CLAIMS

1. An isolated anti-Sortilin antibody that binds to human Sortilin, wherein the anti-Sortilin antibody increases extracellular levels of Progranulin and decreases cellular levels of Sortilin, wherein the decrease in cellular levels of Sortilin is a decrease in cell surface levels of Sortilin, a decrease in intracellular levels of Sortilin, a decrease in total levels of Sortilin, or any combination thereof.

2. The anti-Sortilin antibody of claim 1, wherein the anti-Sortilin antibody induces Sortilin degradation, Sortilin cleavage, Sortilin internalization, Sortilin down regulation, inhibits the interaction between Sortilin and Progranulin, or any combination thereof.

3. The anti-Sortilin antibody of claim 1 or claim 2, wherein the anti-Sortilin antibody further inhibits interaction between Sortilin and one or more proteins by: a) reducing the effective levels of Sortilin available for interacting with the one or more proteins; b) inducing degradation of Sortilin; or both.

4. The anti-Sortilin antibody of claim 3, wherein the anti-Sortilin antibody further inhibits interaction between Sortilin and pro-nerve growth factor (pro-NGF).

5. The anti-Sortilin antibody of any one of claims 1-4, wherein the anti-Sortilin antibody binds specifically to human Sortilin and mouse Sortilin.

6. The anti-Sortilin antibody of claim 5, wherein the anti-Sortilin antibody binds with a disassociation constant (K_D) for human Sortilin that ranges from about 100 nM to about 0.005 nM, or less than 0.005 nM.

7. The anti-Sortilin antibody of claim 5, wherein the anti-Sortilin antibody binds with a disassociation constant (K_D) for mouse Sortilin that ranges from about 100 nM to about 0.005 nM, or less than 0.005 nM.

8. The anti-Sortilin antibody of any one of claims 1-7, wherein the anti-Sortilin antibody is a human antibody, a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody.

9. The anti-Sortilin antibody of any one of claims 1-8, wherein the anti-Sortilin antibody is a multivalent antibody recognizing a second antigen.

10. The anti-Sortilin antibody of claim 9, wherein the second antigen is an antigen facilitating transport across the blood-brain-barrier.

11. The anti-Sortilin antibody of claim 10, 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, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, and ANG1005.

12. The anti-Sortilin antibody of any one of claims 1-11, wherein the anti-Sortilin antibody is an antibody fragment that binds to an epitope comprising amino acid residues on human Sortilin or a mammalian Sortilin protein, and in particular wherein the fragment is an Fab, Fab', Fab'-SH, $F(ab')_2$, Fv, or scFv fragment.

13. The anti-Sortilin antibody of any one of claims 1-12, wherein the anti-Sortilin antibody further comprises one or more activities selected from the group consisting of:

(a) inducing one or more Progranulin activities;

(b) reducing endosomal internalization of Progranulin, or fragments thereof; and

(c) increasing the effective concentration of Progranulin.

14. The anti-Sortilin antibody of any one of claims 1-13, wherein the anti-Sortilin antibody inhibits the interaction between Sortilin and Progranulin.

15. The anti-Sortilin antibody of any one of claims 1-13, wherein the anti-Sortilin antibody does not inhibit the interaction between Sortilin and Progranulin.

16. The anti-Sortilin antibody of any one of claims 1-14, wherein the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein:

(a) the light chain variable domain comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 30, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 100, and the heavy chain variable domain comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142, an HVR-H2 comprising the amino acid sequence of SEQ

ID NO: 170, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 233; or

(b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 430 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 431.

17. The anti-Sortilin antibody of any one of claims 1-14, wherein the anti-Sortilin antibody competes with a reference anti-Sortilin antibody for binding to human Sortilin, wherein the reference anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein:

(a) the light chain variable domain of the reference anti-Sortilin antibody comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 30, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 100, and the heavy chain variable domain of the reference anti-Sortilin antibody comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 170, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 233; or

(b) the light chain variable domain of the reference anti-Sortilin antibody comprises the amino acid sequence of SEQ ID NO: 430 and the heavy chain variable domain of the reference anti-Sortilin antibody comprises the amino acid sequence of SEQ ID NO: 431.

18. The anti-Sortilin antibody of any one of claims 1-14, wherein the anti-Sortilin antibody binds to an epitope of human Sortilin that is the same as the Sortilin epitope bound by a reference anti-Sortilin antibody, wherein the reference anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, and wherein:

(a) the light chain variable domain of the reference anti-Sortilin antibody comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 30, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 100, and the heavy chain variable domain of the reference anti-Sortilin antibody comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142, an HVR-H2 comprising the amino acid sequence of SEQ

ID NO: 170, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 233; or

(b) the light chain variable domain of the reference anti-Sortilin antibody comprises the amino acid sequence of SEQ ID NO: 430 and the heavy chain variable domain of the reference anti-Sortilin antibody comprises the amino acid sequence of SEQ ID NO: 431.

19. The anti-Sortilin antibody of any one of claims 1-13 and 15, wherein the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein:

(a) the light chain variable domain comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 55, and the heavy chain variable domain comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 520, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 533, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 553; or

(b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 343 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 648.

20. The anti-Sortilin antibody of any one of claims 1-13 and 15, wherein the anti-Sortilin antibody competes with a reference anti-Sortilin antibody for binding to human Sortilin, wherein the reference anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein:

(a) the light chain variable domain of the reference anti-Sortilin antibody comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 55, and the heavy chain variable domain of the reference anti-Sortilin antibody comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 129, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 155, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 190.; or

(b) the light chain variable domain of the reference anti-Sortilin antibody comprises the amino acid sequence of SEQ ID NO: 343 and the heavy chain variable domain of the reference anti-Sortilin antibody comprises the amino acid sequence of SEQ ID NO: 342.

21. The anti-Sortilin antibody of any one of claims 1-13 and 15, wherein the anti-Sortilin antibody binds to an epitope of human Sortilin that is the same as the Sortilin epitope bound by a reference anti-Sortilin antibody, wherein the reference anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, and wherein:

(a) the light chain variable domain of the reference anti-Sortilin antibody comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 55, and the heavy chain variable domain of the reference anti-Sortilin antibody comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 129, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 155, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 190.; or

(b) the light chain variable domain of the reference anti-Sortilin antibody comprises the amino acid sequence of SEQ ID NO: 343 and the heavy chain variable domain of the reference anti-Sortilin antibody comprises the amino acid sequence of SEQ ID NO: 342.

22. The anti-Sortilin antibody of any one of claims 1-21, wherein the anti-Sortilin antibody has an IgG1 or IgG4 isotype.

23. The anti-Sortilin antibody of claim 22, wherein:

(a) the anti-Sortilin antibody has a human IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, N297Q, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or

(b) the anti-Sortilin antibody has a human IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: E233P, F234V, L234A/F234A, L235A, G237A, E318A, S228P,

L236E, S241P, L248E, T394D, M252Y, S254T, T256E, N297A, N297Q, and any combination thereof, wherein the numbering of the residues is according to EU numbering.

24. The anti-Sortilin antibody of claim 23, wherein:

(a) the IgG1 Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of A330L, L234F, L235E, P331S, and any combination thereof, wherein the numbering of the residues is according to EU numbering;

(b) the IgG1 or IgG4 Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or

(c) the IgG4 Fc region further comprises a S228P amino acid substitution according to EU numbering.

25. The anti-Sortilin antibody of claim 22, wherein the anti-Sortilin antibody has a human IgG4 isotype and comprises an amino acid substitution at residue positions S228P, F234A, and L235A, wherein the numbering of the residue position is according to EU numbering.

26. An isolated nucleic acid comprising a nucleic acid sequence encoding the anti-Sortilin antibody of any one of claims 1-25.

27. A vector comprising the nucleic acid of claim 26.

28. An isolated host cell comprising the vector of claim 27.

29. A method of producing an anti-Sortilin antibody, comprising culturing the host cell of claim 28 so that the anti-Sortilin antibody is produced, optionally wherein the method further comprises recovering the anti-Sortilin antibody produced by the host cell.

30. An isolated anti-Sortilin antibody produced by the method of claim 29.

31. A pharmaceutical composition comprising the anti-Sortilin antibody of any one of claims 1-25, and a pharmaceutically acceptable carrier.

32. The anti-Sortilin antibody of any one of claims 1-25 for use in increasing extracellular levels of Progranulin, decreasing cellular levels of Sortilin from one or more cells, and/or decreasing expression of one or more pro-inflammatory mediators, optionally wherein the one or more pro-inflammatory mediators are selected from the group consisting of IL-6, IL12p70, IL12p40, IL-1β, TNF-α, CXCL1, CCL2, CCL3, CCL4, and CCL5.

33. Use of the anti-Sortilin antibody of any one of claims 1-25 in the manufacture of a medicament for preventing, reducing risk, or treating a disease, disorder, or injury in an individual in need thereof, 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. Use of the anti-Sortilin antibody of any one of claims 1-25 in the manufacture of a medicament for preventing, reducing risk, or treating frontotemporal dementia in an individual in need thereof.

35. Use of the anti-Sortilin antibody of any one of claims 1-25 in the manufacture of a medicament for preventing, reducing risk, or treating Alzheimer's disease in an individual in need thereof.

36. Use of the anti-Sortilin antibody of any one of claims 1-25 in the manufacture of a medicament for inhibiting one or more of neuroinflammation, axonopathy characterized by short axonal outgrowth and aberrant branching, microglial activation, and inflammatory response and/or promoting one or more of wound healing, autophagy, and clearance of aggregate proteins.