immunological epitopes that are disease-specific epitopes (DSE) and develop immunotherapies that specifically target the toxic Aβ oligomeric molecular species. It is also desirable to develop immunotherapies to target toxic Aβ oligomeric molecular species and avoid autoimmune recognition of APP at the cell surface. Such DSE epitopes would be targets for immunotherapies and prophylactic vaccines, which specifically neutralize the toxicity of target proteins. It is also desirable to develop diagnostic tools to provide an indication of populations at risk for developing AD, for differential diagnosis to distinguish AD from other dementing syndromes, and for monitoring biomarker response to AD therapy.

[0008] It is, therefore, desirable to provide a disease specific epitope that is unique to toxic Aβ oligomeric molecular species.

SUMMARY

[0009] It is an object of the present disclosure to obviate or mitigate at least one disadvantage of previous epitopes, antibodies, compositions and methods for diagnosis, treatment and prevention of Alzheimer's disease.

[0010] In ~~a first aspect~~one embodiment, the present disclosure is based, in part, on the surprising discovery of a novel structural epitope in Aβ with advantageous properties for selective antibody binding.

[0010a] In one aspect, there is provided an antigenic cyclic peptide which derives from Aβ and which comprises a conformational epitope having an amino acid sequence of at least SNK, wherein the K (lysine) is solvent-accessible.

[0011] In one embodiment, there is provided a cyclic peptide derived from Aβ, having an amino acid the sequence of at least SNK corresponding to a solvent-exposed, antibody accessible "knuckle region" of oligomeric Aβ.

[0012] In another embodiment, there is provided an antigenic peptide comprising an epitope having a constrained cyclic configuration, the epitope having an amino acid sequence of at least SNK corresponding to a solvent-exposed, antibody accessible knuckle region of oligomeric Aβ.

[0013] In another embodiment, there is provided an antigenic peptide comprising an epitope having a constrained cyclic configuration, the epitope having an amino acid sequence corresponding to SEQ ID NO: 1 corresponding to a solvent-exposed, antibody accessible knuckle region of oligomeric Aβ.

[0014] In one ~~aspect~~embodiment, the epitope of the antigenic peptide corresponds to residues 25 to 29 of oligomeric Aβ(1-40) or oligomeric Aβ (1-42).

[0014a] In one aspect, there is provided an isolated antibody that specifically binds to a cyclic peptide derived from Aβ, wherein the cyclic peptide comprises a conformational epitope having an amino acid sequence of at least SNK, wherein the K (Lysine) is solvent-accessible.

[0014b] In another aspect, there is provided an isolated antibody that specifically binds to a cyclic peptide derived from Aβ, wherein the cyclic peptide consists of amino acid sequence GSNKG (SEQ ID NO: 1) or CGSNKGC.

[0015] In another embodiment, there is provided an isolated antibody that specifically binds to a cyclic peptide derived from Aβ, the cyclic peptide comprising a

conformational epitope having an amino acid sequence of at least SNK corresponding to a solvent-exposed, antibody accessible knuckle region of oligomeric Aβ.

[0016] In another embodiment, there is provided an isolated antibody that specifically binds to a cyclic peptide derived from Aβ, the cyclic peptide comprising a conformational epitope having an amino acid sequence corresponding to SEQ ID NO: 1 corresponding to a solvent-exposed, antibody accessible knuckle region of oligomeric Aβ.

[0017] In one ~~aspect~~embodiment, the isolated antibody specifically binds with greater affinity to an oligomeric form of Aβ than to a non-oligomeric form of Aβ.

[0018] In another ~~aspect~~embodiment, the isolated antibody is monoclonal.

[0019] In another ~~aspect~~embodiment, the isolated antibody is humanized.

[0020] In another embodiment, there is provided an immunoconjugate comprising an isolated antibody that specifically binds to a cyclic peptide derived from Aβ, the cyclic peptide comprising a conformational epitope having an amino acid sequence of at least SNK corresponding to a solvent-exposed, antibody accessible knuckle region of oligomeric Aβ, conjugated with a detectable label.

[0020a] In one aspect, there is provided an immunoconjugate comprising an antibody as defined above conjugated with a detectable label.

[0021] In another ~~aspect~~embodiment, there is provided a nucleic acid encoding the isolated antibody.

[0021a] In one aspect, there is provided a nucleic acid encoding the isolated antibody as defined above.

[0022] In another embodiment, there is provided a composition comprising a therapeutically effective amount of an isolated antibody that specifically binds to a cyclic peptide derived from Aβ, the cyclic peptide comprising a conformational epitope having an amino acid sequence of at least SNK corresponding to a solvent-exposed, antibody accessible knuckle region of oligomeric Aβ; and a pharmaceutically acceptable adjuvant.

[0022a] In one aspect, there is provided a composition comprising a therapeutically effective amount of the isolated antibody as defined above and a pharmaceutically acceptable adjuvant.

[0023] In another embodiment, there is provided an anti-oligomeric vaccine composition comprising an antigenic peptide comprising an epitope having a constrained cyclic configuration, the epitope having an amino acid sequence of at least SNK corresponding to a solvent-exposed, antibody accessible knuckle region of oligomeric Aβ; and a pharmaceutically acceptable adjuvant.

[0023a] In one aspect, there is provided an anti-oligomeric vaccine composition comprising the antigenic peptide as defined above and a pharmaceutically acceptable adjuvant.

[0024] In another ~~aspect~~embodiment, there is provided a method of treating or preventing Alzheimer's Disease in a patient in need of said treatment comprising administering a pharmaceutically effective amount of the isolated antibody or immunconjugate.

[0025] In another ~~aspect~~embodiment, there is provided a method of treating or preventing Alzheimer's Disease in a patient in need of said treatment comprising administering the vaccine.

[0025a] In one aspect, there is provided the isolated antibody as defined above, the immunoconjugate as defined above, the composition as defined above, or the vaccine composition as defined above, for use in treating or preventing Alzheimer's Disease in a patient.

[0026] In another ~~aspect~~embodiment, there is provided a method of diagnosing Alzheimer's Disease in a patient suspected of having Alzheimer's Disease comprising the steps of: a)

isolating a biological sample from the patient; b) contacting the biological sample with the isolated antibody for a time and under conditions sufficient to allow for formation of antigen/antibody complexes in the sample; and c) detecting the presence of the antigen/antibody complexes in the sample, wherein presence of the complexes indicates a diagnosis of Alzheimer's Disease in the patient.

[0026a] In one aspect, there is provided an in vitro method of diagnosing Alzheimer's Disease in a patient suspected of having Alzheimer's Disease comprising:
a) contacting a biological sample isolated from the patient with the isolated antibody as defined above or the immunoconjugate as defined above; and
b) detecting the presence of the antigen/antibody complexes in the sample, wherein presence of the complexes indicates a diagnosis of Alzheimer's Disease in the patient.

[0026b] In one aspect, there is provided a kit comprising:
the isolated antibody as defined above; and one or more detection agents.

[0027] In another embodiment, there is provided a kit for comprising: the isolated antibody and a conjugate comprising an antigen attached to a signal-generating compound.

[0028] In a further ~~aspect~~embodiment, the kit comprises one or more detection agents.

[0029] In another embodiment, there is provided an article of manufacture comprising: the isolated antibody; a conjugate comprising an antigen attached to a signal-generating compound; and instructions for use in diagnosing Alzheimer's Disease.

[0030] In another ~~aspect~~embodiment, there is provided use of the antibody or immunoconjugate for the treatment or prevention of Alzheimer's disease.

[0031] In another ~~aspect~~embodiment, there is provided use of the vaccine for the treatment or prevention of Alzheimer's disease.

[0031a] In one aspect, there is provded the use of an antibody as defined above, the immunoconjugate as defined above, the composition as defined above or the vaccine composition as defined above in the manufacture of a medicament for the treatment or prevention of Alzheimer's disease.

[0032] In another embodiment, there is provided isolated antibodies that are capable of binding to a cyclic peptide derived from Aβ and having an amino acid sequence of SNK corresponding to a solvent-exposed knuckle region of oligomeric Aβ. In one ~~aspect~~embodiment, such antibodies bind oligomeric forms of Aβ with greater affinity than non-oligomeric forms of Aβ.

[0033] In another embodiment, there is provided a method of treatment of a subject having or suspected of having Alzheimer's disease, the method comprising administering to the subject a therapeutically effective amount of an antibody that is capable of binding to a cyclic peptide derived from Aβ having an amino acid composition comprising the sequence SNK. In one ~~aspect~~embodiment, the antibody binds oligomeric forms of Aβ with greater affinity than non-oligomeric forms of Aβ.

[0034] In another embodiment, there is provided a method of preventing the development or progression of AD in a subject, the method comprising administering to the subject a therapeutically effective amount of an antigenic peptide comprising an epitope having a constrained cyclic configuration having an amino acid sequence of SNK corresponding to a knuckle region oligomeric Aβ. On administration, the antigenic peptide produces an immune response against oligomeric Aβ. Antibodies produced are capable of specifically binding to oligomeric Aβ. In certain embodiments, the antibody binds oligomeric forms of Aβ with greater affinity than non-oligomeric forms of Aβ.