Furthermore, several antibodies have been described to detect Aβ peptides and to be used in immunological assays. For example, the monoclonal anti-Aβ(1-17) (6E10) is an antibody directed to the N-terminal region of the Aβ peptide, generated against the peptide Aβ(1-17) (Kim KS, et al. Neurosci. Res. Comm. 7; 1988) and recognizing the Aβ peptides including said region or the monoclonal antibody generated against the peptide Aβ(1-28) (Pierce).

However, there is a need in the art for improved immunological assays and kits to detect Aβ-derived peptides which overcome the problems of the methods and kits known in the art, in particular, which are sensitive enough to detect Aβ peptides in a reliable manner in plasma of patients suffering from sporadic AD. There is also a need for identifying biomarkers for the early diagnosis of AD which are sensitive and specific and which allow distinguishing cognitive impairment due to age from those associated with the early symptoms of the process, as well as to distinguish changes due to AD and due to other degenerative conditions. According to Growdon et al. (Neurobiol. Aging, 1998, 19:109-116), the ideal marker for AD should meet the following requirements:

- It should detect a fundamental feature of the neuropathology
- It should be validated in neuropathologically-confirmed cases of the disease
- It should show a sensitivity of at least 80% for detecting AD
- It should show a specificity of at least 80% to distinguish AD from other types of dementia and
- It should be reliable, reproducible, non-invasive, simple to perform and inexpensive.

SUMMARY OF THE INVENTION

In one aspect, there is provided an antibody that specifically binds to amyloid-beta (Aβ) (1-17) peptide, wherein the antibody does not show substantial cross-reactivity with an Aβ peptide selected from the group consisting of Aβ(1-15), Aβ(1-16), Aβ(1-38), Aβ(1-40), Aβ(1-42), and combinations thereof.

In one aspect, there is provided a kit for the detection of Aβ(1-17) peptide, comprising:

(i) the antibody as defined above and

(ii) a second antibody that is not the first antibody.

In one aspect, there is provided a method for determining or detecting Aβ(1-17) peptide in a sample comprising the steps of: (i) capturing the Aβ(1-17) present in the sample with a first antibody which binds specifically to said peptide to form first complexes, (ii) contacting the first complexes formed in step (i) with a second antibody to form second complexes, wherein said second antibody is the antibody of claim 1, and wherein said second antibody is different than the first antibody and is coupled to a first member of a binding pair selected from the group consisting of hapten-antibody, antigen-antibody, biotin-avidin, biotin analogue-avidin, biotin-streptavidin, biotin analogue-streptavidin, sugar-lectin, enzyme-cofactor, folic acid-folate, double stranded oligonucleotides that selectively bind to proteins-transcription factors, nucleic acid-complementary nucleic acid, nucleic acid analogue-complementary nucleic acid, and receptor-ligand (iii) contacting the second complexes formed in step (ii) with the second member of the binding pair, which is coupled to a detectable tag, and (iv) detecting or determining the activity or amount of the detectable tag.

In one aspect, the invention relates to an antibody which specifically binds to the Aβ (1-17) peptide.

In a second aspect, the invention relates to a kit for the detection of the Aβ (1-17) peptide, comprising:

(i) a first antibody which is an antibody as defined in any of claims 1 to 3 and

CLAIMS

1. A polyclonal antibody which specifically binds to the Aβ (1-17) peptide

which does not show substantial cross-reactivity against a Aβ peptide selected from the group consisting of Aβ(1-15), Aβ(1-16), Aβ(1-38), Aβ(1-40), Aβ(1-42) and a combination of one or more of them.

2. A kit for the detection of the Aβ (1-17) peptide, comprising:
   (i) a first antibody which is an antibody as defined in claim 1 and
   (ii) a second antibody which recognises a region of the Aβ (1-17) peptide different from the region that is recognised by the first antibody.

3. Kit according to claim 2 wherein the first or the second antibody is coupled to a first member of a binding pair;

4. Kit according to claim 3 further comprising a second member of said binding pair wherein said second member of the binding pair is coupled to a detectable tag.

5. A method for determining or detecting the Aβ (1-17) peptide in a sample comprising the steps of:
   (i) capturing the Aβ(1-17) peptide present in the sample with a first antibody which binds specifically to said peptide,
   (ii) contacting the immune complexes formed in step (i) with a second antibody, wherein said second antibody is as defined in any of claims 1 to 4 and wherein said second antibody recognises a different region than the first antibody and is coupled to a first member of a binding pair;
   (iii) contacting the complexes formed in step (ii) with a second member of a binding pair which is coupled to a detectable tag, and
   (iv) detecting or determining the activity or amount of the detectable tag.

6. Method as defined in claim 5 wherein the sample is selected from the group of blood, serum, plasma and CSF.

7. A method for the monitoring of a neurodegenerative disease in a subject, comprising:

(a) determining in a sample from said subject at a first time point the level of the Aβ17 peptide free in a plasma sample and the level of Aβ17 peptide bound to cells in a blood sample in a sample of said subject;

(b) determining in a sample from said subject at a second time point the level of the Aβ17 peptide free in a plasma sample and the level of Aβ17 peptide bound to cells in a blood sample in a sample of said subject and

(c) comparing the ratio of level of Aβ17 peptide free in a plasma sample and the level of Aβ17 peptide bound to cells in a blood sample at said first and second time points;

wherein if said ratio is increased at the second time point with respect to the first time point, it is indicative of a worsening of Alzheimer's disease in the subject between said first and said second time points.

8. Method according to claim 7 wherein the neurodegenerative disease is Alzheimer's disease.

9. Method according to any of claims 7 or 8 wherein the determination of the level of the Aβ17 peptide levels is carried out using a method as defined in any of claims 5 or 6.

10. A method for determining whether a subject is suffering from mild Alzheimer's disease comprising determining the value of one or more parameters selected from the group of consisting of:

(a) the added values of Aβ17, Aβ40 and Aβ42 peptides levels bound to cells in a blood sample from said subject sample;

(b) the added value of the Aβ17, Aβ40 and Aβ42 total peptides levels in a plasma sample from said subject and the Aβ17, Aβ40 and Aβ42 peptides levels bound to cells in a blood sample from said subject;

(c) the added value of total Aβ42 peptide level in a plasma sample from the subject and the level of Aβ42 peptide bound to cells in a blood sample from the subject;

(d) the added values of total Aβ40 and Aβ42 peptides levels in a plasma sample from the subject and the Aβ40 and Aβ42 peptides levels bound to cells in a blood sample from the subject; and

(e) the ratio value between the level of the Aβ17 free in a plasma sample from said subject and the Aβ17 peptide bound to cells in a blood sample from the subject;

wherein if the value of one or more of said parameters is increased with respect to the value of said parameters in a reference sample of a healthy subject, then the subject is suffering from mild Alzheimer's disease.

11. A method for determining whether a subject suffers from MCI with prodromal Alzheimer's disease comprising determining the value of one or more parameters selected from the group of:

(a) the added values of the total Aβ42 peptide level in a plasma sample from said subject and the Aβ42 peptide level bound to cells in a blood sample of said subject;

(b) the added values of the total Aβ40 and Aβ42 peptides level in a plasma sample from the subject and the Aβ40 and Aβ42 peptides levels bound to cells in a blood sample from said subject;

(c) the ratio value between the level of the Aβ17 peptide free in a plasma sample from the subject and the level of Aβ17 peptide bound to cells in a blood sample from said subject;

(d) the ratio value between the level of Aβ17 bound to cells in a blood sample and the level of Aβ42 peptide bound to cells in a blood sample;

(e) the ratio value between two parameters, wherein the first parameter corresponds to the added levels of total Aβ17 peptide in a plasma sample

and the level of Aβ17 peptide bound to cells in a blood sample and the second parameter correspond to the added levels of total Aβ42 peptide in a plasma sample and the level of Aβ42 peptide bound to cells in a blood sample;

(f) the ratio value between two parameters, wherein the first parameter corresponds to the level of Aβ17 peptide bound to cells in a blood sample and the second parameter corresponds to the added value of the levels of the Aβ40 peptide bound to cells in a blood sample and of the Aβ42 peptide bound to cells in a blood sample; and

(g) the ratio value between two parameters, wherein the first parameter corresponds to the added values of the level of total Aβ17 peptide in a plasma sample from said subject and the level of the Aβ17 peptide bound to cells in a blood sample and the second parameter corresponds to the added value of the total Aβ40 and Aβ42 peptides in a plasma sample and the levels of Aβ40 and Aβ42 peptides bound to cells in a blood sample;

wherein if the value of one or more of the parameters (a), (b) or (c) is increased and/or the value of one or more of the parameters (d), (e), (f) or (g) is decreased with respect to the value in a reference sample of a healthy subject, the subject is suffering from MCI with prodromal Alzheimer's disease.

12. A method for determining whether a subject suffers from MCI with prodromal Alzheimer's disease comprising determining the value of one or more parameters *selected from the group of*:

(a) the added values of Aβ17, Aβ40 and Aβ42 peptides levels bound to cells in a blood sample from said subject sample;

(b) the ratio value between the Aβ17 peptide level bound to cells in a blood sample of the subject and the Aβ42 peptide level bound to cells in a blood sample of said subject;

(c) the ratio value between two parameters, wherein the first parameter corresponds to the added values of Aβ17 total peptide level in a plasma sample from said subject and the level of Aβ17 peptide bound to cells in a blood sample and the second parameter corresponds to the added values of Aβ42 total peptide level in

a plasma sample from said subject and the level of Aβ42 peptide bound to cells in a blood sample;

(d) the ratio value between two parameters, wherein the first parameter corresponds to the level of Aβ17 peptide bound to cells in a blood sample and the second parameter corresponds to the added values of the Aβ40 and Aβ42 peptides levels bound to cells in a blood sample;

(e) the ratio value between two parameters, wherein the first parameter corresponds to the added values of the Aβ17 total peptide level in a plasma sample from said subject and the Aβ17 peptide level bound to cells in a blood sample and the second parameter corresponds to the added values of Aβ40 and Aβ42 total peptides levels in a plasma sample and of Aβ40 and Aβ42 peptide levels bound to cells in a blood sample;

wherein if the value of (a) is increased and/or the value of one or more of said parameters (b), (c), (d) and (e) is decreased with respect to the value of a reference sample of a subject suffering from MCI with non-prodromal Alzheimer's disease, the subject is suffering from MCI with prodromal Alzheimer's disease.

13. A method for determining whether a subject is suffering from mild Alzheimer's disease comprising determining the value of one or more parameters selected from the group of:

(a) the added values of the Aβ17, Aβ40 and Aβ42 peptides levels bound to cells in a blood sample;

(b) the added values of the Aβ17, Aβ40 and Aβ42 total peptides levels in a plasma sample and the levels of the Aβ17, Aβ40 and Aβ42 peptides bound to cells in a blood sample;

(c) the added values of total Aβ42 peptide in a plasma sample and the level of Aβ42 peptide bound to cells in a blood sample;

(d) the added values of the total Aβ40 and Aβ42 peptides levels in a plasma sample and the levels of the Aβ40 and Aβ42 peptides bound to cells in a blood sample;

(e) the added values of total Aβ40 peptide level in a plasma sample and the level of Aβ40 peptide bound to cells in a blood sample;

(f) the ratio value between two parameters, wherein the first parameter corresponds to the level of the Aβ17 peptide bound to cells in a blood sample and the second parameter corresponds to the added values of the levels of Aβ40 and Aβ42 peptides bound to cells in a blood sample; and

(g) the ratio value between the level of the Aβ17 peptide free in a plasma sample and the Aβ17 peptide level bound to cells in a blood sample;

wherein if the value of one or more of said parameters is increased with respect to the value of a reference sample of a subject having MCI with non-prodromal Alzheimer's disease, the subject is suffering from mild Alzheimer's disease.

14. A method for determining whether a subject is suffering from mild Alzheimer's disease comprising determining the value of one or more parameters selected from the group of:

(a) the ratio value between the Aβ17 peptide level free in a plasma sample and the level of the Aβ40 peptide free in a plasma sample; and

(b) the ratio between two parameters, wherein the first parameter corresponds to the level of the Aβ17 peptide free in a plasma sample and the second parameter corresponds to the added levels of the Aβ40 and Aβ42 peptides free in a plasma sample;

wherein if the value of one or more of said parameters is increased with respect to the value of a reference sample of a prodromal mild cognitive impairment subject, the subject is suffering from mild Alzheimer's disease.

Claims

1. An antibody that specifically binds to amyloid-beta (Aβ) (1-17) peptide, wherein the antibody does not show substantial cross-reactivity with an Aβ peptide selected from the group consisting of Aβ(1-15), Aβ(1-16), Aβ(1-38), Aβ(1-40), Aβ(1-42), and combinations thereof.

2. The antibody of claim 1, wherein the antibody is polyclonal.

3. The antibody of claim 1, wherein the antibody is monoclonal.

4. A kit for the detection of Aβ(1-17) peptide, comprising:

(i) the antibody of claim 1 and

(ii) a second antibody that is not the first antibody.

5. The kit of claim 4, wherein the first or second antibody is coupled to a first member of a binding pair selected from the group consisting of hapten-antibody, antigen-antibody, biotin-avidin, biotin analogue-avidin, biotin-streptavidin, biotin analogue-streptavidin, sugar-lectin, enzyme-cofactor, folic acid-folate, double stranded oligonucleotides that selectively bind to proteins-transcription factors, nucleic acid-complementary nucleic acid, nucleic acid analogue-complementary nucleic acid, and receptor-ligand.

6. The kit of claim 5, further comprising a second member of said binding pair, wherein said second member is coupled to a detectable tag.

7. A method for determining or detecting Aβ(1-17) peptide in a sample comprising the steps of: (i) capturing the Aβ(1-17) present in the sample with a first antibody which binds specifically to said peptide to form first complexes, (ii) contacting the first complexes formed in step (i) with a second antibody to form second complexes, wherein said second antibody is the antibody of claim 1, and wherein said second antibody is different than the first antibody and is coupled to a first member of a binding pair selected from the group consisting of hapten-antibody, antigen-antibody, biotin-avidin, biotin analogue-avidin, biotin-streptavidin, biotin analogue-streptavidin, sugar-lectin, enzyme-cofactor, folic acid-folate, double stranded oligonucleotides that selectively bind to proteins-transcription factors, nucleic acid-complementary nucleic acid, nucleic acid analogue-complementary nucleic acid, and receptor-ligand (iii) contacting the second complexes formed in step (ii) with the second member of the binding pair, which is coupled to a detectable tag, and (iv) detecting or determining the activity or amount of the detectable tag.

8. The method of claim 7, wherein the sample is selected from the group consisting of blood, serum, plasma and CSF.