[0010] Further, having crossed the BBB, it is advantageous for a therapeutic to exert its therapeutic effect, and then be efficiently cleared from the brain and CNS and returned to the general circulation for elimination from a patient's body.

[0011] Accordingly, there remains a need in the art for therapeutics for treating and managing AD, and related disorders, in particular, a need for therapeutics capable of crossing the BBB specifically and then being cleared therefrom efficiently, as well as delivery systems that safely deliver therapeutics across the barrier to the CNS. There also remains a need for effective diagnosis of initial and late stages of AD. The instant invention addresses these and other needs.

SUMMARY

[0012] Disclosed are antibody molecules that selectively target non-fibrillar forms of beta-amyloid peptide, such as monomeric and oligomeric forms, over fibrillar forms of the peptide. In one aspect, there is provided an antibody molecule, said molecule having immunospecificity to at least one oligomeric form of beta-amyloid peptide 42 (BAP42) and to monomeric BAP42, wherein said molecule does not have immunospecificity to fibrillar BAP42. In a particular embodiment, the antibody molecule is a single domain antibody having immunospecificity to oligomers of the beta-amyloid peptide known as beta-amyloid peptide 42, such as a single domain antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-21, as well as dimeric forms thereof and humanized form thereof, where one or more CDRs of the sequences are combined with framework regions of corresponding human antibody domains. In particular embodiments, the antibody molecule is used in conjunction with a delivery system to facilitate passage across the blood-brain barrier.

[0013] Also disclosed are peptides that cross the blood-brain barrier, in particular, fragments of the amino acid sequence corresponding to SEQ ID NO: 127 that specifically cross this barrier. The peptides provide delivery systems, facilitating transfer of cargo molecules across the blood-brain barrier for delivery to the brain and central nervous system. In particular embodiments, an antibody molecule of the disclosure is linked to the delivery peptide to form an antibody-peptide construct with greater ability to cross the blood-brain barrier, and to do so more specifically, than the antibody molecule without the linked peptide. In particular embodiments, the antibody-peptide construct then is cleared more efficiently from the brain than the antibody molecule without the linked peptide.

[0014] Further disclosed are methods of making the antibody molecules, delivery peptides, and antibody-peptide constructs, described above. The disclosure also provides polynucleotides encoding polypeptides comprising the antibody molecules, delivery peptides, and/or antibody-peptide constructs described herein, as well as vectors and host cells containing same, in particular, expression vectors and host cells that allow expression of the polypeptides.

[0015] Also disclosed are pharmaceutical compositions comprising effective amounts of the antibody molecules, delivery peptides, and/or antibody-peptide constructs, described above, as well as to methods of making the pharmaceutical compositions, *e.g.*, mixing with a pharmaceutically acceptable carrier. In one aspect, there is provided a pharmaceutical composition comprising the antibody molecule described above, and a pharmaceutically acceptable carrier. In a particular embodiment, the pharmaceutical compositions are formulated for parenteral administration. In another aspect, there is provided a method of making the pharmaceutical composition described above comprising: providing the antibody molecule described above; and mixing with a pharmaceutically acceptable carrier, preferably wherein said antibody molecule is humanized.

[0016] The disclosure also relates to use of the pharmaceutical compositions for treating or preventing a neurological disorder, such as Alzheimer's disease, a related disorder, or a symptom thereof. In particular embodiments, a pharmaceutical composition of the disclosure, comprising an effective amount of an antibody molecule, with or without linkage to a delivery peptide, is administered to a patient with Alzheimer's to prevent or reduce formation of plaques in the brain, by crossing the blood-brain barrier and specifically binding oligomeric and/or monomeric forms of beta-amyloid peptide 42, but preferably not fibrillar forms, thus preventing or reducing plaque formation. In particular embodiments, the antibody molecule, with or without linkage to a delivery peptide, then is cleared from the brain, quickly and efficiently returning to the circulation for excretion. In one aspect, there is provided use of an effective amount of the pharmaceutical composition described above for the preparation of a medicament for treating, delaying, slowing, preventing, or reducing the incidence of Alzheimer's disease, a related disorder, or a symptom thereof, in a subject in need thereof.

[0017] The disclosure further relates to diagnostic use of the antibody molecules, delivery peptides, and antibody-peptide constructs, such as in diagnosing Alzheimer's disease or a related disorder. In one aspect, there is provided a method of detecting an aggregation-prone peptide in a subject, said method comprising: contacting the antibody molecule described above with a test sample from said subject under conditions allowing immmunospecific binding, preferably wherein said sample comprises cerebrospinal fluid or serum; and

detecting said immunospecific binding,
preferably wherein said aggregation-prone peptide is selected from the group consisting of BAP42, a peptide of α-synuclein, a peptide of islet amyloid polypeptide, Huntington peptide, and a peptide of prion protein,
more preferably wherein said aggregation-prone peptide is BAP42.

[0017a] In one aspect, there is provided a method for imaging an aggregation-prone peptide in the brain of a subject, said method comprising:

administering to said subject the antibody molecule described above in association with a label; and

obtaining an image of the brain of said subject, said image indicating said aggregation-prone peptide,

preferably wherein said aggregation-prone peptide is selected from the group consisting of BAP42, a peptide of α-synuclein, a peptide of islet amyloid polypeptide, Huntington peptide, and a peptide of prion protein,

preferably wherein said aggregation-prone peptide is BAP42; and

preferably wherein said antibody molecule is humanized,

more preferably wherein said humanized antibody molecule comprises one or more CDRs of said antibody molecule and one or more framework regions of a human antibody domain.

[0017b] The disclosure also provides kits comprising the antibody molecules, delivery peptides, and/or antibody-peptide constructs of the present disclosure, such as kits for use in diagnosing Alzheimer's disease or a related disorder. In one aspect, there is provided a kit comprising a plurality of the antibody molecule described above, said plurality providing a sufficient amount of said antibody molecule to detect immunospecific binding when contacted with a sample from a first subject having Alzheimer's disease or a related disorder, preferably wherein said sample comprises cerebrospinal fluid. In another aspect, there is provided a kit comprising the antibody molecule described above in association with a label, preferably wherein said label is selected from the group consisting of a radioactive moiety, a fluorescent moiety, a fluorescence-quenching moiety, a paramagnetic moiety, a detectable protein, a gene encoding a detectable protein, and a dye, more preferably wherein said label is covalently linked to said antibody molecule.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 depicts a BAP42 aggregation scheme, progressing from monomers of the peptide to dimers, oligomers, and then fibrils, capable of forming plaques.

[0019] FIG. 2 shows a determination of molar absorption coefficient for BAP42, using different solutions of known concentration of the peptide to measure absorbance and correlate it in order to calculate the coefficient ε280nm = 0.3265 ± 0.0043 $(mg/mL)^{-1}cm^{-1}$ or ± 1474.041 ε280nm = 19,287 $M^{-1}cm^{-1}$.

[0020] FIGs. 3A-3B depict representative schemes for preparing different species of BAP42, to give oligomers (**FIG. 3A**) or fibrils (**FIG. 3B**).

[0021] FIG. 4 depicts a characterization of BAP42 species, isolated in an optimized process, using a thioflavin T assay.

[0022] FIG. 5 shows the results of Western blotting a mixture of BAP42 species, separated by SDS-PAGE electrophoresis.

We claim:

1. An antibody molecule, said molecule having immunospecificity to at least one oligomeric form of beta-amyloid peptide 42 (BAP42) and to monomeric BAP42,

wherein said molecule does not have immunospecificity to fibrillar BAP42.

2. The antibody molecule of claim 1, wherein said molecule crosses the blood brain barrier.

3. The antibody molecule of claim 1 or 2, wherein said molecule is linked as a fusion to an Fc domain or an scFv molecule, or a domain of a polypeptide consisting of SEQ ID NO: 127,

preferably by a peptide linker,

more preferably wherein said Fc domain is a human Fc domain; and

most preferably wherein said molecule is linked to the N-terminus of said human Fc domain.

4. The antibody molecule of claim 3, further comprising a second antibody molecule wherein each of said first and said second antibody molecules is fused to the N-terminus of each of a first and a second Fc domain,

preferably wherein each of said linkages is via a peptide linker,

preferably wherein said two Fc domains make up a complete Fc region,

most preferably a human complete Fc region.

5. The antibody molecule of any one of the above claims, wherein said molecule is monovalent or bivalent,

preferably wherein said molecule is monovalent,

more preferably wherein said monovalent molecule is a single domain antibody.

6. The antibody molecule of claim 5, wherein said single domain is a rabbit light chain variable domain (VL), or a BAP42-binding fragment thereof,

preferably wherein said molecule is humanized,

44. The kit of claims 42 or 43, wherein said antibody molecule immunospecifically binds a BAP42 oligomer characteristic of an early stage of Alzheimer's disease or a stage associated with mild cognitive impairment.

45. The kit of any one of claims 42-44, further comprising at least a second antibody molecule of any one of claims 1-18, in association with a second label,

wherein said second antibody immunospecifically binds a BAP42 oligomer characteristic of a later stage of Alzheimer's disease compared to a stage associated with mild cognitive impairment.