CLAIMS

1. An anti-α-synuclein/anti-insulin-like growth factor 1 receptor (IGF1R) bispecific antibody, comprising

a) an anti-α-synuclein (α-syn) antibody or an antigen binding fragment thereof; and

b) an anti-IGF1R antibody or an antigen binding fragment thereof that comprises

i) a heavy chain variable region (VH) comprising

a heavy chain complementarity-determining region (H-CDR) 1 comprising SEQ ID NO: 1,

an H-CDR2 comprising SEQ ID NO: 5 and

an H-CDR3 comprising SEQ ID NO: 8; and

ii) a light chain variable region (VL) comprising

a light chain CDR (L-CDR) 1 comprising SEQ ID NO: 20,

an L-CDR2 comprising SEQ ID NO: 23, and

an L-CDR3 comprising SEQ ID NO: 27.

2. The bispecific antibody according to claim 1, wherein the anti-IGF1R antibody or antigen binding fragment thereof binds to at least one of V397, W434, D435, Y460, C488, L641, R650, Y775, P776, F778, E779, S791, L798, H808, E809, and L813 in a protein comprising SEQ ID NO: 174.

3. The bispecific antibody of claim 1 or 2, wherein the anti-IGF1R antibody or antigen binding fragment thereof binds to at least one binding site selected from the group consisting of binding sites 1 to 3 in a protein comprising SEQ ID NO: 174, and wherein

binding site 1 comprises at least one of R650, Y775, P776, F778, E779, S791, and L798;

binding site 2 comprises at least one of L641, H808, E809 and L813; and

binding site 3 comprises at least one of V397, W434, D435, Y460, and C488.

4. The bispecific antibody of any one of claims 1-3, wherein the anti-IGF1R antibody or antigen-binding fragment thereof comprises at least one of

a heavy chain framework region (H-FR) 1 comprising SEQ ID NO: 32,

an H-FR2 comprising SEQ ID NO: 34,

an H-FR3 comprising SEQ ID NO: 35, and
an H-FR4 comprising SEQ ID NO: 36, and
a light chain framework region (L-FR) 1 comprising SEQ ID NO: 37,
an L-FR2 comprising SEQ ID NO: 38,
an L-FR3 comprising SEQ ID NO: 39, and
an L-FR4 comprising SEQ ID NO: 42.

5. An anti-α-synuclein/anti-IGF1R bispecific antibody, comprising
   a) an anti-α-syn antibody or an antigen-binding fragment thereof; and
   b) an anti-IGF1R antibody or an antigen-binding fragment thereof comprising a VH and a VL that comprise SEQ ID NOs: 52 and 97, respectively.

6. The bispecific antibody of any one of claims 1-5, wherein the anti-IGF1R antigen-binding fragment is selected from an scFv, $(scFv)_2$, scFv-Fc, Fab, Fab' and $F(ab')_2$.

7. The bispecific antibody of claim 6, wherein the anti-IGF1R antigen-binding fragment is an scFv that comprises, from N-terminus to C-terminus, SEQ ID NO: 97, SEQ ID NO: 134, and SEQ ID NO: 52.

8. The bispecific antibody of any one of claims 1-7, comprising an anti-α-syn antibody and an anti-IGF1R scFv.

9. The bispecific antibody of claim 8, wherein the anti-α-syn antibody is of isotype subtype IgG1, IgG2, IgG3, or IgG4, optionally comprising an M428L mutation (Eu numbering).

10. The bispecific antibody of any one of claims 7-9, wherein the anti-IGF1R scFv is fused to the C-terminus of a heavy chain of the anti-α-syn antibody, optionally wherein the two heavy chains of the anti-α-syn antibody comprise knob-in-hole mutations.

11. The bispecific antibody of any one of claims 1-10, wherein the anti-α-syn antibody or antigen binding fragment thereof specifically binds to the C-terminal region of human alpha-synuclein.

12. The bispecific antibody of any one of claims 1-11, wherein the anti-α-syn antibody or antigen binding fragment thereof specifically binds to a peptide comprising residues 110-120 or residues 111-122 from the N-terminus of SEQ ID NO: 173.

13. The bispecific antibody of any one of claims 1-12, wherein the anti-α-syn antibody or antigen binding fragment thereof comprises,

an H-CDR1 comprising SEQ ID NO: 135,

an H-CDR2 comprising SEQ ID NO: 136 or 137,

an H-CDR3 comprising SEQ ID NO: 138;

an L-CDR1 comprising SEQ ID NO: 139,

an L-CDR2 comprising SEQ ID NO: 140, and

an L-CDR3 comprising SEQ ID NO: 141.

14. The bispecific antibody of claim 13, wherein the anti-α-syn antibody or antigen binding fragment thereof comprises a VH and a VL comprising

SEQ ID NOs: 142 and 147, respectively;

SEQ ID NOs: 143 and 147, respectively;

SEQ ID NOs: 144 and 147, respectively;

SEQ ID NOs: 145 and 147, respectively; or

SEQ ID NOs: 146 and 148, respectively.

15. The bispecific antibody of claim 13, wherein the anti-α-syn antibody or antigen binding fragment thereof comprises a VH and a VL comprising SEQ ID NOs: 143 and 147, respectively.

16. An anti-α-synuclein/anti-IGF1R bispecific antibody comprising

a first heavy chain and a second heavy chain comprising SEQ ID NOs: 166 and 152, respectively; and

two identical light chains each comprising SEQ ID NO: 150.

17. An anti-α-synuclein/anti-IGF1R bispecific antibody comprising

a first heavy chain and a second heavy chain comprising SEQ ID NOs: 169 and 155, respectively; and

two identical light chains each comprising SEQ ID NO: 150.

18. A pharmaceutical composition, comprising the bispecific antibody of any one of claims 1-17 and a pharmaceutically acceptable excipient.

19. One or more nucleic acid molecules encoding the bispecific antibody of any one of claims 1-17.

20. One or more expression vectors or a host cell comprising the one or more nucleic acid molecules of claim 19.

21. A method of making a bispecific antibody, comprising

culturing the host cell of claim 20 under conditions that permit expression of the bispecific antibody, and

isolating the bispecific antibody from the cell culture.

22. Use of the bispecific antibody of any one of claims 1-17 or the pharmaceutical composition of claim 18 in the manufacture of a medicament for treating an α-synucleinopathy in a subject in need thereof.

23. The use of claim 22, wherein the α-synucleinopathy is Parkinson's disease (PD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), combined Alzheimer's and Parkinson's disease, or multiple system atrophy (MSA).