to early AD pathology we demonstrate the presence of fibrillated alpha-synuclein in brains from AD patients independent of the presence of Lewy body pathology. This supports that soluble extracellular forms of fibrillated alpha-synuclein can potentially play a role in contributing to Tau-patholgy in tauopathies such as all AD patients and not only in those characterised with visible alpha-synuclein aggregates (determined by brain imaging or post mortem staining).

Summary of the invention

[00015] The present invention relates to the use of an alpha-synuclein binding monoclonal antibody for inhibiting aggregation of tau.

[00016] The antibodies of the invention, as disclosed herein and in the claims, can be used in treating patients with Alzheimer's disease or patients with a taupathy such as Argyrophilic Grain Disease (AGD), Psychosis, particularly Psychosis due to AD or Psychosis in patients with AD, psychiatric symptoms of patients with Lewy body dementia, Progressive Supranuclear Palsy (PSP), Frontotemporal dementia (FTD or variants thereof), TBI (traumatic brain injury, acute or chronic), Corticobasal Degeneration (CBD), Picks Disease, Primary age-related tauopathy (PART), Neurofibrillary tangle-predominant senile dementia, Dementia pugilistica, Chronic traumatic encephalopathy, stroke, stroke recovery, neurodegeneration in relation to Parkinson's disease, Parkinsonism linked to chromosome, Lytico-Bodig disease (Parkinson-dementia complex of Guam), Ganglioglioma and gangliocytoma, Meningioangiomatosis, Postencephalitic parkinsonism, Subacute sclerosing panencephalitis, Huntington's disease, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease and lipofuscinosis. More typically, the taupathy is selected from the group consisting of Alzheimer's disease, Argyrophilic Grain Disease (AGD), Psychosis, particularly Psychosis due to AD or Psychosis in patients with AD, psychiatric symptoms of patients with Lewy body dementia, Progressive Supranuclear

Palsy (PSP), Frontotemporal dementia (FTD or variants thereof), TBI (traumatic brain injury, acute or chronic), Corticobasal Degeneration (CBD), and Picks Disease.

[00016a] In one aspect of the present disclosure, there is provided a use of an alpha-synuclein binding monoclonal antibody, or an antigen-binding fragment thereof in the manufacture of a medicament for inhibiting aggregation of tau.

[00016b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the monoclonal antibody, or an antigen-binding fragment thereof as described herein, and a pharmaceutical acceptable carrier.

Brief description of figures

[00017] Fig. 1 shows immunization protocols for generation of hybridomas. The table outlines the differences of the immunogens and mouse strains used for the identification of GM37 and GM285. Different HCo17-Balb/c and HCo12/Balb/c mice were immunized independently (description of these mice are provided below). The hybridoma expressing GM37 was identified from mice immunized with full length alpha-synuclein containing amino acids 1-140 fibrils and boosted with truncated alpha-synuclein fragments 1-60 and 1-119 of full length (FL) alpha-synuclein (**SEQ ID NO 10**). The hybridoma expressing antibody GM285 came from an immunization protocol in which HCo12-Balb/c mice were immunized with full length monomeric alpha-synuclein, amino acids 1-140 followed by a boost with full length fibrillary alpha-synuclein (Example 1).

[00018] Fig. 2 (PANEL A-C) shows screening of GM37 for binding to alpha synuclein, alpha-synuclein homologs and orthologs.

[00019] A) Binding of antibody GM37 to alpha-synuclein using a no wash solution based ELISA (FMAT).

[00020] B) Using SPR (Fortebio) binding of antibody GM37 is specific for alpha-synuclein (Alpha Panel) and does not bind the other related synuclein family proteins, beta-synuclein (Beta Panel) and gamma-synuclein (Gamma Panel). Measurements were performed using SPR (Fortebio Octetred) GM37 shows similar binding to alpha-synuclein from cynomolgus monkey (Cyno Panel) and mouse (Mouse Panel). (Example 1).

[00021] C) Using SPR (Fortebio Octetred) binding of antibody GM285 is specific for alpha-synuclein and does not bind the other related synuclein family proteins, beta-synuclein and gamma-synuclein. Measurements were performed

CLAIMS

1. Use of an alpha-synuclein binding monoclonal antibody, or an antigen-binding fragment thereof in the manufacture of a medicament for inhibiting aggregation of tau.
2. The use according to claim 1, wherein the antibody binds aggregated soluble forms of alpha-synuclein
3. The use according to claims 1 or 2, wherein inhibition of tau aggregation is *in vivo* or *in vitro*.
4. The use according to any one of the preceding claims, wherein said alpha-synuclein antibody is to be administered to a patient with Alzheimer's disease.
5. The use according to any one of the preceding claims, wherein the patient does not have Lewy body variant of Alzheimer's disease or combined Parkinson and Alzheimer's disease.
6. The use according to claims 1-3, wherein said alpha-synuclein antibody is to be administered to a patient with a taupathy selected from the group comprising Argyrophilic Grain Disease (AGD), Psychosis, particularly Psychosis due to AD or Psychosis in patients with AD, psychiatric symptoms of patients with Lewy body dementia, Progressive Supranuclear Palsy (PSP), Frontotemporal dementia (FTD or variants thereof), TBI (traumatic brain injury, acute or chronic), Corticobasal Degeneration (CBD), Picks Disease, Primary age-related tauopathy (PART), Neurofibrillary tangle-predominant senile dementia, Dementia pugilistica, Chronic traumatic encephalopathy, stroke, stroke recovery, neurodegeneration in relation to Parkinson's disease, Parkinsonism linked to chromosome, Lytico-Bodig disease (Parkinson-dementia complex of Guam), Ganglioglioma and gangliocytoma, Meningioangiomatosis, Postencephalitic parkinsonism, Subacute sclerosing panencephalitis, Huntington's disease, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease and lipofuscinosis; more typically, the taupathy is selected from the group consisting of Alzheimer's disease,

Argyrophilic Grain Disease (AGD), Psychosis, particularly Psychosis due to AD or Psychosis in patients with AD, psychiatric symptoms of patients with Lewy body dementia, Progressive Supranuclear Palsy (PSP), Frontotemporal dementia (FTD or variants thereof), TBI (traumatic brain injury, acute or chronic), Corticobasal Degeneration (CBD), and Picks Disease.

7. The use according to any one of the preceding claims, wherein said alpha-synuclein antibody binds to the C-terminal part of alpha-synuclein

8. The use according to claim 7, wherein the antibody binds to an epitope within the C-terminal amino acids 110-140 of human alpha-synuclein.

9. The use according to claims 7 or 8, wherein said epitope is within amino acids 112-117, 112-115, 118-126, 126-138 or 136-140 of human alpha-synuclein **(SEQ ID NO 10)**.

10. The use according to claims 1-9 wherein the antibody, or a fragment thereof, comprises:

(a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;

(b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:2**;

(c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;

(d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;

(e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and

(f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.

11. The use according to claims 1-9 wherein the antibody, or a fragment thereof, comprises:

(a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;

(b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:33**;

(c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;

(d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;

(e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and

(f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.

12. The use according to claims 1-9 wherein the antibody, or a fragment thereof, comprises:

(a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;

(b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:34**;

(c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;

(d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;

(e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and

(f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.

13. The use according to claims 1-9 wherein the antibody, or a fragment thereof, comprises:

(a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;

(b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:35**;

(c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;

(d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;

(e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and

(f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.

14. The use according to any claims 1-9 wherein the antibody, or a fragment thereof, comprises:

(a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:20**;

(b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:21**;

(c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:22**;

(d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:23**;

(e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:24**; and

(f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:25**.

15. A pharmaceutical composition comprising the monoclonal antibody, or an antigen-binding fragment thereof, as defined in any one of the previous claims, and a pharmaceutical acceptable carrier.