

Claims

1. An antibody that binds to alpha synuclein or an antigen-binding fragment of the antibody thereof which binds to alpha synuclein, wherein the antibody or the antigen binding fragment of the antibody comprises:
 - a. a light chain variable region comprising:
 - i. a CDR-L1 comprising SEQ ID NO: 144;
 - ii. a CDR-L2 comprising SEQ ID NO: 2 and
 - iii. a CDR-L3 comprising SEQ ID NO: 3; and
 - b. a heavy chain variable region comprising:
 - i. a CDR-H1 comprising SEQ ID NO: 4;
 - ii. a CDR-H2 comprising SEQ ID NO: 545 and
 - iii. a CDR-H3 comprising SEQ ID NO: 646.
2. The antibody or antigen-binding fragment of claim 1, wherein the antibody comprises a light chain variable region comprising SEQ ID NO: 15 and a heavy chain variable region comprising SEQ ID NO: 31.
3. The antibody or antigen-binding fragment of claim 1, wherein the antibody comprises a light chain comprising SEQ ID NO: 17 and a heavy chain comprising SEQ ID NO: 33.
- 4.2. The antibody or the antigen-binding fragment ~~thereof according to~~ claim 1, wherein the antibody which binds ante alpha synuclein ~~to an~~ epitope comprising, with reference to SEQ ID NO: 10, residues E123, Y125, E126, M127, P128, S129, E130 and E131, wherein the epitope optionally comprises A124 and G132.
53. The antibody or antigen-binding fragment thereof according to ~~any one of~~ claims ~~1 or 2~~, wherein the antibody or antigen-binding fragment prevents aggregation of alpha synuclein induced by alpha synuclein fibrils.
64. The antibody or the antigen-binding fragment ~~thereof according to any one~~ of claims ~~1 to 3~~, wherein the antibody or antigen-binding fragment ~~thereof~~ is capable of binding alpha synuclein as a monomer and in fibrils.
75. The antibody or the antigen-binding fragment ~~thereof according to any one of the preceding claim~~ 1s, wherein the antibody or the antigen-binding fragment which has a higher binding affinity for alpha synuclein in fibrils compared to monomeric alpha synuclein

characterized by a constant of dissociation (K_D) at least 10-fold higher for monomeric alpha synuclein than for alpha synuclein in fibrils.

- 86. The antibody or the antigen-binding fragment ~~thereof according to any one of the preceding~~ claim 1, wherein the antibody or the antigen-binding fragments which has a (K_D) for alpha synuclein in fibrils of 300pM or less.
- 97. The antibody or the antigen-binding fragment ~~thereof according to any one of the preceding~~ claim 1, wherein the antibody or the antigen-binding fragments which does not bind beta synuclein and/or gamma synuclein.
- 108. The antibody or the antigen-binding fragment ~~thereof according to any one of the preceding~~ claim 1s, wherein the antibody is a chimeric or, humanized ~~or human~~ antibody.
- 119. The antibody or antigen-binding fragment of claim 1, according to any one of the preceding claims, wherein the antibody is a full-length antibody.
- 1240. The antibody or antigen-binding fragment of claim 11 ~~according to claim 9~~, wherein the full-length antibody is ~~selected from~~ an IgG1, IgG4 or IgG4P.
- 1344. The antibody or antigen-binding fragment ~~thereof according to any one of claims 1 to 8~~, wherein the antigen-binding fragment is ~~selected from~~ a Fab, a Fab', a F(ab')₂ or, a scFv, a dAb ~~or a V_HH~~.
- ~~12.~~ ~~The antibody or antigen-binding fragment thereof according to any one of the preceding claims wherein the antibody or antigen-binding fragment thereof comprises:~~
 - ~~a. a light chain variable region comprising a CDR-L1 comprising SEQ ID NO: 1; a CDR-L2 comprising SEQ ID NO: 2 and a CDR-L3 comprising SEQ ID NO: 3; and a heavy chain variable region comprising a CDR-H1 comprising SEQ ID NO: 4; a CDR-H2 comprising SEQ ID NO: 5 and a CDR-H3 comprising SEQ ID NO: 6; or~~
 - ~~b. a light chain variable region comprising SEQ ID NO: 15 and a heavy chain variable region comprising SEQ ID NO: 31; or~~
 - ~~c. a light chain comprising SEQ ID NO: 17 and a heavy chain comprising SEQ ID NO: 33.~~

- ~~13. The antibody or antigen-binding fragment thereof according to claim any one of claims 1 to 11, wherein the antibody or antigen-binding fragment thereof comprises:~~
- ~~a. a light chain variable region comprising a CDR-L1 comprising SEQ ID NO: 1; a CDR-L2 comprising SEQ ID NO: 2 and a CDR-L3 comprising SEQ ID NO: 3; and a heavy chain variable region comprising a CDR-H1 comprising SEQ ID NO: 4; a CDR-H2 comprising SEQ ID NO: 5 and a CDR-H3 comprising SEQ ID NO: 6; or~~
 - ~~b. a light chain variable region comprising SEQ ID NO: 15 and a heavy chain variable region comprising SEQ ID NO: 23; or~~
 - ~~c. a light chain comprising SEQ ID NO: 17 and a heavy chain comprising SEQ ID NO: 25.~~
- ~~14. The antibody or antigen-binding fragment thereof according to any one of claims 1 to 11 wherein the antibody or antigen-binding fragment thereof comprises:~~
- ~~a. a light chain variable region comprising a CDR-L1 comprising SEQ ID NO: 1; a CDR-L2 comprising SEQ ID NO: 2 and a CDR-L3 comprising SEQ ID NO: 3; and a heavy chain variable region comprising a CDR-H1 comprising SEQ ID NO: 4; a CDR-H2 comprising SEQ ID NO: 8 and a CDR-H3 comprising SEQ ID NO: 9; or~~
 - ~~b. a light chain variable region comprising SEQ ID NO: 15 and a heavy chain variable region comprising SEQ ID NO: 27 or 35; or~~
 - ~~c. a light chain comprising SEQ ID NO: 17 and a heavy chain comprising SEQ ID NO: 29 or 37.~~
- ~~15. The antibody or antigen-binding fragment thereof according to any one of claims 1 to 11 wherein the antibody or antigen-binding fragment thereof comprises:~~
- ~~a. a light chain variable region comprising a CDR-L1 comprising SEQ ID NO: 7; a CDR-L2 comprising SEQ ID NO: 2 and a CDR-L3 comprising SEQ ID NO: 3; and a heavy chain variable region comprising a CDR-H1 comprising SEQ ID NO: 4; a CDR-H2 comprising SEQ ID NO: 5 and a CDR-H3 comprising SEQ ID NO: 6; or~~
 - ~~b. a light chain variable region comprising SEQ ID NO: 19 and a heavy chain variable region comprising SEQ ID NO: 23 or 31; or~~

- ~~c. a light chain comprising SEQ ID NO: 21 and a heavy chain comprising SEQ ID NO: 25 or 33.~~
- ~~16. The antibody or antigen-binding fragment thereof according to any one of claims 1 to 11, wherein the antibody or antigen-binding fragment thereof comprises:~~
- ~~a. a light chain variable region comprising a CDR-L1 comprising SEQ ID NO: 7; a CDR-L2 comprising SEQ ID NO: 2 and a CDR-L3 comprising SEQ ID NO: 3; and a heavy chain variable region comprising a CDR-H1 comprising SEQ ID NO: 4; a CDR-H2 comprising SEQ ID NO: 8 and a CDR-H3 comprising SEQ ID NO: 9; or~~
- ~~b. a light chain variable region comprising SEQ ID NO: 19 and a heavy chain variable region comprising SEQ ID NO: 27 or 35; or~~
- ~~c. a light chain comprising SEQ ID NO: 21 and a heavy chain comprising SEQ ID NO: 29 or 37.~~
- ~~17. An antibody or antigen-binding fragment thereof which:~~
- ~~a. Competes for binding alpha-synuclein with the antibody or antigen-binding fragment thereof according to any one of the preceding claims; and/or~~
- ~~b. cross-blocks or is cross-blocked by the antibody or antigen-binding fragment thereof according to any one of the preceding claims for binding alpha-synuclein; and/or~~
- ~~c. binds alpha-synuclein to the same epitope as the antibody or antigen-binding fragment thereof according to any one of the preceding claims; and/or~~
- ~~d. comprises a heavy chain variable region having at least 80% identity or similarity to the sequence according to SEQ ID NO: 23, SEQ ID NO: 31, SEQ ID NO: 27 or SEQ ID NO: 35; and/or~~
- ~~e. comprises a light chain variable region having at least 80% identity or similarity to the sequence according to SEQ ID NO: 15 or SEQ ID NO: 19.~~
1418. An isolated polynucleotide encoding the antibody or the antigen-binding fragment thereof according to any one of claims ~~1 to 16~~.
1519. The isolated polynucleotide according to claim 1418, wherein the polynucleotide encodes:

- a. a light chain variable region, wherein the polynucleotide:
 - i. comprises a sequence that is at least 90% identical to SEQ ID NO: 16 ~~or SEQ ID NO: 20~~; or
 - ii. comprises SEQ ID NO: 16 ~~or 20~~; or
 - iii. ~~consists essentially of SEQ ID NO: 16 or SEQ ID NO: 20;~~
- b. a heavy chain variable region, wherein the polynucleotide:
 - i. comprises a sequence that is at least 90% identical to ~~SEQ ID NO: 24 or SEQ ID NO: 28 or SEQ ID NO: 32 or SEQ ID NO: 36~~; or
 - ii. comprises ~~SEQ ID NO: 24 or SEQ ID NO: 28 or SEQ ID NO: 32 or SEQ ID NO: 36~~; or
 - iii. ~~consists essentially of SEQ ID NO: 24 or SEQ ID NO: 28 or SEQ ID NO: 32 or SEQ ID NO: 36;~~
- c. ~~a light chain, wherein the polynucleotide:~~
 - i. ~~is at least 90% identical to SEQ ID NO: 18 or SEQ ID NO: 22; or~~
 - ii. ~~comprises SEQ ID NO: 18 or 22; or~~
 - iii. ~~consists essentially of SEQ ID NO: 18 or SEQ ID NO: 22;~~
- d. ~~a heavy chain, wherein the polynucleotide:~~
 - i. ~~is at least 90% identical to SEQ ID NO: 26 or SEQ ID NO: 30 or SEQ ID NO: 34 or SEQ ID NO: 38; or~~
 - ii. ~~comprises SEQ ID NO: 26 or SEQ ID NO: 30 or SEQ ID NO: 34 or SEQ ID NO: 38; or~~
 - iii. ~~consists essentially of SEQ ID NO: 26 or SEQ ID NO: 30 or SEQ ID NO: 34 or SEQ ID NO: 38.~~

16. A host cell comprising the polynucleotide of claim 14.

1720. A cloning or expression vector comprising ~~one or more~~the polynucleotides ~~according to any one~~ of claim ~~14s~~ 14 or 19.

1821. A host cell comprising:

a. ~~one or more polynucleotides according to any one of claims 18 or 19 or~~

b. ~~one or more~~ the expression vectors ~~according to~~ of claim 1720.

1922. A process for ~~the production of~~ anproducing the antibody or antigen-binding fragment thereof ~~according to any one of claims 1 to 16~~, comprising culturing ~~a~~the host cell comprising a polynucleotide encoding the antibody or antigen-binding fragment according to claim 21 under suitable conditions for producing the antibody or antigen-binding fragment ~~thereof~~ and isolating the antibody or antigen-binding fragment ~~thereof~~.

2023. A pharmaceutical composition comprising the antibody or antigen-binding fragment ~~thereof according to any one of claims 1 to 17~~ and one or more pharmaceutically acceptable carriers, excipients ~~or~~of diluents.

21. An antibody that binds to alpha-synuclein or an antigen-binding fragment of the antibody, wherein the antibody comprises a light chain variable region that is at least 80% identical to SEQ ID NO: 15 and a heavy chain variable region that is at least 80% identical to SEQ ID NO: 31, wherein the antibody or the antigen-binding fragment of the antibody comprises:

i) a CDR-L1 comprising SEQ ID NO: 1;

ii) a CDR-L2 comprising SEQ ID NO: 2;

iii) a CDR-L3 comprising SEQ ID NO: 3;

iv) a CDR-H1 comprising SEQ ID NO: 4;

v) a CDR-H2 comprising SEQ ID NO: 5; and

vi) a CDR-H3 comprising SEQ ID NO: 6.

24. ~~The antibody or antigen-binding fragment thereof according to any one of claims 1 to 17 or the pharmaceutical composition according to claim 23 for use in therapy.~~

- ~~25. The antibody or antigen-binding fragment thereof according to any one of claims 1 to 17 or the pharmaceutical composition according to claim 23 for use in the treatment of one or more synucleinopathies.~~
- ~~26. The antibody or antigen-binding fragment thereof of use according to claim 25 wherein the synucleinopathy is selected from Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), dementia with Lewy bodies (DLB), Diffuse Lewy Body Disease (DLBD), Lewy body variant of Alzheimer's disease (LBVAD), combined Alzheimer's and Parkinson's disease, multiple system atrophy (MSA), and neurodegeneration with brain iron accumulation type 1 (NBIA-1).~~
- ~~27. The antibody or antigen-binding fragment thereof of use according to claim 26 wherein the synucleinopathy is Parkinson's disease.~~
- ~~28. A method of treating a synucleinopathy in a patient comprising administering to said patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof according to any one of claims 1 to 17 or the pharmaceutical composition according to claim 23.~~
- ~~29. The method according to claim 28 wherein the synucleinopathy is selected from Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), dementia with Lewy bodies (DLB), Diffuse Lewy Body Disease (DLBD), Lewy body variant of Alzheimer's disease (LBVAD), combined Alzheimer's and Parkinson's disease, multiple system atrophy (MSA), and neurodegeneration with brain iron accumulation type 1 (NBIA-1), preferably Parkinson's disease.~~
- ~~30. The antibody or antigen-binding fragment thereof according to any one of claims 1 to 17 for use in the diagnosis of alpha synucleinopathy, preferably in the diagnosis of Parkinson's disease.~~