

CLAIMS

1. A humanized antibody or antigen-binding fragment thereof that binds to human alpha-synuclein, wherein the antibody or the antigen-binding fragment comprises:
 - a heavy chain variable region (VH) comprising
 - a heavy chain complementarity-determining region (HCDR) 1 set forth in SEQ ID NO:64,
 - an HCDR2 set forth in SEQ ID NO:65, and
 - an HCDR3 set forth in SEQ ID NO:66; and
 - a light chain variable region (VL) comprising
 - a light chain complementarity-determining region (LCDR) 1 set forth in SEQ ID NO:67,
 - an LCDR2 set forth in SEQ ID NO:68, and
 - an LCDR3 set forth in SEQ ID NO:69.
2. The antibody or antigen-binding fragment of claim 1, wherein
 - the VH comprises SEQ ID NO:1; and
 - the VL comprises SEQ ID NO:11.
3. The antibody or antigen-binding fragment of claim 1 or claim 2, wherein the antibody comprises a human kappa light chain constant region.
4. The antibody or antigen-binding fragment of claim 3, wherein the human kappa light chain constant region comprises SEQ ID NO:43.
5. The antibody of any one of claims 1-4, wherein the antibody comprises a human IgG1 constant region.
6. The antibody of claim 5, wherein
 - one heavy chain of the antibody comprises one or more knob mutations, optionally
 - wherein the one or more knob mutations comprise T366W, and

the other heavy chain of the antibody comprises one or more hole mutations, optionally wherein the one or more hole mutations comprise T366S, L368A, and Y407V (Eu numbering).

7. The antigen-binding fragment of any one of claims 1-4, wherein the antigen-binding fragment is a single-chain variable fragment (scFv).
8. The antibody or antigen-binding fragment of any one of claims 1-7, wherein the antibody or antigen-binding fragment is bispecific.
9. The antibody or antigen-binding fragment of claim 8, wherein the bispecific antibody or antigen-binding fragment comprises a second antigen-binding portion that binds insulin-like growth factor 1 receptor (IGF1R).
10. The antibody or antigen-binding fragment of claim 9, wherein the IGF1R-binding portion comprises a VH and a VL, wherein
 - the VH of the IGF1R-binding portion comprises
 - an HCDR1 set forth in SEQ ID NO:51,
 - an HCDR2 set forth in SEQ ID NO:52, and
 - an HCDR3 set forth in SEQ ID NO:53; and
 - the VL of the IGF1R-binding portion comprises
 - an LCDR1 set forth in SEQ ID NO:46,
 - an LCDR2 set forth in SEQ ID NO:47, and
 - an LCDR3 set forth in SEQ ID NO:48.
11. The antibody or antigen-binding fragment of claim 10, wherein the VH of the IGF1R-binding portion comprises SEQ ID NO:50 and the VL of the IGF1R-binding portion comprises SEQ ID NO:45.
12. The antibody or antigen-binding fragment of any one of claims 9-11, wherein the IGF1R-binding portion is an scFv, optionally comprising SEQ ID NO:54.

13. The antibody of any one of claims 9-12, wherein the IGF1R-binding portion is fused to the C-terminus of both heavy chains of the antibody.
14. The antibody of any one of claims 9-12, wherein the IGF1R-binding portion is fused to the C-terminus of only one heavy chain of the antibody.
15. The antibody of any one of claims 9-14, wherein
one heavy chain of the antibody comprises one or more knob mutations, optionally wherein the one or more knob mutations comprise T366W, and
the other heavy chain of the antibody comprises one or more hole mutations, optionally wherein the one or more hole mutations comprise T366S, L368A, and Y407V (Eu numbering).
16. The antibody of claim 6 or 15, wherein the knob heavy chain comprises SEQ ID NO:39 and/or the hole heavy chain comprises SEQ ID NO:40.
17. The antibody of any one of claims 1-6 and 8-16, wherein the heavy chains of the antibody further comprise an M428L mutation (Eu numbering).
18. The antibody of claim 17, wherein the knob heavy chain comprises SEQ ID NO:41 and the hole heavy chain comprises SEQ ID NO:42.
19. The antibody of any one of claims 15-18, wherein the IGF1R-binding portion is located at the C-terminus of the knob heavy chain.
20. The antibody of any one of claims 15-18, wherein the IGF1R-binding portion is located at the C-terminus of the hole heavy chain, optionally wherein the hole heavy chain comprises SEQ ID NO:55 or 56.
21. A bispecific antibody that binds to human alpha-synuclein and IGF1R, wherein the antibody comprises a heavy chain comprising SEQ ID NO:57 and a heavy chain comprising SEQ ID NO:58; and two light chains, each comprising SEQ ID NO:59.

22. The antibody or antigen-binding fragment of any one of claims 1-21, wherein the antibody or antigen-binding fragment binds to aggregated or oligomeric alpha-synuclein.
23. The antibody or antigen-binding fragment of claim 22, wherein the antibody or antigen-binding fragment binds to aggregated or oligomeric alpha-synuclein with a K_D no more than 200 pM, 100 pM, 50 pM, 30 pM, 20 pM or 10 pM.
24. The antibody or antigen-binding fragment of claim 22 or claim 23, wherein the antibody or antigen-binding fragment does not bind to monomeric alpha-synuclein.
25. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1-24 and a pharmaceutically acceptable carrier.
26. One or more nucleic acid molecules encoding the antibody or antigen-binding fragment of any one of claims 1-24.
27. The one or more nucleic acid molecule of claim 26, wherein the one or more nucleic acid molecules are expression constructs.
28. The one or more nucleic acid molecules of claim 26 or 27, wherein the one or more nucleic acid molecules comprise a nucleotide sequence selected from SEQ ID NOs:17-25 and a nucleotide sequence selected from SEQ ID NOs:27-31.
29. A host cell comprising the one or more nucleic acid molecules of any one of claims 26-28.
30. The host cell of claim 29, wherein the host cell is a mammalian cell.
31. A method of producing an antibody or antigen-binding fragment, comprising:
culturing the host cell of claim 29 or 30 under conditions that allow expression of the antibody or antigen-binding fragment, and
isolating the antibody or antigen-binding fragment from the cell culture.

32. Use of the antibody or antigen-binding fragment of any one of claims 1-24 for the manufacture of a medicament for treating an alpha-synucleinopathy in a human subject in need thereof.
33. The use of claim 32, wherein the alpha-synucleinopathy is dementia with Lewy bodies, or Alzheimer's disease with amygdala Lewy bodies.
34. The use of claim 32, wherein the alpha-synucleinopathy is Parkinson's disease.
35. The use of claim 32, wherein the alpha-synucleinopathy is multiple system atrophy.
36. The antibody or antigen-binding fragment of any one of claims 1-24 for use in treating an alpha-synucleinopathy in a human subject in need thereof.
37. The antibody or antigen-binding fragment for use of claim 36, wherein the alpha-synucleinopathy is dementia with Lewy bodies, or Alzheimer's disease with amygdala Lewy bodies.
38. The antibody or antigen-binding fragment for use of claim 36, wherein the alpha-synucleinopathy is Parkinson's disease.
39. The antibody or antigen-binding fragment for use of claim 36, wherein the alpha-synucleinopathy is multiple system atrophy.
40. The pharmaceutical composition of claim 25 for use in treating an alpha-synucleinopathy in a human subject in need thereof.
41. The pharmaceutical composition for use according to claim 40, wherein the alpha-synucleinopathy is dementia with Lewy bodies, or Alzheimer's disease with amygdala Lewy bodies.

42. The pharmaceutical composition for use of claim 40, wherein the alpha-synucleinopathy is Parkinson's disease.
43. The pharmaceutical composition for use of claim 40, wherein the alpha-synucleinopathy is multiple system atrophy.