preferable. The ease of administering antibiotics in oral dosage forms results in an increase of patient compliance during treatment.

What is needed are effective methods and compositions for the generation of highly specific and highly effective antibodies, which is a prerequisite if the antibodies are to be provided in an oral dosage form. Preferably such antibodies would recognize specific epitopes on various antigens such as amyloid protein.

What is also needed therefore, are effective compositions and methods for addressing the complications associated with diseases and disorders which are caused by or associated with amyloid or amyloid-like proteins including amyloidosis, a group of diseases and disorders associated with amyloid plaque formation including secondary amyloidosis and age-related amyloidosis including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), including diseases or conditions characterized by a loss of cognitive memory capacity such as, for example, mild cognitive impairment (MCI), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia complex; as well as other diseases which are based on or associated with amyloid-like proteins such as progressive supranuclear palsy, multiple sclerosis; Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), inclusion-body myositis (IBM), Adult Onset Diabetes; senile cardiac amyloidosis; endocrine tumors, and others, including macular degeneration. In particular what is need are specialized and highly effective antibodies capable of counteracting the physiological manifestations of the disease such as the formation of plaques associated with aggregation of fibers of the amyloid or amyloid-like peptide.

Summary

In one aspect, there is provided an antibody or active fragment thereof, which antibody or active fragment thereof recognizes and binds to an epitope of β-amyloid ("Aβ") peptide and,

(a) upon co-incubation with Aβ monomeric peptides 1-42, at a molar ratio of 1:100, antibody:peptides, inhibits the aggregation of the Aβ monomers into high molecular polymeric fibrils or filaments and, in addition,

(b) upon co-incubation with preformed high molecular polymeric amyloid fibrils or filaments formed by the aggregation of Aβ monomeric peptides 1-42, at a molar ratio of 1:100, antibody:preformed amyloid fibrils or filaments, is capable of disaggregating the preformed polymeric fibrils or filaments; and

(c) upon co-incubation with preformed high molecular polymeric amyloid fibrils or filaments formed by the aggregation of Aβ1-42 monomeric peptides is capable of inducing a transition of the β-sheet conformation towards an α-helix and/or a random coil conformation in the Aβ1-42 molecule.

In another aspect, there is provided an antibody or active fragment thereof, wherein said antibody or active fragment thereof binds to β-amyloid and comprises:

(1) the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 8 and the Light Chain Variable Region (LCVR) of SEQ ID NO: 7; or

(2) (i) a Light Chain Variable Region (LCVR) wherein the Light Chain Variable Region (LCVR) has an amino acid sequence that is 97%, 98% or 99% identical to the sequence given in SEQ ID NO: 7, and

(ii) a Heavy Chain Variable Region (HCVR) wherein the Heavy Chain Variable Region (HCVR) has an amino acid sequence that is 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the sequence given in SEQ ID NO: 8; or

(3) a Light Chain Variable Region (LCVR) and a Heavy Chain Variable Region (HCVR) that together have an amino acid sequence that is 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence given in SEQ ID NOs: 7 and 8; or

(4) the complementarity determining regions (CDRs) of the Light Chain Variable Region (LCVR) of SEQ ID NO: 7 and the CDRs of the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 8; or

(5) the epitope-binding fragments of the Light Chain Variable Region (LCVR) of SEQ ID NO: 7 and the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 8; or

(6) (i) a Light Chain Variable Region (LCVR) comprising a CDR1 having the amino acid sequence of SEQ ID NO: 23; a CDR2 having the amino acid sequence of SEQ ID NO: 24, and a CDR3 having the amino acid sequence of SEQ ID NO: 25; and (ii) a Heavy Chain Variable Region (HCVR) comprising a CDR1 having the amino acid sequence of SEQ ID NO: 26; a CDR2 having the amino acid sequence of SEQ ID NO: 27, and a CDR3 having the amino acid sequence of SEQ ID NO: 28.

In another aspect, there is provided a monoclonal antibody produced by:

(i) hybridoma cell line FP 12H3-C2, deposited on December 01, 2005 as DSM ACC2750, or an active fragment thereof or a functional equivalent thereof; or

(ii) hybridoma cell line FP 12H3-G2, deposited on December 01, 2005 as DSM ACC2751, or an active fragment thereof or a functional equivalent thereof.

In another aspect, there is provided an antibody or active fragment thereof, wherein said antibody or active fragment thereof binds to β-amyloid and comprises:

(1) the Light Chain Variable Region (LCVR) complementarity determining regions (CDRs) and the Heavy Chain Variable Region (CDRs) of the antibody produced by hybridoma cell line FP 12H3-C2, deposited on December 1, 2005 as DSM ACC2750; or

(2) a Light Chain Variable Region (LCVR) and a Heavy Chain Variable Region (HCVR) having the sequences of the LCVR and HCVR, respectively, of the antibody produced by hybridoma cell line FP 12H3-C2, deposited on December 1, 2005 as DSM ACC2750; or

(3) the epitope-binding fragments of the Light Chain Variable Region (LCVR) and the Heavy Chain Variable Region (HCVR) of the antibody produced by hybridoma cell line FP 12H3-C2, deposited on December 1, 2005 as DSM ACC2750.

In another aspect, there is provided a polynucleotide comprising a nucleotide sequence encoding an antibody or active fragment thereof as defined above.

In another aspect, there is provided a composition comprising the antibody or active fragment thereof as defined above in a therapeutically effective amount.

In another aspect, there is provided the composition as defined above, for use in the treatment of Alzheimer's disease.

In another aspect, there is provided a mixture comprising the antibody or active fragment thereof as defined above in a therapeutically effective amount and a further biologically active substance and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

In another aspect, there is provided a composition as defined above for use in decreasing the total amount of soluble Aβ in the brain of a mammal suffering from amyloidosis.

In another aspect, there is provided a hybridoma cell line that produces an antibody as defined above, or an active fragment thereof.

In another aspect, there is provided a hybridoma cell line FP 12H3-C2, deposited on December 01, 2005 as DSM ACC2750.

In another aspect, there is provided a hybridoma cell line FP 12H3-G2, deposited on December 01, 2005 as DSM ACC2751.

In another aspect, there is provided a method for monitoring minimal residual disease in a patient following treatment with an antibody or active fragment thereof as defined above or a composition as defined above, wherein said method comprises:

(a) bringing a patient sample suspected to contain amyloid antigen into contact with an antibody or active fragment thereof as defined above;
(b) allowing the antibody or active fragment thereof to bind to the amyloid antigen to form an immunological complex;
(c) detecting the formation of the immunological complex;
(d) correlating the presence or absence of the immunological complex with the presence or absence of amyloid antigen in the sample; and
(e) comparing the amount of said immunological complex to a normal control value,

wherein an increase in the amount of said immunological complex compared to a normal control value indicates that said patient still suffers from a minimal residual disease.

In another aspect, there is provided a method for predicting responsiveness of a patient being treated with an antibody or active fragment thereof as defined above or a composition as defined above comprising:

(a) bringing a patient sample suspected to contain amyloid antigen into contact with an antibody or active fragment thereof as defined above;

(b) allowing the antibody or active fragment thereof to bind to the amyloid antigen to form an immunological complex;

(c) detecting the formation of the immunological complex;

(d) correlating the presence or absence of the immunological complex with the presence or absence of amyloid antigen in the sample; and

(e) comparing the amount of said immunological complex before and after onset of the treatment,

wherein a decrease in the amount of said immunological complex indicates that said patient has a high potential of being responsive to the treatment.

In another aspect, there is provided the use of the antibody or active fragment thereof as defined above in the preparation of a medicament for decreasing the total amount of soluble Aβ in the brain of an animal suffering from amyloidosis.

In another aspect, there is provided a cell line that produces an antibody or active fragment thereof as defined above.

In another aspect, there is provided a cell line comprising the polynucleotide as defined above.

In another aspect, there is provided a method of producing an antibody or an active fragment thereof, comprising the step of culturing the cell line as defined above.

In another aspect, there is provided a method of producing antibody or an active fragment thereof, comprising the step of expressing the polynucleotide as defined above.

Description

Anti-amyloid antibodies elicited by the inoculation of $A\beta_{1-42}$ mixed with Freund complete or incomplete adjuvant had proved capable to reduce the amyloid burden in transgenic mice for human Alzheimer disease (Schenk et al., 1999).

Intraperitonal inoculation of tetrapalmitoylated $A\beta_{1-16}$ reconstituted in liposomes to NORBA transgenic mice elicited significant titers of anti-amyloid antibodies, which also proved capable to solubilize amyloid fibers and plaques *in vitro* and *in vivo*. (Nicolau et al., 2002).