglobulin single variable domain is VHH domain ABII035 (SEQ ID NO:44), and said second immunoglobulin single variable domain is VHH domain ABII059 (SEQ ID NO:45), or wherein said first immunoglobulin single variable domain is VHH domain ABII059 (SEQ ID NO:45), and said second immunoglobulin single variable domain is VHH domain ABII035 (SEQ ID NO:44).

~~313~~. The polypeptide according to claim ~~29~~ 1 or claim ~~302~~, wherein the polypeptide additionally includes a half-life extending moiety, said half-life extending moiety being preferably selected from the group consisting of an albumin binding moiety, such as an anti-albumin immunoglobulin domain, a transferrin binding moiety, such as an anti-transferrin immunoglobulin domain, a polyethylene glycol molecule, a recombinant polyethylene glycol molecule, human serum albumin, a fragment of human serum albumin, and an albumin binding peptide.

~~324~~. A polypeptide selected from the group consisting of polypeptides having any of SEQ ID NOs: 26 to 32, 34 to 43, 142, 143, and 145 to 152.

5. A PEGylated polypeptide having a sequence selected from the group of sequences consisting of SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 142, SEQ ID NO: 143, wherein a Cys residue is bearing the PEG moiety and wherein the position of said Cys residue bearing the PEG moiety (indicated by C*) is as indicated below:

Clone	Sequence information	Description	SEQ ID NO:
ABII322	VQLLESGGGLVQPGGSLRLSCAASGRTFNNYNMGWFRQAPGKGREFVAAVSRSGVSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAAAYRGTAINVRRSYSSWGQGTLVTVSSGGGSGGGGSGGGGC*GGGGSGGGGSGGGEVQLLESGGGLVQPGGSLRLSCVHSGPTFRTDTMGWFRQAPGKGREFVAAVTWNSGRINYADSVKGRFTISRDNSKNTAYLQMNSLRPEDTAVYYCAAHRFVVGGNRVEDWRYWGQGTLVTVSS	ABII059-27GS linker with C at position 14-ABII035	40
ABII323	VQLLESGGGLVQPGGSLRLSCAASGRTFNNYNMGWFRQAPGKGREFVAAVSRSGVSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAAAYRGTAINVRRSYSSWGQGTLVTVSSGGGGSGGGGSGGGGC*GGGGSGGGG	ABII059-35GS linker with C at	41

	SGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCVHS GPTFRTDTMGWFRQAPGKGREFVAAVTWNSGRINYAD SVKGRFTISRDNSKNTAYLQMNSLRPEDTAVYYCAAHR FVVGGNRVEDWRYWGQGTLVTVSS	position 15-ABII035	
ABII314	EVQLLESGGGLVQPGGSLRLSCAASGRTFNNYNMGWF RQAPGKGREFVAAVSRSGVSTYYADSVKGRFTISRDNS KNTVYLQMNSLRPEDTAVYYCAAAYRGTAINVRRSYSS WGQGTLVTVSSGGGGC*GGGGSGGGGSGGGGSGGG GSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCVHS GPTFRTDTMGWFRQAPGKGREFVAAVTWNSGRINYAD SVKGRFTISRDNSKNTAYLQMNSLRPEDTAVYYCAAHR FVVGGNRVEDWRYWGQGTLVTVSS	ABII059-35GS linker with C at position 5-ABII035	142
ABII315	EVQLLESGGGLVQPGGSLRLSCAASGRTFNNYNMGWF RQAPGKGREFVAAVSRSGVSTYYADSVKGRFTISRDNS KNTVYLQMNSLRPEDTAVYYCAAAYRGTAINVRRSYSS WGQGTLVTVSSGGGGC*GGGSEVQLLESGGGLVQPGG SLRLSCVHSGPTFRTDTMGWFRQAPGKGREFVAAVTW NSGRINYADSVKGRFTISRDNSKNTAYLQMNSLRPEDTA VYYCAAHRFVVGGNRVEDWRYWGQGTLVTVSS	ABII059-9GS linker with C at position 5-ABII035	143

6. A nucleic acid molecule, preferably in isolated form, comprising a region encoding a polypeptide according to any of claims 1 to 5.

7. An expression vector comprising a nucleic acid molecule according to claim 6.

8. A host cell carrying an expression vector according to claim 7, wherein said host cell is capable of expressing a polypeptide according to any of claims 1 to 5, and wherein said host cell is a prokaryotic or a eukaryotic cell.

9. A pharmaceutical composition comprising (i) as the active ingredient, one or more polypeptides according to any of claims 1 to 5, and (ii) a pharmaceutically acceptable carrier, and optionally (iii) a diluent, excipient, adjuvant and/or stabilizer.

10. A method of manufacturing a polypeptide according to any of claims 1 to 5, comprising the steps of

- culturing a host cell according to claim 8 under conditions that allow expression of a polypeptide according to any of claims 1 to 5;
- recovering said polypeptide; and
- purifying said polypeptide.

11. A polypeptide according to any of claims 1 to 5 or a pharmaceutical composition according to claim 9 for use as a medicament for the treatment, prevention or alleviation of a disease, disorder or condition in a human being.

12. A polypeptide according to any of claims 1 to 5 or a pharmaceutical composition according to claim 9 for use as a medicament for the therapeutical treatment, prevention or alleviation of a disease, disorder or condition in a human being, wherein said disease, disorder or condition is selected from the group consisting of neurodegenerative diseases or disorders, Alzheimer's disease, dementia of the Alzheimer type, dry AMD, glaucoma, cerebral amyloid angiopathy, trisomy 21 (Down's Syndrome), adult Down syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch-type (HCHWA-D), dementia with Lewy Bodies, frontotemporal lobar degeneration, glaucoma, amyotrophic lateral sclerosis, sporadic inclusion body myositis, and anxiety disorder in an elderly human subject.

13. A polypeptide according to any of claims 1 to 5 or a pharmaceutical composition according to claim 9 prepared for being administered to a human being in need thereof by intravenous or subcutaneous injection.

14. A pharmaceutical composition comprising (i) one or more polypeptides according to any of claims 1 to 5, and (ii) one or more additional therapeutic agents, preferably selected from the group consisting of ELND-005, Caprospinol, NRM-8499, PBT-2, Posiphen, EHT-0202, CTS-21166, Semagacest, BMS-708163, BMS-299897, BMS-433796, ELND-006, ELN-475516, ELN-318463, ELN-475513,Begacestat, E-2012, CHF-5074, Dimebolin, and PF-4494700, and (iii) a pharmaceutically acceptable carrier, and optionally (iv) a diluent, excipient, adjuvant and/or stabilizer.

15. Use of a polypeptide according to any of claims 1 to 5 for reducing A-beta levels *in vitro* in a body fluid.