

CLAIMS:

1. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein:
 - (a) ~~the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIQQGYYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);~~
 - (b) ~~the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIQQGYYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRVS (SEQ ID NO: 30), and an HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);~~
 - (c) ~~the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLES (SEQ ID NO: 3), an HVR-H3 comprising the amino acid sequence ARQGSIQQGYYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);~~
 - (~~d~~a) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIQQGYYGMDV (SEQ ID NO: 6); and the light chain

- variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32); or
- (e**b**) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYWYG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);
- ~~(f) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYWYG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);~~
- ~~(g) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYWYG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIQQGYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLHSNGYNYLD (SEQ ID NO: 26), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);~~
- ~~(h) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYWYG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable~~

region comprises an HVR-L1 comprising the amino acid sequence RSSQGLLR~~S~~NGYNYLD (SEQ ID NO: 27), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);

(i) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLR~~S~~SGYNYLD (SEQ ID NO: 10), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32); or

(j) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLR~~S~~IGYNYLD (SEQ ID NO: 21), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

2. The antibody of claim 1, wherein the antibody:

- (a) decreases cell surface levels of Sortilin more than the level of decrease caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79;
- (b) increases extracellular levels of Progranulin more than the level of increase caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79;

- (c) inhibits the interaction between Sortilin expressed on a cell and Progranulin more than the level of inhibition caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79; or
- (d) any combination of (a)–(c).
3. The antibody of claim 1 or claim 2, wherein the antibody has a dissociation constant (K_D) for human Sortilin that is at least 1.1-fold lower than an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79, wherein the K_D is determined by FACS.
 4. The antibody of any one of claims 1-3, wherein the antibody has a dissociation constant (K_D) for human Sortilin that ranges from ~~about~~ 5.0E-10 M to ~~about~~ 1.0E-9 M wherein the K_D is determined by FACS, or ~~about~~ 250-500 pM wherein the K_D is determined by Bio-layer interferometry.
 5. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein: the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNLYD (SEQ ID NO: 9), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).
 6. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein: the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino

acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

7. An antibody that binds to a Sortilin protein, wherein the antibody comprises:

- ~~(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57;~~
- ~~(b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 58;~~
- ~~(c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 59;~~
- ~~(d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 55, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57;~~
- ~~(e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 55, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 58;~~
- (af) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57; or
- ~~(g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;~~
- ~~(h) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78;~~
- ~~(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;~~
- ~~(j) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 80;~~
- (kb) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 60;
- ~~(l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 61; or~~

~~(m) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 72.~~

8. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 60.
9. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57.
10. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 137 and a light chain comprising the amino acid sequence of SEQ ID NO: 142.
11. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 138 and a light chain comprising the amino acid sequence of SEQ ID NO: 142.
12. The antibody of any one of claims 1-9, wherein the antibody is of the IgG class, the IgM class, or the IgA class.
13. The antibody of claim 12, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.
14. The antibody of claim 13, wherein:
 - (a) the antibody is an IgG1 or IgG2 isotype and the Fc region comprises an amino acid substitution at position P331S, wherein the numbering of the residue position is according to EU numbering;
 - (b) the antibody is an IgG1 isotype and the Fc region comprises amino acid substitutions at positions L234A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering;
 - (c) the antibody is an IgG1, IgG2, or IgG4 isotype and the Fc region comprises an amino acid substitution at position N297A, wherein the numbering of the residue position is according to EU numbering; or

- (d) the Fc region comprises an amino acid substitution at positions S267E and L328F, wherein the numbering of the residue position is according to EU numbering.
- 15. The antibody of claim 14, wherein the antibody is an IgG1 isotype and the Fc region comprises amino acid substitutions at positions L234A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering.
- 16. The antibody of any one of claims 1-15, wherein the Sortilin protein is a human Sortilin protein.
- 17. The antibody of claim 16, wherein the human Sortilin protein comprises the amino acid sequence of SEQ ID NO: 81.
- 18. The antibody of any one of claims 1-16, wherein the Sortilin protein is a wild-type protein, a naturally occurring variant, or a disease variant.
- 19. The antibody of any one of claims 1-18, wherein the antibody is a human antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, or a conjugated antibody.
- 20. The antibody of claim 19, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen.
- 21. The antibody of claim 20, wherein the first antigen is Sortilin and the second antigen is an antigen facilitating transport across the blood-brain-barrier.
- 22. The antibody of claim 21, wherein the second antigen is selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, basigin, Glut1, CD98hc, and ANG1005.
- 23. The antibody of any one of claims 1-9 and 12-22, wherein the antibody is an antibody fragment that binds to a human Sortilin protein.

24. The antibody of claim 23, wherein the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.
25. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of claims 1-24.
26. A vector comprising the nucleic acid of claim 25.
27. An isolated host cell comprising the vector of claim 26.
28. A method of producing an antibody that binds to Sortilin, comprising culturing the host cell of claim 27 so that the antibody is produced.
29. The method of claim 28, further comprising recovering the antibody produced by the host cell.
30. An isolated antibody that binds to Sortilin produced by the method of claim 28 or claim 29.
31. A pharmaceutical composition comprising the antibody of any one of claims 1-24 and claim 30 and a pharmaceutically acceptable carrier.
32. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for preventing, reducing risk for, or treating a disease, disorder, or injury in an individual, wherein the disease, disorder, or injury is selected from the group consisting of frontotemporal dementia, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, dementia, stroke, Parkinson's disease, retinal degeneration, arthritis, and osteoarthritis.
- ~~33. The use of claim 32, wherein the disease, disorder, or injury is selected from the group consisting of frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, dementia, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis, septic shock, bacterial infection, arthritis, and osteoarthritis.~~

~~34.33.~~ 33.33. The use of claim ~~3332~~, wherein the disease, disorder, or injury is selected from the group consisting of frontotemporal dementia, ~~progressive supranuclear palsy~~ Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis.

~~35.34.~~ 34.34. ~~Use of the~~ The antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 ~~in the manufacture of a medicament for use~~ in inhibiting one or more of neuroinflammation, axonopathy characterized by short axonal outgrowth and aberrant branching, aberrant microglial activation, and inflammatory response in an individual in need thereof.

~~36.35.~~ 35.35. ~~Use of the~~ The antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 ~~in the manufacture of a medicament for use~~ in promoting one or more of wound healing, autophagy, and clearance of aggregate proteins in an individual in need thereof.

~~37.36.~~ 36.36. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for preventing, reducing risk of, or treating arthritis in an individual in need thereof.

~~38.37.~~ 37.37. ~~Use of the~~ The antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 ~~in the manufacture of a medicament for use~~ in decreasing expression of one or more pro-inflammatory mediators in an individual in need thereof.

~~39.38.~~ 38.38. ~~The use antibody or pharmaceutical composition~~ of claim ~~3738~~, wherein the one or more pro-inflammatory mediators are selected from the group consisting of IL-6, IL12p70, IL12p40, IL-1 β , TNF- α , CXCL1, CCL2, CCL3, CCL4, and CCL5.

~~40.39.~~ 39.39. A method of inhibiting the interaction between Sortilin expressed on a cell and Progranulin, the method comprising exposing a cell expressing Sortilin on the cell surface to the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31, wherein the cell is *in vitro*.

~~41.40.~~ 40.40. The method of claim ~~4039~~, further comprising decreasing the level of Sortilin expressed on the cell surface.

42.41. ~~_____~~ The method of claim 40~~39~~ or claim 41~~40~~, wherein extracellular levels of Progranulin are increased.

43.42. ~~_____ Use of the~~ The antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 ~~in the manufacture of a medicament for use~~ in increasing levels of Progranulin in an individual in need thereof.

44.43. ~~_____ The antibody or pharmaceutical composition use of~~ claim 43~~42~~, wherein levels of Progranulin are increased in plasma.

45.44. ~~_____ The antibody or pharmaceutical composition use of~~ claim 43~~42~~, wherein levels of Progranulin are increased in cerebrospinal fluid.

46.45. ~~_____ Use of the~~ The antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 ~~in the manufacture of a medicament for use~~ in decreasing levels of Sortilin in an individual in need thereof.

47.46. ~~_____ The antibody or pharmaceutical composition use of~~ claim 46~~45~~, wherein the levels of Sortilin are decreased in peripheral white blood cells.

48.47. ~~_____ The use of any one of claims 32-33 and 36, or the antibody or pharmaceutical composition of any one of claims 34-35, 37-38 and 42-46~~ use of any one of claims 32-34 and 43-47, wherein the individual has one or more mutations in the gene encoding Progranulin.

49.48. ~~_____ The use, antibody, or pharmaceutical composition use of~~ claim 48~~47~~, wherein the individual is heterozygous for one or more loss-of-function mutations in the gene encoding Progranulin.

50.49. ~~_____ The use, antibody, or pharmaceutical composition use of~~ claim 48~~47~~ or claim 49~~48~~, wherein the individual has or is at risk for frontotemporal dementia, Alzheimer's disease, or amyotrophic lateral sclerosis.

51.50. ~~_____ The use of any one of claims 32-33, 36, and 47-49, the antibody or pharmaceutical composition use of any one of claims 32-39 and 43-50~~ 34-35, 37-38 and 42-49, or the method of any one of claims 40~~39~~-42~~41~~, wherein the antibody comprises two or more antibodies that bind to a Sortilin protein.