

CLAIMS:

1. A non-aggregating peptide analogue of the A β 42 peptide;
wherein the N-terminal domain of the analogue comprises an amino-acid sequence differing from residues 1-28 of SEQ ID NO:1 by no more than 3 (preferably 2, more preferably 1, most preferably 0) deletions, insertions and/or substitutions, preferably conservative substitutions;
wherein the beta-sheet aggregation domain of the analogue comprises an amino-acid sequence differing from residues 29-42 of SEQ ID NO:1 by no more than 5 deletions, insertions and/or substitutions; and
the non-aggregating peptide analogue substantially retaining native function of the A β 42 peptide except for being non-aggregating.
2. The non-aggregating peptide analogue of claim 1, wherein the retained native peptide function comprises capability of enhancing or inducing α 7 nicotinic acetylcholine receptor (α 7nAChR) mediated Ca²⁺ influx.
3. The non-aggregating peptide analogue of claim 2, wherein the retained native peptide function is the capability of enhancing or inducing α 7nAChR-mediated Ca²⁺ influx in cortical neurons at <3000 pM concentration, at <300 pM, at <30 pM, or at <3 pM.
4. The non-aggregating peptide analogue of claim 1, wherein the beta-sheet destabilizing modification comprises substitution of a naturally occurring amino acid residue of the peptide with an amino acid analogue.
5. The non-aggregating peptide analogue of claim 1, wherein the beta-sheet destabilizing modification comprises substitution of at most three naturally occurring amino acid residues at three separate positions relative to SEQ ID NO:1 with an amino acid analogue.

6. The non-aggregating peptide analogue of claim 1, wherein the amino acid analogue is one of: 3-hydroxyproline, 4-hydroxyproline, selenocysteine, pyroglutamic acid, carboxyglutamic acid, octenyl alanine, pyrrolysine, palmitoyl aspartate, D-amino acids, β -amino acids, γ -amino acids, Homo-amino acids, β -Homo-amino acids, α -methyl amino acids, N-alkylated amino acid derivatives, pyruvic acid derivatives, branched-chain amino acid derivatives, nitro amino acid derivatives, halogenated amino acid derivatives, ring-substituted amino acid derivatives, aromatic amino acid derivatives, linear core amino acids, peptoid derivatives, hydroxylated amino acid derivatives, cyclic amino acids, bicyclic amino acids, 3-amino-3-aryl-propionic acids, 3-amino-4-aryl-butyric acids, amino acids with aromatic spacers, alicyclic amino acids, α -phenylglycine derivatives.

7. The non-aggregating peptide analogue of claim 1, wherein the amino acid analogue comprises an N-alkylated amino acid analogue, preferably with 1-3 carbons in the alkyl moiety.

8. The non-aggregating peptide analogue of claim 1, wherein the beta-sheet destabilizing modification comprises a substitution of M35, preferably with an amino acid analogue.

9. The non-aggregating peptide analogue of claim 1, wherein the beta-sheet destabilizing modification comprises a substitution of M35 to proline, N-methyl methionine or pyrrolysine, preferably N-methyl methionine.

10. The non-aggregating peptide analogue of claim 1, wherein the beta-sheet destabilizing modification comprises one or more of:

- replacement of G29 with methyl glycine or N-ethyl glycine;
- replacement of A30 with N-methyl alanine or N-ethyl alanine;
- replacement of I31 is N-methyl isoleucine or N-ethyl isoleucine;
- replacement of I32 with N-methyl isoleucine or N-ethyl isoleucine;
- replacement of G33 with N-methyl glycine or N-ethyl glycine;

replacement of L34 with N-methyl leucine or N-ethyl leucine;
replacement of M35 with N-methyl methionine or N-ethyl methionine;
replacement of V36 with N-methyl valine or N-ethyl valine;
replacement of G37 with N-methyl glycine or N-ethyl glycine;
replacement of G38 with N-methyl glycine or N-ethyl glycine;
replacement of V39 with N-methyl valine or N-ethyl valine;
replacement of V40 with N-methyl valine or N-ethyl valine;
replacement of I41 with N-methyl isoleucine or N-ethyl isoleucine; and/or
replacement of A42 with N-methyl alanine or N-ethyl alanine.

11. The non-aggregating peptide analogue of claim 1, wherein the beta-sheet destabilizing modification comprises a replacement of M35 with N-methyl methionine or N-ethyl methionine.

12. The non-aggregating peptide analogue of claim 1, having the amino acid sequence of one of SEQ ID NO:3, SEQ ID NO:88, SEQ ID NO: 100, SEQ ID NO: 190 or SEQ ID NO: 192 with at most three conservative amino acid substitutions in either or both of the N-terminal domain and the beta-sheet aggregation domain.

13. The non-aggregating peptide analogue of claim 1, having the amino acid sequence of one of SEQ ID NO:88, SEQ ID NO:100, SEQ ID NO: 190 or SEQ ID NO:192.

14. Use of a compound having the amino acid sequence of one of SEQ ID NO:88 or SEQ ID NO:190 in the manufacture of a medicament for the treatment and/or prophylaxis of Alzheimer's disease or mild cognitive impairment.

15. Use of a compound having the amino acid sequence of one of SEQ ID NO:88 or SEQ ID NO:190 in the manufacture of a medicament for the treatment and/or prophylaxis of autosomal dominant Alzheimer's disease, sporadic Alzheimer's disease, or early-onset sporadic Alzheimer's disease.

16. Use of a compound having the amino acid sequence of one of SEQ ID NO:88 or SEQ ID NO:190 in the manufacture of a medicament for the treatment and/or prophylaxis of autosomal dominant Alzheimer's disease.

17. Use of a compound having the amino acid sequence of one of SEQ ID NO:88 or SEQ ID NO:190 in the manufacture of a medicament for the treatment and/or prophylaxis of autosomal dominant Alzheimer's disease caused by mutations in *PSEN1*, *PSEN2*, or *APP*.

18. Use of a compound having the amino acid sequence of one of SEQ ID NO:88 or SEQ ID NO:190 in the manufacture of a medicament for the treatment and/or prophylaxis of Amyotrophic lateral sclerosis (ALS), frontotemporal dementia, Parkinson's disease, Parkinson's disease dementia, progressive supranuclear palsy, corticobasal degeneration, hereditary cerebral hemorrhage with amyloidosis, dementia with Lewy bodies, or multiple system atrophy.

19. The use according to any one of claims 14 to 18, wherein the peptide analogue is to be administered to a subject having an A β 42 level in the cerebrospinal fluid of less than about 500 pM, preferably less than about 400 pM, preferably less than about 300 pM, more preferably less than 200 pM.

20. The use according to any one of claims 14 to 18, wherein the peptide is to be administered by subcutaneous, intravenous, intracerebroventricular, intracerebral, intrathecal, intraperitoneal or intramuscular injection or infusion; or topical, nasal, oral (including sublingual or buccal), rectal, ocular or otic delivery.

21. A compound having the amino acid sequence of one of SEQ ID NO:88 or SEQ ID NO:190, for use in therapy.