Biol Chem 286: 12602-12616). Sortilin also binds to apolipoprotein E (APOE), to the A beta peptide (Carlo, AS et al., (2013) J, Neurosc, 33: 358-370), and to PCSK9 (Gustafsen et al, (2014) Cell Metab, 19: 310-318). Sortilin has also been shown to bind to and regulate extracellular levels of PCSK9, which directs low-density lipoprotein receptor for degradation in lysosomes, resulting in increased levels of LDL cholesterol (Gustafsen C et al., (2014). Cell Metab. 2014 Feb 4;19(2):310-8).

[0009] When present at intracellular vesicles such as endosomes, the amino-terminal extracellular domain of Sortilin is directed towards the lumen, where cargo of the vesicle is present. The carboxy-terminal intracellular/cytoplasmic domain of Sortilin, however, binds to a series of adaptor proteins, which regulate its trafficking from the surface and within intracellular compartments. These include AP2 (a clathrin adaptor to modulate endocytosis from the cell surface), and the Retromer Complex/AP1, which modulate movement from early endosomes to Golgi for recycling; and interaction with GGA (Golgi-localizing, gamma-ear containing, ADP-ribosylation factor binding) family proteins for movement from Golgi directly to early endosomes, usually for subsequent degradation through lysosomes. Thus, Sortilin can bind to ligands at its luminal domain, while engaging the cytoplasmic adaptors that determine its destination to determine intracellular fates, such as degradation for Progranulin and other factors.

[0010] Through its various interactions with proteins, such as Progranulin, Sortilin and its multiple ligands have been shown to be involved in various diseases, disorders, and conditions, such as frontotemporal dementia, amyotrophic lateral sclerosis, amyotrophic lateral sclerosis-frontotemporal dementia phenotypes, Alzheimer's disease, Parkinson's disease, depression, neuropsyciatric disorders, vascular dementia, seizures, retinal dystrophy, age related macular degeneration, glaucoma, traumatic brain injury, aging, seizures, wound healing, stroke, arthritis, and atherosclerotic vascular diseases.

[0011] Accordingly, there is a need for therapeutic antibodies that specifically bind Sortilin proteins and block the binding of Sortilin to its ligands, such as Progranulin, or otherwise modulate the effective concentration of the ligands, in order to treat one or more diseases, disorders, and conditions associated with Sortilin activity.

[0012] All references cited herein, including patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0013] The present disclosure is generally directed to anti-Sortilin antibodies and methods of using such antibodies. The methods provided herein find use in preventing, reducing risk, or treating an individual having frontotemporal dementia, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, a traumatic brain injury, a spinal cord injury, long-term depression, atherosclerotic vascular diseases, undesirable symptoms of normal aging, dementia, mixed dementia, Creutzfeldt-

Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, taupathy disease, stroke, acute trauma, chronic trauma, lupus, acute and chronic colitis, Crohn's disease, inflammatory bowel disease, ulcerative colitis, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, Sarcoidosis, diseases of aging, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, inflammatory disorders, arthritis, multiple sclerosis, metabolic disorder, obesity, insulin resistance, type 2 diabetes, tissue or vascular damage, an injury, intervertebral disc degeneration, or one or more undesirable symptoms of normal aging.

[0014] Certain embodiments of the present disclosure are based, at least in part, on the identification of anti-Sortilin antibodies that are capable of blocking the interaction between Sortilin and Progranulin (*see, e.g.*, **Example 4**), anti-Sortilin antibodies that are capable of increasing extracellular levels of Progranulin secreted by cells in culture and from cells in the brains of mouse models of Alzheimer's disease (*see, e.g.*, **Example 5**), anti-Sortilin antibodies that are capable of decreasing cellular levels of Sortilin in human primary monocytes (*see, e.g.*, **Example 25**), and anti-Sortilin antibodies that are capable of increasing cellular levels of Progranulin *in vivo* (*see, e.g.*, **Example 26**). Surprisingly, one class of antibodies was shown to be capable of increasing extracellular levels of Progranulin without being able to block the interaction between Sortilin and Progranulin (*e.g.*, antibodies S-2, S-15, and S-22) while a second class of antibodies was shown to be capable of both blocking the interaction between Sortilin and Progranulin and increasing extracellular levels of Progranulin (*e.g.*, antibodies S-8, S-49, and S-60). Moreover, anti-Sortilin antibodies capable of increasing extracellular levels of Progranulin (*e.g.*, antibodies S-2, S-8, S-15, S-22, S-49, and S-60) were surprisingly shown to also reduce cellular levels of Sortilin, such as cell surface levels of Sortilin (*see, e.g.*, **Example 5**). Furthermore, cellular levels of Sortilin were shown to be strongly and inversely correlated with increases in cellular levels of Progranulin (*see, e.g.*, **FIG. 10B-10E and FIG. 23B and 23C**). Anti-Sortilin antibodies capable of increasing extracellular levels of Progranulin are also capable of blocking pro-NGF binding to Sortilin (*see, e.g.*, **Example 6**). Other embodiments of the present disclosure are based, at least in part, on the identification of anti-Sortilin antibodies that block the interaction between Sortilin and Progranulin and are capable of increasing extracellular levels of Progranulin without reducing cellular levels of Sortilin (*e.g.*, antibody S-30 and **Example 30**). Other embodiments of the present disclosure are based, at least in part, on the identification of anti-Sortilin antibodies that block the interaction between Sortilin and Progranulin without

increasing extracellular levels of Progranulin or reducing cellular levels of Sortilin (*e.g.*, antibodies S-5 and S-64 and **Example 5**).

[0015] Accordingly, certain embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody has a property selected from the group consisting of: increasing extracellular levels of Progranulin, increasing cellular levels of Progranulin, decreasing cellular levels of Sortilin, inhibiting interaction between Sortilin and Progranulin, and any combination thereof.

[0015a] In one aspect, there is provided an isolated monoclonal 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.

[0016] In certain embodiments that may be combined with any of the preceding embodiments, the antibody decreases cell surface levels of Sortilin, decreases intracellular levels of Sortilin, decreases total levels of Sortilin, or any combination thereof. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody induces Sortilin degradation, Sortilin cleavage, Sortilin internalization, Sortilin down regulation, or any combination thereof. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody decreases cellular levels of Sortilin and does not inhibit the interaction between Sortilin and Progranulin. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody decreases cellular levels of Sortilin and inhibits the interaction between Sortilin and Progranulin. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody decreases cellular levels of Sortilin and increases cellular levels of Progranulin. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody increases cellular levels of Progranulin and does not inhibit the interaction between Sortilin and Progranulin. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody inhibits the interaction between Sortilin and Progranulin and increases cellular levels of Progranulin. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody increases levels of Progranulin *in vivo*. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody increases levels of Progranulin *in vivo* without decreasing cellular levels of Sortilin. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody increases levels of Progranulin in brain. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody increases cellular levels of Progranulin in blood. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody increases cellular levels of Progranulin in one or more peripheral organs. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody increases levels of Progranulin in brain, blood, one or more more peripheral organs, or any combination thereof. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody decreases

consisting of SEQ ID NOs:150-153, 155-158, 160-166, 169-175, and 177-178, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:150-153, 155-158, 160-166, 169-175, and 177-178; and (c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:179-186, 188, 190-191, 193-197, 199-201, 203-204, 206, 208, 213-214, 216-219, 222-225, 229, 231-234, 236-239, 241, 243-247, 249, and 252-256 or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:179-186, 188, 190-191, 193-197, 199-201, 203-204, 206, 208, 213-214, 216-219, 222-225, 229, 231-234, 236-239, 241, 243-247, 249, and 252-256.

[0022] In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-6, S-8, S-49, S-60, S-63, S-72, S-83, and any combination thereof for binding to Sortilin. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-5, S-45, S-64, S-65, and any combination thereof for binding to Sortilin. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-5, S-30, S-60, and any combination thereof for binding to Sortilin.

[0023] Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody comprises at least one, two, three, four, five, or six HVRs of an antibody selected from the group consisting of: S-1, S-2, S-3, S-4, S-5, S-6, S-7, S-8, S-9, S-10, S-12, S-14, S-15, S-16, S-18, S-19, S-20, S-21, S-22, S-24, S-25, S-26, S-28, S-29, S-30, S-32, S-34, S-39, S-40, S-42, S-43, S-44, S-45, S-48, S-49, S-50, S-51, S-55, S-57, S-58, S-59, S-60, S-61, S-63, S-64, S-65, S-66, S-67, S-69, S-71, S-72, S-73, S-74, S-75, S-76, S-78, S-81, S-82, S-83, S-84, and S-85. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody comprises: (a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:6-16, 20-22, and 24-25; (b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:26-40; (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:41-50, 52, 54-56, 58-62, 64-66, 68-70, 72, 74, 79-80, 82-85, 88-91, 95, 97-101, 103-107, 109, 111-116, 118, and 121-125; (d) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:126-127, 129-130, 133-140, 142, 144-145, and 147-149; (e) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:150-153, 155-158, 160-166, 169-175, and 177-178; or (f) an HVR-H3 v an amino acid sequence selected from the group consisting of SEQ ID NOs:179-186, 188, 190-191, 193-197, 199-201, 203-204, 206, 208, 213-214,

216-219, 222-225, 229, 231-234, 236-239, 241, 243-247, 249, and 252-256. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:6-16, 20-22, and 24-25, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:6-16, 20-22, and 24-25; (b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:26-40, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:26-40; and (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:41-50, 52, 54-56, 58-62, 64-66, 68-70, 72, 74, 79-80, 82-85, 88-91, 95, 97-101, 103-107, 109, 111-116, 118, and 121-125, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:41-50, 52, 54-56, 58-62, 64-66, 68-70, 72, 74, 79-80, 82-85, 88-91, 95, 97-101, 103-107, 109, 111-116, 118, and 121-125; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:126-127, 129-130, 133-140, 142, 144-145, and 147-149, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:126-127, 129-130, 133-140, 142, 144-145, and 147-149; (b) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:150-153, 155-158, 160-166, 169-175, and 177-178, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:150-153, 155-158, 160-166, 169-175, and 177-178; and (c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:179-186, 188, 190-191, 193-197, 199-201, 203-204, 206, 208, 213-214, 216-219, 222-225, 229, 231-234, 236-239, 241, 243-247, 249, and 252-256 or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:179-186, 188, 190-191, 193-197, 199-201, 203-204, 206, 208, 213-214, 216-219, 222-225, 229, 231-234, 236-239, 241, 243-247, 249, and 252-256. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody comprises a light chain variable domain and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:317-334, 337-338, 341-345, 348-357, 360-365, 368-372, 375-376, 379-380, 389-392, 395-402, 407-414, 421-422, 425-433, 436-444, 447-448, 451-461, 464-465, and 470-479.

[0024] Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-2, S-16, S-18, S-19, S-20, S-21, S-22, S-28, S-29, S-82, and any

combination thereof for binding to Sortilin. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-1, S-3, S-4, S-6, S-7, S-9, S-10, S-14, S-15, S-26, S-32, S-48, S-51, S-55, S57, S-58, S-59, S-61, S-69, S-71, S-73, S-74, S-75, S-85, and any combination thereof for binding to Sortilin. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-5, S-12, S-24, S-25, S-30, S-34, S-39, S-40, S-42, S-43, S-44, S-45, S-60, S-63, S-64, S-65, S-66, S-67, S-72, S-76, S-78, S-81, S-83, S-84, and any combination thereof for binding to Sortilin. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-8, S-49, S-50, and any combination thereof for binding to Sortilin. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody which binds essentially the same Sortilin epitope as an antibody selected from the group consisting of: S-1, S-2, S-3, S-4, S-5, S-6, S-7, S-8, S-9, S-10, S-12, S-14, S-15, S-16, S-18, S-19, S-20, S-21, S-22, S-24, S-25, S-26, S-28, S-29, S-30, S-32, S-34, S-39, S-40, S-42, S-43, S-44, S-45, S-48, S-49, S-50, S-51, S-55, S-57, S-58, S-59, S-60, S-61, S-63, S-64, S-65, S-66, S-67, S-69, S-71, S-72, S-73, S-74, S-75, S-76, S-78, S-81, S-82, S-83, S-84, and S-85.

[0025] Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:6-16, 20-22, and 24-25, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:6-16, 20-22, and 24-25; (b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:26-40, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:26-40; and (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:41-50, 52, 54-56, 58-62, 64-66, 68-70, 72, 74, 79-80, 82-85, 88-91, 95, 97-101, 103-107, 109, 111-116, 118, and 121-125, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:41-50, 52, 54-56, 58-62, 64-66, 68-70, 72, 74, 79-80, 82-85, 88-91, 95, 97-101, 103-107, 109, 111-116, 118, and 121-125; or wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:126-127, 129-130, 133-140, 142, 144-145, and 147-149, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:126-127, 129-130, 133-140, 142, 144-145, and 147-149; (b) an HVR-H2 comprising an amino acid

sequence selected from the group consisting of SEQ ID NOs:150-153, 155-158, 160-166, 169-175, and 177-178, or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:150-153, 155-158, 160-166, 169-175, and 177-178; and (c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:179-186, 188, 190-191, 193-197, 199-201, 203-204, 206, 208, 213-214, 216-219, 222-225, 229, 231-234, 236-239, 241, 243-247, 249, and 252-256 or an amino acid sequence with at least about 95% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs:179-186, 188, 190-191, 193-197, 199-201, 203-204, 206, 208, 213-214, 216-219, 222-225, 229, 231-234, 236-239, 241, 243-247, 249, and 252-256.

[0026] Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that inhibits interaction between Sortilin and Progranulin, increases levels of Progranulin, and decreases cellular levels of Sortilin, wherein the anti-Sortilin antibody comprises at least one, two, three, four, five, or six HVRs of an antibody selected from the group consisting of: S-8, S-49, and S-60. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:11; (b) comprising the amino acid sequence of SEQ ID NO:26; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:48; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:127; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:152; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:185. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:6; (b) comprising the amino acid sequence of SEQ ID NO:26; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:89; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:140; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:166; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:223. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:10; (b) comprising the amino acid sequence of SEQ ID NO:30; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:100; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:142; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:147; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:233. Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that inhibits interaction between Sortilin and Progranulin, increases levels of

Progranulin, and decreases cellular levels of Sortilin, wherein the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-8, S-49, S-60, and any combination thereof for binding to Sortilin. Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that inhibits interaction between Sortilin and Progranulin, increases levels of Progranulin, and decreases cellular levels of Sortilin, wherein the anti-Sortilin antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. amino acid residues 429-443 of SEQ ID NO: 1, or amino acid residues on a mammalian Sortilin protein corresponding to amino acid residues 429-443 of SEQ ID NO: 1; ii. amino acid residues 232-243 of SEQ ID NO: 1, or amino acid residues on a mammalian Sortilin protein corresponding to amino acid residues 232-243 of SEQ ID NO: 1; and iii. amino acid residues 207-231 of SEQ ID NO: 1, or amino acid residues on a mammalian Sortilin protein corresponding to amino acid residues 207-231 of SEQ ID NO: 1.

[0027] Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that increases levels of Progranulin and decreases cellular levels of Sortilin without inhibiting interaction between Sortilin and Progranulin, wherein the anti-Sortilin antibody comprises at least one, two, three, four, five, or six HVRs of an antibody selected from the group consisting of: S-2, S-19, and S-22. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (b) comprising the amino acid sequence of SEQ ID NO:27; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:42; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:126; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:150; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:180. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (b) comprising the amino acid sequence of SEQ ID NO:35; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:59; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:130; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:158; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:194. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (b) comprising the amino acid sequence of SEQ ID NO:27; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:61; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:130; (b) an HVR-H2 comprising the

amino acid sequence of SEQ ID NO:157; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:196. Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that increases levels of Progranulin and decreases cellular levels of Sortilin without inhibiting interaction between Sortilin and Progranulin, wherein the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-2, S-19, S-22, and any combination thereof for binding to Sortilin. Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that increases levels of Progranulin and decreases cellular levels of Sortilin without inhibiting interaction between Sortilin and Progranulin, wherein the anti-Sortilin antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. amino acid residues 237-260 and 297-317 of SEQ ID NO: 1, or amino acid residues on a mammalian Sortilin protein corresponding to amino acid residues 237-260 and 297-317 of SEQ ID NO: 1; and ii. amino acid residues 207-227 and 237-260 of SEQ ID NO: 1, or amino acid residues on a mammalian Sortilin protein corresponding to amino acid residues 207-227 and 237-260 of SEQ ID NO: 1.

[0028] Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that inhibiting interaction between Sortilin and Progranulin without increasing levels of Progranulin and without decreasing cellular levels of Sortilin, wherein the anti-Sortilin antibody comprises at least one, two, three, four, five, or six HVRs of an antibody selected from the group consisting of: S-5 and S-64. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:10; (b) comprising the amino acid sequence of SEQ ID NO:30; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:45; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:126; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:151; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:182. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:15; (b) comprising the amino acid sequence of SEQ ID NO:27; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:104; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:142; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:169; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:236. Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that inhibiting interaction between Sortilin and Progranulin without increasing levels of Progranulin and without decreasing cellular

levels of Sortilin, wherein the anti-Sortilin antibody competes with one or more antibodies selected from the group consisting of S-5, S-64, and any combination thereof for binding to Sortilin.

[0029] Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that inhibiting interaction between Sortilin and Progranulin and increases levels of Progranulin without decreasing cellular levels of Sortilin, wherein the anti-Sortilin antibody comprises at least one, two, three, four, five, or six HVRs of antibody S-30. In some embodiments, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:10; (b) comprising the amino acid sequence of SEQ ID NO:30; and (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:70; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:136; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:163; and (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:204. Other embodiments of the present disclosure relate to an isolated (*e.g.*, monoclonal) anti-Sortilin antibody that inhibiting interaction between Sortilin and Progranulin and increases levels of Progranulin without decreasing cellular levels of Sortilin, wherein the anti-Sortilin antibody competes with antibody S-30 for binding to Sortilin.

[0030] Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of RASQSISSYLN (SEQ ID NO:7); (b) an HVR-L2 comprising the amino acid sequence of AASSLQS (SEQ ID NO:27); and (c) an HVR-L3 comprising the amino acid sequence of QQSDVSPIT (SEQ ID NO:42); and/or wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of $YTFX_1X_2YX_3MX_4$ (SEQ ID NO:480), wherein X_1 is T, G, V, P, L, F, A, or R, X_2 is G, A, or S, X_3 is Y, M, or L, and X_4 is H or W; (b) an HVR-H2 comprising the amino acid sequence of $X_1X_2X_3PX_4X_5GX_6TX_7YAQKFQG$ (SEQ ID NO:481), wherein X_1 is W, I, or G, X_2 is I, V, or T, X_3 is N, G, or L, X_4 is N, S, V, or M, X_5 is S, G, W, or Q, X_6 is G, F, A, Y, S, N, or R, and X_7 is N, R, S, or M; and (c) an HVR-H3 comprising the amino acid sequence of ARGKRSSGWYEGYGMDV (SEQ ID NO:180). In certain embodiments, the anti-Sortilin antibody has at least one, two, three, four, five, or six HVRs selected from (i) HVR-L1 comprising the amino acid sequence of any of the HVR-L1 sequences from an antibody selected from the group consisting of S-2, S-2-1, S-2-2, S-2-3, S-2-4, S-2-5, S-2-6, S-2-7, S-2-8, S-2-9, S-2-10, S-2-11, S-2-12, S-2-13, S-2-14, and S-2-15; (ii) HVR-L2 comprising the amino acid sequence of any of the HVR-L2 sequences from an antibody selected from the group consisting of S-2, S-2-1, S-2-2, S-2-3, S-2-4, S-2-5, S-2-6, S-2-7, S-2-8, S-2-9, S-2-10, S-2-11, S-2-12, S-2-13, S-2-14, and S-2-15; (iii) HVR-L3 comprising the amino acid sequence of any of the HVR-L3 sequences from an antibody

selected from the group consisting of S-2, S-2-1, S-2-2, S-2-3, S-2-4, S-2-5, S-2-6, S-2-7, S-2-8, S-2-9, S-2-10, S-2-11, S-2-12, S-2-13, S-2-14, and S-2-15; (iv) HVR-H1 comprising the amino acid sequence of any of the HVR-H1 sequences from an antibody selected from the group consisting of S-2, S-2-1, S-2-2, S-2-3, S-2-4, S-2-5, S-2-6, S-2-7, S-2-8, S-2-9, S-2-10, S-2-11, S-2-12, S-2-13, S-2-14, and S-2-15; (v) HVR-H2 comprising the amino acid sequence of any of the HVR-H2 sequences from an antibody selected from the group consisting of S-2, S-2-1, S-2-2, S-2-3, S-2-4, S-2-5, S-2-6, S-2-7, S-2-8, S-2-9, S-2-10, S-2-11, S-2-12, S-2-13, S-2-14, and S-2-15; and (vi) HVR-H3 comprising the amino acid sequence of any of the HVR-H3 sequences from an antibody selected from the group consisting of S-2, S-2-1, S-2-2, S-2-3, S-2-4, S-2-5, S-2-6, S-2-7, S-2-8, S-2-9, S-2-10, S-2-11, S-2-12, S-2-13, S-2-14, and S-2-15. In certain embodiments, anti-Sortilin antibody comprises a light chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-2, S-2-1, S-2-2, S-2-3, S-2-4, S-2-5, S-2-6, S-2-7, S-2-8, S-2-9, S-2-10, S-2-11, S-2-12, S-2-13, S-2-14, and S-2-15; and/or a heavy chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-2, S-2-1, S-2-2, S-2-3, S-2-4, S-2-5, S-2-6, S-2-7, S-2-8, S-2-9, S-2-10, S-2-11, S-2-12, S-2-13, S-2-14, and S-2-15. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of $RASQSX_1X_2SNLA$ (SEQ ID NO:508), wherein X_1 is V or I and X_2 is S or G; (b) an HVR-L2 comprising the amino acid sequence of GASTRAT (SEQ ID NO:29); and (c) an HVR-L3 comprising the amino acid sequence of QQARLGPWT (SEQ ID NO:55); and/or wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of $YTX_1X_2X_3X_4X_5X_6S$ (SEQ ID NO:509), wherein X_1 is F or L, X_2 is T or A, X_3 is S or K, X_4 is Y, T, R, L, T, G, Q, or H, X_5 is Y, T, or L, and X_6 is M or I; (b) an HVR-H2 comprising the amino acid sequence of $X_1INPx_2GGX_3X_4SYAX_5X_6FX_7G$ (SEQ ID NO:510), wherein X_1 is I or V, X_2 is S, W, Y, V, F, L, or I, X_3 is S or T, X_4 is T or A, X_5 is Q or R, X_6 is K, or R, and X_7 is Q or R; and (c) an HVR-H3 comprising the amino acid sequence of $X_1RDPX_2GX_3X_4X_5X_6X_7PX_8X_9RX_{10}X_{11}X_{12}GX_{13}DV$ (SEQ ID NO:511), wherein X_1 is A, V, or T, X_2 is S, F, or G, X_3 is I or A, X_4 is A or G, X_5 is A, L, or V, X_6 is A, L, or P, X_7 is G, F, or Y, X_8 is A, G, or F, X_9 is S, G, or A, X_{10} is Y, G, P, H, or S, X_{11} is Y or N, X_{12} is Y, L, Q, or R, and X_{13} is M or L. In certain embodiments, the anti-Sortilin antibody has at least one, two, three, four, five, or six HVRs selected from (i) HVR-L1 comprising the amino acid sequence of any of the HVR-L1 sequences from an antibody selected from the group consisting of S-15, S-15-1, S-15-2, S-15-3, S-15-4, S-15-5, S-15-6, S-15-6-1, S-15-6-2, S-15-6-3, S-15-6-4, S-15-6-5, S-15-6-6, S-15-6-7, S-15-6-8, S-15-6-9, S-15-6-10, S-15-6-11, S-15-6-12, S-15-6-13, S-15-7, S-15-8, S-15-9, S-15-10, S-15-10-1, S-15-10-2, S-15-10-3, S-15-10-4, S-15-10-5, S-15-10-6, S-15-10-7,

10-20, S-15-10-21, S-15-11, S-15-12, S-15-13, S-15-14, S-15-15, and S-15-16. In certain embodiments, anti-Sortilin antibody comprises a light chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-15, S-15-1, S-15-2, S-15-3, S-15-4, S-15-5, S-15-6, S-15-6-1, S-15-6-2, S-15-6-3, S-15-6-4, S-15-6-5, S-15-6-6, S-15-6-7, S-15-6-8, S-15-6-9, S-15-6-10, S-15-6-11, S-15-6-12, S-15-6-13, S-15-7, S-15-8, S-15-9, S-15-10, S-15-10-1, S-15-10-2, S-15-10-3, S-15-10-4, S-15-10-5, S-15-10-6, S-15-10-7, S-15-10-8, S-15-10-9, S-15-10-10, S-15-10-11, S-15-10-12, S-15-10-13, S-15-10-14, S-15-10-15, S-15-10-16, S-15-10-17, S-15-10-18, S-15-10-19, S-15-10-20, S-15-10-21, S-15-11, S-15-12, S-15-13, S-15-14, S-15-15, and S-15-16; and/or a heavy chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-15, S-15-1, S-15-2, S-15-3, S-15-4, S-15-5, S-15-6, S-15-6-1, S-15-6-2, S-15-6-3, S-15-6-4, S-15-6-5, S-15-6-6, S-15-6-7, S-15-6-8, S-15-6-9, S-15-6-10, S-15-6-11, S-15-6-12, S-15-6-13, S-15-7, S-15-8, S-15-9, S-15-10, S-15-10-1, S-15-10-2, S-15-10-3, S-15-10-4, S-15-10-5, S-15-10-6, S-15-10-7, S-15-10-8, S-15-10-9, S-15-10-10, S-15-10-11, S-15-10-12, S-15-10-13, S-15-10-14, S-15-10-15, S-15-10-16, S-15-10-17, S-15-10-18, S-15-10-19, S-15-10-20, S-15-10-21, S-15-11, S-15-12, S-15-13, S-15-14, S-15-15, and S-15-16. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of RASQSISSWLA (SEQ ID NO:8); (b) an HVR-L2 comprising the amino acid sequence of KASSLES (SEQ ID NO:28); and (c) an HVR-L3 comprising the amino acid sequence of QQADGHIT (SEQ ID NO:62); and/or wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of $X_1TFX_2X_3YAX_4X_5$ (SEQ ID NO:565), wherein X_1 is G or Y, X_2 is S, R, G, or T, X_3 is S, G, or N, X_4 is I or M, and X_5 is S or A; (b) an HVR-H2 comprising the amino acid sequence of $GIX_1PX_2X_3GX_4AX_5YAQKFQG$ (SEQ ID NO:566), wherein X_1 is I or V, X_2 is I, R, G, A, S, T, or Q, X_3 is F or G, X_4 is T, R, or W, and X_5 is S, N, Q, or W; and (c) an HVR-H3 comprising the amino acid sequence of ARQGRKTGYYYYYGMDV (SEQ ID NO:197). In certain embodiments, the anti-Sortilin antibody has at least one, two, three, four, five, or six HVRs selected from (i) HVR-L1 comprising the amino acid sequence of any of the HVR-L1 sequences from an antibody selected from the group consisting of S-22, S-22-1, S-22-2, S-22-3, S-22-4, S-22-5, S-22-6, S-22-7, S-22-8, and S-22-9; (ii) HVR-L2 comprising the amino acid sequence of any of the HVR-L2 sequences from an antibody selected from the group consisting of S-22, S-22-1, S-22-2, S-22-3, S-22-4, S-22-5, S-22-6, S-22-7, S-22-8, and S-22-9; (iii) HVR-L3 comprising the amino acid sequence of any of the HVR-L3 sequences from an antibody selected from the group consisting of S-22, S-22-1, S-22-2, S-22-3, S-22-4, S-22-5, S-22-6, S-22-7, S-22-8, and S-22-9; (iv) HVR-H1 comprising the amino acid sequence of any of the HVR-H1 sequences from an antibody selected from the group

consisting of S-22, S-22-1, S-22-2, S-22-3, S-22-4, S-22-5, S-22-6, S-22-7, S-22-8, and S-22-9; (v) HVR-H2 comprising the amino acid sequence of any of the HVR-H2 sequences from an antibody selected from the group consisting of S-22, S-22-1, S-22-2, S-22-3, S-22-4, S-22-5, S-22-6, S-22-7, S-22-8, and S-22-9; and (vi) HVR-H3 comprising the amino acid sequence of any of the HVR-H3 sequences from an antibody selected from the group consisting of S-22, S-22-1, S-22-2, S-22-3, S-22-4, S-22-5, S-22-6, S-22-7, S-22-8, and S-22-9. In certain embodiments, anti-Sortilin antibody comprises a light chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-22, S-22-1, S-22-2, S-22-3, S-22-4, S-22-5, S-22-6, S-22-7, S-22-8, and S-22-9; and/or a heavy chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-22, S-22-1, S-22-2, S-22-3, S-22-4, S-22-5, S-22-6, S-22-7, S-22-8, and S-22-9. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of $RSSQX_1LLX_2SNGYNYLD$ (SEQ ID NO:580), wherein X_1 is S or G and X_2 is H or R; (b) an HVR-L2 comprising the amino acid sequence of LGSNRXS (SEQ ID NO:581), wherein X is A or V; and (c) an HVR-L3 comprising the amino acid sequence of MQQQETPLT (SEQ ID NO:100); and/or wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of $YSISSX_1X_2YWG$ (SEQ ID NO:582), wherein X_1 is G or V and X_2 is Y or R; (b) an HVR-H2 comprising the amino acid sequence of $X_1IYX_2SGSTYYNPSLKS$ (SEQ ID NO:583), wherein X_1 is T, S, or A and X_2 is H or P; and (c) an HVR-H3 comprising the amino acid sequence of ARQGSIKQGYYGMDV (SEQ ID NO:233). In certain embodiments, the anti-Sortilin antibody has at least one, two, three, four, five, or six HVRs selected from (i) HVR-L1 comprising the amino acid sequence of any of the HVR-L1 sequences from an antibody selected from the group consisting of S-60, S-60-1, S-60-2, S-60-3, S-60-4, S-60-5, S-60-6, S-60-7, S-60-8, and S-60-9; (ii) HVR-L2 comprising the amino acid sequence of any of the HVR-L2 sequences from an antibody selected from the group consisting of S-60, S-60-1, S-60-2, S-60-3, S-60-4, S-60-5, S-60-6, S-60-7, S-60-8, and S-60-9; (iii) HVR-L3 comprising the amino acid sequence of any of the HVR-L3 sequences from an antibody selected from the group consisting of S-60, S-60-1, S-60-2, S-60-3, S-60-4, S-60-5, S-60-6, S-60-7, S-60-8, and S-60-9; (iv) HVR-H1 comprising the amino acid sequence of any of the HVR-H1 sequences from an antibody selected from the group consisting of S-60, S-60-1, S-60-2, S-60-3, S-60-4, S-60-5, S-60-6, S-60-7, S-60-8, and S-60-9; (v) HVR-H2 comprising the amino acid sequence of any of the HVR-H2 sequences from an antibody selected from the group consisting of S-60, S-60-1, S-60-2, S-60-3, S-60-4, S-60-5, S-60-6, S-60-7, S-60-8, and S-60-9; and (vi) HVR-H3 comprising the amino acid sequence of any of the HVR-H3 sequences from an antibody selected from the group consisting of S-60, S-60-1, S-60-2,

S-60-3, S-60-4, S-60-5, S-60-6, S-60-7, S-60-8, and S-60-9. In certain embodiments, anti-Sortilin antibody comprises a light chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-60, S-60-1, S-60-2, S-60-3, S-60-4, S-60-5, S-60-6, S-60-7, S-60-8, and S-60-9; and/or a heavy chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-60, S-60-1, S-60-2, S-60-3, S-60-4, S-60-5, S-60-6, S-60-7, S-60-8, and S-60-9. Other embodiments of the present disclosure relate to an isolated (e.g., monoclonal) anti-Sortilin antibody, wherein the anti-Sortilin antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of RASQSVSSSYLA (SEQ ID NO:14); (b) an HVR-L2 comprising the amino acid sequence of GASSRAT (SEQ ID NO:26); and (c) an HVR-L3 comprising the amino acid sequence of QQSHVSPWT (SEQ ID NO:122); and/or wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of $X_1SIX_2SX_3X_4YYWG$ (SEQ ID NO:589), wherein X_1 is G or Y, X_2 is S, V, Y, K, or P, X_3 is S or R, and X_4 is D or E; (b) an HVR-H2 comprising the amino acid sequence of $X_1IYX_2X_3GSTX_4YNPSLKS$ (SEQ ID NO:590), wherein X_1 is S, G, Q, or L, X_2 is Y, W, or R, X_3 is S, R, K, or A, and X_4 is Y or V; and (c) an HVR-H3 comprising the amino acid sequence of ARGVGSGYSYGYRYFDY (SEQ ID NO:253). In certain embodiments, the anti-Sortilin antibody has at least one, two, three, four, five, or six HVRs selected from (i) HVR-L1 comprising the amino acid sequence of any of the HVR-L1 sequences from an antibody selected from the group consisting of S-82, S-82-1, S-82-2, S-82-3, S-82-4, S-82-5, S-82-6, S-82-7, and S-82-8; (ii) HVR-L2 comprising the amino acid sequence of any of the HVR-L2 sequences from an antibody selected from the group consisting of S-82, S-82-1, S-82-2, S-82-3, S-82-4, S-82-5, S-82-6, S-82-7, and S-82-8; (iii) HVR-L3 comprising the amino acid sequence of any of the HVR-L3 sequences from an antibody selected from the group consisting of S-82, S-82-1, S-82-2, S-82-3, S-82-4, S-82-5, S-82-6, S-82-7, and S-82-8; (iv) HVR-H1 comprising the amino acid sequence of any of the HVR-H1 sequences from an antibody selected from the group consisting of S-82, S-82-1, S-82-2, S-82-3, S-82-4, S-82-5, S-82-6, S-82-7, and S-82-8; (v) HVR-H2 comprising the amino acid sequence of any of the HVR-H2 sequences from an antibody selected from the group consisting of S-82, S-82-1, S-82-2, S-82-3, S-82-4, S-82-5, S-82-6, S-82-7, and S-82-8; and (vi) HVR-H3 comprising the amino acid sequence of any of the HVR-H3 sequences from an antibody selected from the group consisting of S-82, S-82-1, S-82-2, S-82-3, S-82-4, S-82-5, S-82-6, S-82-7, and S-82-8. In certain embodiments, anti-Sortilin antibody comprises a light chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-82, S-82-1, S-82-2, S-82-3, S-82-4, S-82-5, S-82-6, S-82-7, and S-82-8; and/or a heavy chain variable region of any one of the antibodies sequences from an antibody selected from the group consisting of S-82, S-82-1, S-82-2, S-82-3, S-82-4, S-82-5, S-82-6, S-82-7, and S-82-8.

[0032] In another aspect, there is provided an isolated nucleic acid comprising a nucleic acid sequence encoding the anti-Sortilin antibody as described herein. In another aspect, there is provided a vector comprising the nucleic acid as described herein. In another aspect, there is provided an isolated host cell comprising the vector as described herein. Other embodiments of the present disclosure relate to a method of producing an anti-Sortilin antibody, comprising culturing the host cell of any of the preceding embodiments so that the anti-Sortilin antibody is produced. In certain embodiments, the method further comprises recovering the anti-Sortilin antibody produced by the host cell. In another aspect, there is provided a method of producing an anti-Sortilin antibody, comprising culturing the host cell as described herein so that the anti-Sortilin antibody is produced, optionally wherein the method further comprises recovering the anti-Sortilin antibody produced by the host cell. Other embodiments of the present disclosure relate to an isolated anti-Sortilin antibody produced by the method of any of the preceding embodiments. In another aspect, there is proivded a pharmaceutical composition comprising the anti-Sortilin antibody as described herein, and a pharmaceutically acceptable carrier.

[0033] Other embodiments of the present disclosure relate to a method of increasing Progranulin levels in the brain of an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an anti-Sortilin antibody. Other embodiments of the present disclosure relate to an anti-Sortilin antibody for use in increasing Progranulin levels in the brain of an individual in need thereof. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody in the manufacture of a medicament for increasing Progranulin levels in the brain of an individual in need thereof. Other embodiments of the present disclosure relate to a method of increasing Progranulin levels in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an anti-Sortilin antibody. Other embodiments of the present disclosure relate to an anti-Sortilin antibody for use in increasing Progranulin levels in an individual in need thereof. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody in the manufacture of a medicament for increasing Progranulin levels in an individual in need thereof. In certain embodiments that may be combined with any of the preceding embodiments, levels of Progranulin are increased in the brain, blood, and/or or one or more peripheral organs of the individual. In certain embodiments that may be combined with any of the preceding embodiments, levels of Progranulin are increased without decreasing cellular levels of Sortilin.

[0034] Other embodiments of the present disclosure relate to a method of increasing extracellular levels of Progranulin from one or more cells, comprising contacting one or more cells with an anti-Sortilin antibody. Other embodiments of the present disclosure relate to an anti-Sortilin antibody for use in increasing extracellular levels of Progranulin from one or more cells. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody in the manufacture of a medicament for increasing extracellular levels of Progranulin from one or more cells. In certain embodiments that may be combined with any of the preceding embodiments, levels of Progranulin are increased without

decreasing cellular levels of Sortilin. Other embodiments of the present disclosure relate to a method of decreasing cellular levels of Sortilin in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an anti-Sortilin antibody. Other embodiments of the present disclosure relate to an anti-Sortilin antibody for use in decreasing cellular levels of Sortilin in an individual in need thereof. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody in the manufacture of a medicament for decreasing cellular levels of Sortilin in an individual in need thereof. In certain embodiments that may be combined with any of the preceding embodiments, levels of Sortilin are decreased in the brain, and/or one or more peripheral organs of the individual. Other embodiments of the present disclosure relate to a method of decreasing cellular levels of Sortilin of one or more cells, comprising contacting one or more cells with an anti-Sortilin antibody. Other embodiments of the present disclosure relate to an anti-Sortilin antibody for use in decreasing cellular levels of Sortilin of one or more cells. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody in the manufacture of a medicament for decreasing cellular levels of Sortilin of one or more cells.

[0035] Other embodiments of the present disclosure relate to a method for inhibiting one or more interactions between a Sortilin protein and one or more proteins selected from the group consisting of Progranulin, neurotensin, p75, Sortilin propeptide (Sort-pro), amyloid precursor protein (APP), the A beta peptide, lipoprotein lipase (LpL), apolipoprotein AV (APOA5), apolipoprotein E (APOE), PCSK9, and receptor associated protein (RAP), the method comprising: contacting the Sortilin protein with an anti-Sortilin antibody that binds to an epitope comprising SEQ ID NO: 4. Other embodiments of the present disclosure relate to an anti-Sortilin antibody that binds to an epitope comprising SEQ ID NO: 4 for use in inhibiting one or more interactions between a Sortilin protein and one or more proteins selected from the group consisting of Progranulin, neurotensin, p75, Sortilin propeptide (Sort-pro), amyloid precursor protein (APP), the A beta peptide, lipoprotein lipase (LpL), apolipoprotein AV (APOA5), apolipoprotein E (APOE), PCSK9, and receptor associated protein (RAP). Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody that binds to an epitope comprising SEQ ID NO: 4in the manufacture of a medicament for inhibiting one or more interactions between a Sortilin protein and one or more proteins selected from the group consisting of Progranulin, neurotensin, p75, Sortilin propeptide (Sort-pro), amyloid precursor protein (APP), the A beta peptide, lipoprotein lipase (LpL), apolipoprotein AV (APOA5), apolipoprotein E (APOE), PCSK9, and receptor associated protein (RAP).

[0036] In certain embodiments that may be combined with any of the preceding embodiments, (a) the anti-Sortilin antibody has a property selected from the group consisting of: increasing extracellular levels of Progranulin, increasing cellular levels of Progranulin, decreasing cellular levels of Sortilin, inhibiting interaction between Sortilin and Progranulin, and any combination thereof; (b)

wherein the numbering of the residues is according to EU or Kabat numbering; or (c) a S228P amino acid substitution according to EU or Kabat numbering. In certain embodiments that may be combined with any of the preceding embodiments, (a) the anti-Sortilin antibody has a dissociation constant (K_D) for human Sortilin, mouse Sortilin, or both, that ranges from about 100 nM to about 0.005 nM, or less than 0.005 nM; (b) the anti-Sortilin antibody has dissociation constant (K_D) for human Sortilin that ranges from about 70.4 nM to about 0.005 nM, or less than 0.005 nM; or (c) the anti-Sortilin antibody has dissociation constant (K_D) for mouse Sortilin that ranges from about 40.3 nM to about 0.07 nM, or less than 0.07 nM. In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody is the anti-Sortilin antibody of any of the preceding embodiments.

[0039] Other embodiments of the present disclosure relate to a method of preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of frontotemporal dementia, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, a traumatic brain injury, a spinal cord injury, long-term depression, atherosclerotic vascular diseases, undesirable symptoms of normal aging, dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, taupathy disease, stroke, acute trauma, chronic trauma, lupus, acute and chronic colitis, Crohn's disease, inflammatory bowel disease, ulcerative colitis, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, degenerative disc disease, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, Sarcoidosis, diseases of aging, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, inflammatory disorders, arthritis, multiple sclerosis, metabolic disorder, obesity, insulin resistance, type 2 diabetes, tissue or vascular damage, an injury, and one or more undesirable symptoms of normal aging, comprising administering to the individual a therapeutically effective amount of the anti-Sortilin antibody of any of the preceding embodiments. Other embodiments of the present disclosure relate to an anti-Sortilin antibody of any of the preceding embodiments for use in preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of frontotemporal dementia, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, a traumatic brain injury, a spinal cord injury, long-term depression, atherosclerotic vascular diseases, undesirable symptoms of normal aging, dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, taupathy disease, stroke, acute trauma, chronic trauma, lupus, acute and chronic colitis, Crohn's disease, inflammatory bowel disease, ulcerative colitis, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease,

dementia with Lewy bodies, multiple system atrophy, degenerative disc disease, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, Sarcoidosis, diseases of aging, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, inflammatory disorders, arthritis, multiple sclerosis, metabolic disorder, obesity, insulin resistance, type 2 diabetes, tissue or vascular damage, an injury, and one or more undesirable symptoms of normal aging. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody of any of the preceding embodiments in the manufacture of a medicament for preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of frontotemporal dementia, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, a traumatic brain injury, a spinal cord injury, long-term depression, atherosclerotic vascular diseases, undesirable symptoms of normal aging, dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, taupathy disease, stroke, acute trauma, chronic trauma, lupus, acute and chronic colitis, Crohn's disease, inflammatory bowel disease, ulcerative colitis, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, degenerative disc disease, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, Sarcoidosis, diseases of aging, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, inflammatory disorders, arthritis, multiple sclerosis, metabolic disorder, obesity, insulin resistance, type 2 diabetes, tissue or vascular damage, an injury, and one or more undesirable symptoms of normal aging. Other embodiments of the present disclosure relate to a method of preventing, reducing risk, or treating an individual having a disease, disorder, or injury 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, comprising administering to the individual a therapeutically effective amount of the anti-Sortilin antibody of any of the preceding embodiments. Other embodiments of the present disclosure relate to an anti-Sortilin antibody of any of the preceding embodiments for use in preventing, reducing risk, or treating an individual having a disease, disorder, or injury 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. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody of any of the preceding embodiments in the manufacture of a medicament for preventing, reducing risk, or treating an individual having a disease, disorder, or injury 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.

[0039a] In another aspect, there is provided use of the anti-Sortilin antibody as described herein 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, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis, arthritis, and osteoarthritis.

[0039b] In another aspect, there is provided use of the anti-Sortilin antibody as described herein in the manufacture of a medicament for preventing, reducing risk, or treating frontotemporal dementia in an individual in need thereof.

[0039c] In another aspect, there is provided use of the anti-Sortilin antibody as described herein in the manufacture of a medicament for preventing, reducing risk, or treating Alzheimer's disease in an individual in need thereof.

[0040] Other embodiments of the present disclosure relate to a method of inhibiting one or more of neuroinflammation, axonopathy characterized by short axonal outgrowth and aberrant branching, microglial activation, and inflammatory response, comprising administering to the individual a therapeutically effective amount of the anti-Sortilin antibody of any of the preceding embodiments. Other embodiments of the present disclosure relate to an anti-Sortilin antibody of any of the preceding embodiments for use in inhibiting one or more of neuroinflammation, axonopathy characterized by short axonal outgrowth and aberrant branching, microglial activation, and inflammatory response. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody of any of the preceding embodiments 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. Other embodiments of the present disclosure relate to a method of promoting one or more of wound healing, autophagy, and clearance of aggregate proteins, comprising administering to the individual a therapeutically effective amount of the anti-Sortilin antibody of any of the preceding embodiments. Other embodiments of the present disclosure relate to an anti-Sortilin antibody of any of the preceding embodiments for use in promoting one or more of wound healing, autophagy, and clearance of aggregate proteins. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody of any of the preceding embodiments in the manufacture of a medicament for promoting one or more of wound healing, autophagy, and clearance of aggregate proteins. Other embodiments of the present disclosure relate to a method of preventing, reducing risk, or treating an individual having arthritis, comprising administering to the individual a therapeutically effective amount of the anti-Sortilin antibody of any of the preceding embodiments. Other embodiments of the present disclosure relate to an anti-Sortilin antibody of any of the preceding embodiments for use in preventing, reducing risk, or treating an individual having arthritis. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody of any of the preceding embodiments in the manufacture of a medicament for preventing, reducing risk, or treating an individual having arthritis. Other embodiments of the present disclosure relate to a method of decreasing

expression of one or more pro-inflammatory mediators, comprising administering to the individual a therapeutically effective amount of the anti-Sortilin antibody of any of the preceding embodiments. Other embodiments of the present disclosure relate to an anti-Sortilin antibody of any of the preceding embodiments for use in decreasing expression of one or more pro-inflammatory mediators. Other embodiments of the present disclosure relate to use of an anti-Sortilin antibody of any of the preceding embodiments in the manufacture of a medicament for decreasing expression of one or more pro-inflammatory mediators. In certain embodiments, 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.

[0040a] In another aspect, there is provided the anti-Sortilin antibody as described herein 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.

[0040b] In another aspect, there is provided use of the anti-Sortilin antibody as described herein in the manufacture of a medicament for inhibiting one or more of neuroinflammation, and axonopathy characterized by short axonal outgrowth and aberrant branching, and/or promoting clearance of aggregate proteins.

[0040c] In another aspect, there is provided an in vitro method of inhibiting one or more of microglial activation, and inflammatory response, comprising contacting one or more cells with the anti-Sortilin antibody as described herein.

[0041] In certain embodiments that may be combined with any of the preceding embodiments, the anti-Sortilin antibody comprises two or more anti-Sortilin antibodies.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0043] **FIG. 1** depicts several views of human Sortilin protein showing the Sortilin binding sites of anti-Sortilin antibodies S-1, S-65, S-49, S-78, S-44, and S-8. The Sortilin backbone is rendered in a transparent grey representation. Highlighted in colors are linear binding regions identified for antibodies S-1 (green), S-65 (red), S-49 (blue), S-78 (yellow), S-44 (pink), and S-8 (purple). The binding sites are found within flexible loop regions of Sortilin,

[0044] **FIG. 2A-2C** show the characterization of interactions between Sortilin and Progranulin using surface plasmon resonance (SPR) and ELISA. **FIG. 2A** shows kinetic analysis of Progranulin (PGRN) binding to His-captured Sortilin 1(SORT1) using Biacore SPR. **FIG. 2B** shows binding of biotinylated human PGRN to immobilized human SORT1 on an ELISA plate. **FIG. 2C** shows binding of biotinylated mouse PGRN to immobilized mouse SORT1 on an ELISA plate.

[0045] **FIG. 3A** shows antibody avidity binding to human Sortilin (b-H Sort) on a sensor chip and competition with anti-Sortilin antibodies (IgG). **FIG. 3B** shows the characterization of interactions between Sortilin (SORT) and Progranulin (PGRN) using Forte Bio analysis and competition with anti-Sortilin antibodies (IgG). Left column: biotinylated Progranulin peptide is immobilized on the sensor chip and SORT added in solution, followed by IgG. Center column: biotinylated recombinant human SORT is immobilized on a sensor chip and recombinant PGRN is added in solution followed by the IgG. Right column: biotinylated recombinant PGRN is immobilized on a sensor chip and human SORT is added in solution, followed by IgG. (SORT= Sortilin, PGRN= Progranulin, b = biotinylated, H= human, mono= monomeric).

CLAIMS

1. An isolated monoclonal 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 100 nM to 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 100 nM to 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 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 bivalent 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 1-13 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.

19. 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.

20. The anti-Sortilin antibody of any one of claims 1-19, wherein the anti-Sortilin antibody has an IgG1 or IgG4 isotype.

21. The anti-Sortilin antibody of claim 20, 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.

22. The anti-Sortilin antibody of claim 21, 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.

23. The anti-Sortilin antibody of claim 20, 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.

24. An isolated nucleic acid comprising a nucleic acid sequence encoding the anti-Sortilin antibody of any one of claims 1-23.

25. A vector comprising the nucleic acid of claim 24.

26. An isolated host cell comprising the vector of claim 25.

27. A method of producing an anti-Sortilin antibody, comprising culturing the host cell of claim 26 so that the anti-Sortilin antibody is produced, optionally wherein the method further comprises recovering the anti-Sortilin antibody produced by the host cell.

28. A pharmaceutical composition comprising the anti-Sortilin antibody of any one of claims 1-23, and a pharmaceutically acceptable carrier.

29. The anti-Sortilin antibody of any one of claims 1-23 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.

30. Use of the anti-Sortilin antibody of any one of claims 1-23 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, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis, arthritis, and osteoarthritis.

31. Use of the anti-Sortilin antibody of any one of claims 1-23 in the manufacture of a medicament for preventing, reducing risk, or treating frontotemporal dementia in an individual in need thereof.

32. Use of the anti-Sortilin antibody of any one of claims 1-23 in the manufacture of a medicament for preventing, reducing risk, or treating Alzheimer's disease in an individual in need thereof.

33. Use of the anti-Sortilin antibody of any one of claims 1-23 in the manufacture of a medicament for inhibiting one or more of neuroinflammation, and axonopathy characterized by short axonal outgrowth and aberrant branching, and/or promoting clearance of aggregate proteins.

34. An in vitro method of inhibiting one or more of microglial activation, and inflammatory response, comprising contacting one or more cells with the anti-Sortilin antibody of any one of claims 1-23.