SUMMARY ~~OF THE INVENTION~~

The present invention refers to subject matter as defined in the attached set of claims.

The present disclosure~~invention~~ relates to an isolated antibody that shows specific binding to a conformational epitope of a protofibril form of β-amyloid peptide. The monomer of wild type beta-amyloid (Aβ) peptide is known in the art and is shown herein as SEQ ID NO: 1. The isolated antibodies of the present disclosure~~invention~~ have affinity for such a repeated conformational epitope for the larger molecular weight protofibril form of the Aβ peptide while showing minimal or no affinity for other forms of Aβ peptide, such as monomer or dimer forms of Aβ peptide.

The present disclosure~~invention~~ also relates to an isolated antibody that specifically interacts with and shows a measurable affinity to a conformational epitope of a protofibril form of Aβ peptide, whereby the protofibril epitope is represented by an exposed region of a Aβ-protofibril form comprising the amino terminal portion of an exposed portion of the Aβ peptide.

The present disclosure~~invention~~ further relates to an isolated antibody that specifically interacts and shows a measurable affinity to a conformational epitope of a protofibril form of Aβ peptide, whereby the protofibril epitope is represented by an exposed region of a Aβ-protofibril form comprising amino acids 1-20 (SEQ ID NO:2) of an exposed portion of the Aβ peptide.

The present disclosure~~invention~~ also relates to an isolated antibody that specifically interacts and shows a measurable affinity to a conformational epitope of a protofibril form of Aβ peptide, whereby the protofibril epitope is represented by an exposed region of a Aβ-protofibril form

which comprises amino acids 4-12 and 9-20 (SEQ ID NOS: 3 and 4, respectively) of an exposed portion of the Aβ peptide.

The present disclosure~~invention~~ relates in part to monoclonal antibodies 13C3, 1D1 and 19A6, and any affinity matured form of 13C3, 1D1 and 19A6. The present disclosure~~invention~~ further relates to an antibody which mimics the functional specificity as described herein for 13C3, 1D1 and 19A6. To this end, the present disclosure~~invention~~ also relates to biologically active fragments and/or mutants of the 13C3, 1D1, 19A6 or a 13C3-, 1D1-, or 19A6-like antibody, including but not necessarily limited to amino acid substitutions (e.g., as a directed form of affinity maturation of the V_H or V_L regions), deletions, additions, amino terminal truncations and carboxy-terminal truncations such that these mutations provide a basis for an antibody or antibody binding portion that results in a similar or improved version of a 13C3, 1D1, 19A6 or 13C3-like antibody binding protein. In one example~~embodiment of this portion of the invention~~, the V_H and V_L region of 13C3 comprises the amino acid sequence as set forth in SEQ ID NO: 7 (V_H) and/or SEQ ID NO:5 (V_L), respectively.

The present disclosure~~invention~~ further relates to an isolated nucleic acid molecule comprising a nucleotide sequence which encodes the V_H and/or V_L regions of a 13C3, 1D1 or 19A6 antibody; and especially an isolated nucleic acid molecule (polynucleotide) encoding a biologically relevant portion of 13C3, or affinity matured version or otherwise mutated version of 13C3, 1D1 or 19A6 antibody. To this end, one example~~embodiment of the present invention~~ relates to a nucleic acid molecule which comprises a nucleotide sequence encoding the V_H and V_L region of 13C, as set forth in SEQ ID NO:8

(13C3: V_H region) and SEQ ID NO:6 (13C3: V_L region), respectively.

The present disclosure~~invention~~ also relates to isolated antibodies 13C3, 1D1 or 19A6 as disclosed herein, antibodies that specifically interact and show a measurable affinity to a conformational epitope of a protofibril form of Aβ peptide.

The present disclosure~~invention~~ also relates to a hybridoma capable of producing a monoclonal antibody of the present disclosure~~invention~~. Particular hybridomas of the present disclosure~~invention~~ include hybridomas which produce exemplified monoclonal antibodies 13C3, 19A6 and 1D1, respectively. The present invention refers to subject matter as defined in the attached set of claims.

The present disclosure~~invention~~ relates to pharmaceutically effective compositions which comprise an isolated antibody as disclosed and further defined herein: an isolated antibody that specifically interacts with and shows a measured affinity to and ability to specifically bind to a repeating conformational epitope of a protofibril form of Aβ while showing minimal or no measurable affinity to low molecular weight forms of Aβ. These compositions may optionally comprise one or more carriers, one or more excipients, and/or one or more chemical derivatives.

The present disclosure~~invention~~ also relates to methods of treating an individual afflicted with Alzheimer's disease comprising administering to the individual a pharmaceutically effective composition which comprises an isolated antibody disclosed herein, namely an antibody that specifically interacts and shows a measured affinity to a repeating conformational epitope of a protofibril form of Aβ peptide while showing minimal or no detectable affinity toward lower molecular weight forms of Aβ peptide. These methods will provide for a therapeutic intervention so as to

reduce the amount of amyloid deposits in the brain of an individual afflicted with Alzheimer's disease. One example~~Particular embodiments of this portion of the present invention~~ relates to methods of treating an individual afflicted with Alzheimer's disease comprising administering a pharmaceutically effective composition formulated with an antibody showing specific affinity (as at least compared to low molecular weight forms of Aβ peptide) to a conformational epitope of a protofibril form of Aβ peptide, especially whereby the protofibril epitope is represented by an exposed region of a Aβ-protofibril form which comprises amino acids 1-20 (SEQ ID NO:2) of an exposed portion of the Aβ peptide. Specific example~~embodiments~~ relating to these therapeutic and prophylactic methods disclosed herein may utilize exemplified mouse monoclonal antibodies 13C3, 19A6, 1D1, as well as affinity matured versions of any such antibody, chimeric antibody, humanized antibody, human monoclonal antibody, and/or any other such antibody form known in the art, including but not limited to the antibody or specific binding members reviewed herein. Any such antibody or specific binding member may be referred to within this specification as a "13C3-like antibody." Thus, a "13C3-like antibody" is meant to also encompass the 13C3 monoclonal antibody disclosed herein.

The present disclosure~~invention~~ also relates to methods of screening for and selecting compounds which may act as an inhibitor of fibril and/or senile plaque formation associated with Alzheimer's disease. Such a methodology comprises utilizing an antibody with 13C3-like characteristics (e.g., specific affinity to the PF vs. LMW forms of Aβ peptide) in various antibody/peptide/test compound interaction assays in order to select a compound

which modulates the process of fibril and/or plaque formation.

The present disclosure~~invention~~ further relates to diagnostic assay methods to specifically determine protofibril levels within a subject or patient. Such assays may be carried out by any techniques known and available to the artisan, including but not limited to Western blots, ELISAs, radioimmunoassays, immunohistochemical assays, immunoprecipitations, or other immunochemical assays known in the art. Thus, one example~~embodiment of this portion of the invention~~ relates to taking a tissue sample from a subject or patient and determining the level of PF Aβ in the sample using a diagnostic kit and associated assay; whereby the kit comprises a 13C3-like antibody, thus allowing for the specific determination of PF Aβ levels in the tissue sample. The tissue sample for analysis is typically blood, plasma, serum, mucus or cerebral spinal fluid from the subject or patient

To this end, the antibodies of the present disclosure~~invention~~ may be utilized for at least the following uses: (1) as a prophylactic or therapeutic agent to prevent or reduce plaque deposits associated with Alzheimer's disease, either alone or in conjunction with any available combination therapy; (2) in designing peptide immunogens that may be used to elicit an effective antibody response in prophylactic or therapeutic vaccination strategies relating to treatment of Alzheimer's disease; (3) to generate a prophylactic or therapeutic anti-idiotypic antibody (Ab2) mimicking the cryptic epitope(s) that bind the antibodies of the present disclosure~~invention~~; and, (4) in designing peptides derived from the complementarity determining regions (CDRs) of the neutralizing antibodies of the present disclosure~~invention~~ for

use in either screening inhibitors of protofibril formation for use in prophylactic and/or therapeutic regimes and (4) as a diagnostic reagent to determine the level of protofibrillar Aβ in serum or CSF of a patient at risk for developing AD.

It is an object of the present disclosure~~invention~~ to describe~~provide for~~ antibodies that specifically interact and show affinity to an exposed, conformational epitope of a protofibril form of Aβ peptide which comprises amino acids 1-20 (SEQ ID NO:2) of an exposed portion of the Aβ peptide.

It is a further object of the present disclosure~~invention~~ to describe~~provide for~~ antibodies that interact and show affinity to an exposed conformational epitope of a protofibril form of Aβ peptide which comprises amino acids 4-12 and 9-20 (SEQ ID NO:3, 4) of an exposed portion of the the Aβ peptide.

Another object of the present disclosure~~invention~~ is to describe~~provide~~ 13C3-like antibodies which prevent or reduce Aβ peptide protofibril formation linked to the deposition of plaques associated with Alzheimer's disease.

Another object of the present disclosure~~invention~~ is to describe~~provide~~ assays utilizing 13C3-like antibodies in antibody/peptide/test compound interaction assays to select compounds which will be useful in treating plaque deposition associated with Alzheimer's disease.

As used herein, "Ka" is intended to refer to the association constant of a particular antibody antigen interaction, "Kd" is intended to refer to the dissociation constant of a particular antibody-antigen interaction.

As used herein, the term "epitope" or "antigenic determinant" refers to a site on an antigen to which B and/or T cells respond or a site on a molecule against which an antibody will be produced and/or to which an antibody