

SUMMARY

[0014] The present disclosure is generally directed to compositions that include antibodies, *e.g.*, monoclonal, chimeric, humanized antibodies, antibody fragments, *etc.*, that specifically bind human Sortilin, and to methods of using such compositions.

[0015] In some examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an HVR-H1 comprising SEQ ID NO: 1, an HVR-H2 comprising SEQ ID NO: 2 or SEQ ID NO:3, and an HVR-H3 comprising SEQ ID NO: 5 or SEQ ID NO: 6; and the light chain variable region comprises an HVR-L1 comprising any of SEQ ID NOs: 8-27, an HVR-L2 comprising SEQ ID NO: 29 or SEQ ID NO: 30, and an HVR-L3 comprising SEQ ID NO: 32.

[0016] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIQQGYGMDV (SEQ ID NO: 5); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0017] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIQQGYGMDV (SEQ ID NO: 5); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRVS (SEQ ID NO: 30), and the HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33).

[0018] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLES (SEQ ID NO: 3), the HVR-H3 comprising the amino acid sequence ARQGSIQQGYGMDV (SEQ ID NO: 5); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRAS

(SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0019] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0020] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0021] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 10), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0022] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 21), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0023] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33).

[0024] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIQQGYYGMDV (SEQ ID NO: 5); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLHSNGYNYLD (SEQ ID NO: 26), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33).

[0025] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQGLLSNGYNYLD (SEQ ID NO: 27), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0026] In some examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0027] In some examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the antibody comprises a heavy chain variable region with an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0027a] In one aspect, the present disclosure refers to an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein

(a) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence

YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence

TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence

ARQGSIQGYYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1

comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2

comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the

amino acid sequence MQQQEAPLT (SEQ ID NO: 32);

(b) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence

YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence

TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence

ARQGSIQGYYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1

comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2

comprising the amino acid sequence LGSNRVS (SEQ ID NO: 30), and an HVR-L3 comprising the

amino acid sequence MQQQETPLT (SEQ ID NO: 33);

(c) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence

YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence

TIYHSGSTYYNPSLES (SEQ ID NO: 3), an HVR-H3 comprising the amino acid sequence

ARQGSIQGYYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1

comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2

comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the

amino acid sequence MQQQEAPLT (SEQ ID NO: 32);

- (d) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);
- (e) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);
- (f) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);
- (g) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIQGYYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLHSNGYNYLD (SEQ ID NO: 26), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);
- (h) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQGLLSNGYNYLD (SEQ ID NO: 27), an HVR-L2

comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);

- (i) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSSGYNLYD (SEQ ID NO: 10), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32); or
- (j) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSIGYNLYD (SEQ ID NO: 21), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0027b] In one aspect, the present disclosure refers to an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein: the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0027c] In one aspect, the present disclosure refers to an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein: the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNLYD (SEQ ID NO: 8), an HVR-L2 comprising

the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

[0028] In some examples of any of the above aspects, the anti-Sortilin antibody: (a) decreases cell surface levels of Sortilin more than the level of decrease caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79; (b) increases extracellular levels of Progranulin more than the level of increase caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79; (c) inhibits the interaction between Sortilin and Progranulin more than the level of inhibition caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79; or (d) any combination of (a)–(c). In some examples of any of the above aspects, the anti-Sortilin antibody: (a) decreases cell surface levels of Sortilin more than the level of decrease caused by an anti-Sortilin antibody selected from the group consisting of S-60-1, S-60-2, S-60-3, S-60-4, S-60-7, or S-60-8; (b) increases extracellular levels of Progranulin more than the level of increase caused by an anti-Sortilin antibody selected from the group consisting of S-60-1, S-60-2, S-60-3, S-60-4, S-60-7, or S-60-8; (c) inhibits the interaction between Sortilin and Progranulin more than the level of inhibition caused by an anti-Sortilin antibody selected from the group consisting of S-60-1, S-60-2, S-60-3, S-60-4, S-60-7, or S-60-8; or (d) any combination of (a)–(c).

[0029] Certain examples of the present disclosure provide an anti-Sortilin antibody with a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 54-56; and/or a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 57-58, 60-78, or 80.

[0030] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57.

[0031] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 58.

[0032] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 59.

[0033] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 55, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57.

[0034] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 55, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 58.

[0035] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57.

[0036] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77.

[0037] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78.

[0038] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79.

[0039] In some examples, an anti-Sortilin antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 80.

[0040] In some examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57.

[0041] In certain examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 60.

[0042] In certain examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 61.

[0043] In certain examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 72.

[0043a] In one aspect, the present disclosure refers to an antibody that binds to a Sortilin protein, wherein the antibody comprises:

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

(l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 61; or

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

[0043b] In one aspect, the present disclosure refers to an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 60.

[0043c] In one aspect, the present disclosure refers to an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57.

[0043d] In one aspect, the present disclosure refers to an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 137 and a light chain comprising the amino acid sequence of SEQ ID NO: 142.

[0043e] In one aspect, the present disclosure refers to an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 138 and a light chain comprising the amino acid sequence of SEQ ID NO: 142.

[0044] In some examples that may be combined with any of the previous examples, an anti-Sortilin antibody of the present disclosure is of the IgG class, the IgM class, or the IgA class. In certain specific examples, the anti-Sortilin antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In some examples of the present disclosure, provided is an anti-Sortilin antibody of the IgG1, IgG2, IgG3, or IgG4 isotype, wherein (a) the antibody is an IgG1 or IgG2 isotype and the Fc region comprises an amino acid substitution at position P331S, wherein the numbering of the residue position is according to EU numbering; (b) the antibody is an IgG1 isotype and the Fc region comprises amino acid substitutions at positions L234A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering; (c) the antibody is an IgG1, IgG2, or IgG4 isotype and the Fc region comprises an amino acid substitution at position N297A, wherein the numbering of the residue position is according to EU numbering; or (d) the Fc region comprises an amino acid substitution at positions S267E and L328F, wherein the numbering of the residue position is according to EU numbering. In some examples, the antibody is an IgG1 isotype and the Fc region comprises amino acid substitutions at positions L234A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering.

[0045] In some examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 137 and a light chain comprising the amino acid sequence of SEQ ID NO: 142.

[0046] In some examples, the present disclosure provides an antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 138 and a light chain comprising the amino acid sequence of SEQ ID NO: 142.

[0047] In certain examples of the present disclosure, the Sortilin protein is a human protein. In some examples, the Sortilin protein is a wild-type protein. In certain examples, the Sortilin protein is a naturally occurring variant. In some examples, an anti-Sortilin antibody of the present disclosure binds specifically to a human Sortilin protein. In some examples that may be combined with any of the previous examples, the antibody is a human antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody. In certain examples, an anti-Sortilin antibody of the present disclosure is a monoclonal antibody.

[0048] In some examples, an anti-Sortilin antibody of the present disclosure is a bispecific antibody recognizing a first antigen and a second antigen. In certain examples, bispecific antibodies of the present disclosure recognize both Sortilin and an antigen facilitating transport across the blood-brain-barrier. In some specific examples, the first antigen is Sortilin and the second antigen is Sortilin, transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, basigin, Glut1, CD98hc, or ANG1005.

[0049] In certain examples of the present disclosure, the anti-Sortilin antibody is an antibody fragment that binds to a human Sortilin protein. In some examples, the anti-Sortilin antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human Sortilin, a naturally occurring variant of human Sortilin, and a disease variant of human Sortilin. In certain examples that may be combined with any of the preceding examples, the anti-Sortilin antibody fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.

[0050] In certain examples, the present disclosure provides an anti-Sortilin antibody, wherein (a) the anti-Sortilin antibody has increases extracellular levels of Progranulin, decreases cellular levels of Sortilin, inhibits the interaction between Sortilin and Progranulin, or any combination thereof; (b) the anti-Sortilin antibody decreases cell surface levels of Sortilin, increases extracellular levels of Progranulin, inhibits interaction between Sortilin and Progranulin, or any combination thereof; (c) the anti-Sortilin antibody decreases cell surface levels of Sortilin, decreases intracellular levels of Sortilin, decreases total levels of Sortilin, or any combination thereof; (d) the anti-Sortilin antibody induces Sortilin degradation, Sortilin cleavage, Sortilin internalization, Sortilin down regulation, or any combination thereof; (e) the anti-Sortilin antibody decreases cellular levels of Sortilin and inhibits the interaction between Sortilin and Progranulin; (f) the anti-Sortilin antibody decreases cellular levels of Sortilin and increases cellular levels of Progranulin; and/or (g) the anti-Sortilin antibody increases the effective concentration of Progranulin.

[0051] In certain examples, the present disclosure provides an anti-Sortilin antibody, wherein the anti-Sortilin antibody decreases cell surface levels of Sortilin, increases extracellular levels of Progranulin, inhibits interaction between Sortilin and Progranulin, or any combination thereof. In some examples, the anti-Sortilin antibody has a dissociation constant (K_D) for human Sortilin that is up to 2.5-fold lower than an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79, wherein the K_D is determined by FACS (*see, e.g., Example 1*). In some examples, the antibody has a dissociation constant (K_D) for human Sortilin that is greater than 1- and up to about 2.1-fold lower

than an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79, wherein the K_D is determined by FACS. In some examples, the anti-Sortilin antibody has a dissociation constant (K_D) for human Sortilin that ranges from about $1.10E-8$ M to about $4.68E-10$ M wherein the K_D is determined by FACS (*see, e.g., Example 1*), or about 270 to about 2910 pM wherein the K_D is determined by Bio-layer interferometry (*see, e.g., Example 4*). In some examples, the antibody has a dissociation constant (K_D) for human Sortilin that ranges from about $5.0E-10$ M to about $1.0E-9$ M wherein the K_D is determined by FACS, or about 250-500 pM wherein the K_D is determined by Bio-layer interferometry.

[0052] In some examples that may be combined with any of the previous examples, an anti-Sortilin antibody of the present disclosure (a) reduces cell surface levels of Sortilin with a half maximal effective concentration (EC_{50}) that is less than 150 pM, as measured by flow cytometry; (b) reduces cell surface levels of Sortilin by more than about 50% at 1.25 nM IgG, by more than about 80% at 0.63 nM IgG, or by more than about 69% at 150 nM IgG relative to control, as measured by flow cytometry; increases Progranulin secretion by more than about 1.13 fold over control at 0.63 nM IgG, or by more than about 1.22 fold over control at 50 nM IgG, as measured by standard ELISA; blocks binding of Progranulin to Sortilin with a half maximal effective concentration (EC_{50}) that is less than .325 nM, as measured by flow cytometry; (e) blocks binding of Progranulin to Sortilin by more than about 88% at 50 nM IgG, or by more than about 27.5% at 150 nM IgG relative to control, as measured by flow cytometry; or (f) any combination thereof.

[0053] In some examples, an anti-Sortilin antibody of the present disclosure (a) reduces cell surface levels of Sortilin with a half maximal effective concentration (EC_{50}) that is less than 681 pM, as measured by flow cytometry; (b) reduces cell surface levels of Sortilin by more than about 40% at 1.25 nM IgG, by more than about 29% at 0.6 nM IgG, or by more than about 62% at 150 nM IgG relative to control, as measured by flow cytometry; (c) increases Progranulin secretion by more than about 1.11 fold over control at 0.63 nM IgG, or by more than about 1.75 fold over control at 50 nM IgG, as measured by standard ELISA; (d) blocks binding of Progranulin to Sortilin with a half maximal effective concentration (EC_{50}) that is less than 0.751 nM, as measured by flow cytometry; (e) blocks binding of Progranulin to Sortilin by more than about 90% at 50 nM IgG, or by more than about 95% at 150 nM IgG relative to control, as measured by flow cytometry; or (f) any combination thereof.

[0054] In some examples, an anti-Sortilin antibody of the present disclosure competes with an antibody comprising the heavy chain variable domain and the light chain variable domain of an antibody selected from the group consisting of S-60-10, S-60-11, S-60-12, S-60-13, S-60-14, S-60-15 [N33 (wt)], S-60-15.1 [N33T], S-60-16, S-60-18, S-60-19, S-60-24, and any combination thereof for binding to Sortilin. In some examples that may be combined with any of the previous examples, an anti-

Sortilin antibody of the present disclosure binds essentially the same Sortilin epitope as an antibody comprising the heavy chain variable domain and the light chain variable domain of an antibody selected from the group consisting of S-60-10, S-60-11, S-60-12, S-60-13, S-60-14, S-60-15 [N33 (wt)], S-60-15.1 [N33T], S-60-16, S-60-18, S-60-19, and S-60-24.

[0055] In another example, the present disclosure relates to an antibody produced by any of the methods described herein. In some examples, the present disclosure provides an isolated nucleic acid comprising a nucleic acid sequence encoding an anti-Sortilin antibody of any one of the preceding aspects and examples. In one aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence encoding any one of the antibodies disclosed herein. Accordingly, some examples provide a vector containing a nucleic acid encoding an anti-Sortilin antibody, and some examples provide an isolated host cell containing such a vector. In one aspect, the present disclosure refers to a vector comprising the nucleic acid disclosed herein. In one aspect, the present disclosure refers to an isolated host cell comprising the vector disclosed herein. In certain examples, the present disclosure provides a method of producing an anti-Sortilin antibody that binds to Sortilin, comprising culturing such an isolated host cell so that the anti-Sortilin antibody is produced. In one aspect, the present disclosure refers to a method of producing an antibody that binds to Sortilin, comprising culturing the host cell disclosed herein so that the antibody is produced. In certain examples, the method further comprises recovering the antibody produced by the cell. In some examples, provided herein is an isolated antibody that binds to Sortilin and is produced by a method of the present disclosure. In one aspect, the present disclosure refers to an isolated antibody that binds to Sortilin produced by the method disclosed herein.

[0056] In another example, the present disclosure relates to a pharmaceutical composition comprising any of the anti-Sortilin antibodies described herein and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the antibodies disclosed herein and a pharmaceutically acceptable carrier. In some examples, the present disclosure relates to the use of any of the antibodies or compositions described herein for the preparation or manufacture of a medicament. In some examples, the present disclosure relates to the use of any of the antibodies or compositions described herein for the preparation or manufacture of a medicament for the treatment of frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, neuropathic pain, dementia, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis, septic shock, bacterial infection, arthritis, or osteoarthritis. Some examples provide an antibody or composition described herein for use in a method of treatment. Some examples provide an antibody or composition described herein for use in a method of treatment of frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, neuropathic pain, dementia, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis, septic shock, bacterial infection, arthritis, or osteoarthritis.

[0057] In certain examples, provided herein is a method of preventing, reducing risk for, or treating an individual having a disease, disorder, or injury, comprising administering to an individual in need thereof a therapeutically effective amount of an anti-Sortilin antibody of the present disclosure. In one aspect, the present disclosure refers to use of any one the antibodies disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, reducing risk for, or treating a disease, disorder, or injury in an individual. In some

examples, 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, neuropathic pain, dementia, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis, septic shock, bacterial infection, arthritis, and osteoarthritis. In some examples, the disease, disorder, or injury is selected from frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, and amyotrophic lateral sclerosis.

[0058] In certain examples, provided herein is 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 an anti-Sortilin antibody of the present disclosure. In one aspect, the present disclosure refers to use of any one the antibodies disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting one or more of neuroinflammation, axonopathy characterized by short axonal outgrowth and aberrant branching, aberrant microglial activation, and inflammatory response in an individual in need thereof.

[0059] In certain examples, provided herein is 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 an anti-Sortilin antibody of the present disclosure. In one aspect, the present disclosure refers to use of any one the antibodies disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for promoting one or more of wound healing, autophagy, and clearance of aggregate proteins in an individual in need thereof.

[0060] In certain examples, provided herein is a method of preventing, reducing risk, or treating an individual having arthritis, comprising administering to the individual a therapeutically effective amount of an anti-Sortilin antibody of the present disclosure. In one aspect, the present disclosure refers to use of any one the antibodies disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, reducing risk, or treating arthritis in an individual in need thereof.

[0061] In certain examples, provided herein is a method of decreasing expression of one or more pro-inflammatory mediators, comprising administering to the individual a therapeutically effective amount of an anti-Sortilin antibody of the present disclosure. In one aspect, the present disclosure refers to use of any one the antibodies disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for decreasing expression of one or more pro-inflammatory mediators in an individual in need thereof. In some examples, the one or more pro-inflammatory mediators are selected from the group consisting of IL-6, IL12p70, IL12p40, IL-1 β , TNF- α , CXCL1, CCL2, CCL3, CCL4, and CCL5.

[0062] In some examples, provided herein is a method of inhibiting the interaction between Sortilin and Progranulin, the method comprising exposing a cell expressing Sortilin to an anti-Sortilin antibody or a pharmaceutical composition of the present disclosure. In one aspect, the present disclosure refers to a method of inhibiting the interaction between Sortilin expressed on a cell and Progranulin, the method comprising exposing a cell expressing Sortilin on the cell surface to any one of the antibodies disclosed herein or the pharmaceutical composition disclosed herein, wherein the cell is *in vitro*. In some examples, the cell is *in vitro*. In some examples, the cell is *in vivo*. In some examples, the method further comprises decreasing the level of Sortilin expressed on the cell surface. In some examples, extracellular levels of Progranulin are increased.

[0063] In some examples, provided herein is a method of increasing levels of Progranulin in an individual in need thereof, the method comprising administering to the individual a therapeutically effective amount of the anti-Sortilin antibody or a pharmaceutical composition of the present disclosure. In one aspect, the present disclosure refers to use of any one the antibodies disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for increasing levels of Progranulin in an individual in need thereof. In some examples, levels of Progranulin are increased in plasma. In some examples, levels of Progranulin are increased in cerebrospinal fluid. In some examples, provided herein is a method of decreasing levels of Sortilin in an individual in need thereof, the method comprising administering to the

individual a therapeutically effective amount of an anti-Sortilin antibody or a pharmaceutical composition of the present disclosure. In one aspect, the present disclosure refers to use of any one the antibodies disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for decreasing levels of Sortilin in an individual in need thereof. In some examples, the levels of Sortilin are decreased in peripheral white blood cells. In some examples, the individual has one or more mutations in the gene encoding Progranulin. In some the individual is heterozygous for one or more loss-of-function mutations in the gene encoding Progranulin. In some examples, the individual has a c9orf72 hexanucleotide repeat expansion, the individual has or is at risk for frontotemporal dementia, Alzheimer's disease, or amyotrophic lateral sclerosis.

[0064] In some examples that may be combined with any of the previous aspects or examples, the present disclosure provides a method, wherein the anti-Sortilin antibody comprises two or more anti-Sortilin antibodies.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] **FIGS. 1A-1C** provide pharmacokinetic and pharmacodynamic studies of non-human primates administered single doses of anti-Sortilin antibody S-60-15.1 [N33T] LALAPS (S-60-15.1 [N33T] with huIgG1 with L234A/L235A/P331S mutations). **FIG. 1A** provides the level of SORT1 in peripheral white blood cells as a percentage from baseline at the indicated times after treatment (hours) with the specified anti-Sortilin antibody doses. SORT1 expression decreased with all of the anti-Sortilin antibody doses tested. Higher antibody doses (60 mg/kg, 200 mg/kg) resulted in both an earlier and more prolonged decrease of SORT1 levels compared to lower anti-Sortilin antibody doses (5mg/kg, 20 mg/kg). **FIG. 1B** provides the levels of PGRN in the plasma as a percentage from baseline at the indicated times after treatment (hours) with the specified anti-Sortilin antibody doses. The levels of PGRN increased in a time- and dose-dependent manner. In particular, plasma PGRN levels increased 3- to 4-fold at C_{max} , compared to baseline levels, for all anti-Sortilin antibody doses tested and remained elevated for longer periods of time at the higher antibody doses. **FIG. 1C** provides the levels of PGRN in CSF as a percentage from baseline at the indicated times after treatment (hours) with the specified anti-Sortilin antibody doses. CSF PGRN levels increased 2- to 3-fold above baseline in animals administered either 20 mg/kg, 60 mg/kg, or 200 mg/kg. As observed with plasma PGRN levels (**FIG. 1B**), CSF PGRN levels remained elevated over time in the higher antibody dose groups. For **FIGS. 1A-1C**, n = 3 animals per dose.

[0066] **FIGS. 2A-2C** provide pharmacokinetic and pharmacodynamic studies of non-human primates administered repeat doses of anti-Sortilin antibody S-60-15.1 [N33T] LALAPS. Animals (2 males and 2 females) were administered anti-Sortilin antibody S-60-15.1 [N33T] LALAPS at a dose of 60mg/kg once per week for four weeks. The days on which dosing occurred are represented by the

CLAIMS

What is claimed is:

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

ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);

- (f) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);
- (g) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIQGYGMDV (SEQ ID NO: 5); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLHSNGYNYLD (SEQ ID NO: 26), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);
- (h) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQGLLSNGYNYLD (SEQ ID NO: 27), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);
- (i) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSSGYNYLD (SEQ ID NO: 10), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32); or
- (j) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), an HVR-H3 comprising the amino acid sequence

ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSIGYNYLD (SEQ ID NO: 21), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

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

- (a) decreases cell surface levels of Sortilin more than the level of decrease caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79;
- (b) increases extracellular levels of Progranulin more than the level of increase caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79;
- (c) inhibits the interaction between Sortilin expressed on a cell and Progranulin more than the level of inhibition caused by an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79; or
- (d) any combination of (a)–(c).

- 3. The antibody of claim 1 or claim 2, wherein the antibody has a dissociation constant (K_D) for human Sortilin that is at least 1.1-fold lower than an anti-Sortilin antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 56 and a light chain variable region comprising the sequence of SEQ ID NO: 79, wherein the K_D is determined by FACS.
- 4. The antibody of any one of claims 1-3, wherein the antibody has a dissociation constant (K_D) for human Sortilin that ranges from about $5.0E-10$ M to about $1.0E-9$ M wherein the K_D is determined by FACS, or about 250-500 pM wherein the K_D is determined by Bio-layer interferometry.
- 5. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein: the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), an HVR-L2 comprising the amino acid sequence

LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

6. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein: the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

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

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

(l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 61; or
(m) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 72.

8. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 60.
9. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57.
10. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 137 and a light chain comprising the amino acid sequence of SEQ ID NO: 142.
11. An antibody that binds to a Sortilin protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 138 and a light chain comprising the amino acid sequence of SEQ ID NO: 142.
12. The antibody of any one of claims 1-9, wherein the antibody is of the IgG class, the IgM class, or the IgA class.
13. The antibody of claim 12, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.
14. The antibody of claim 13, wherein:
 - (a) the antibody is an IgG1 or IgG2 isotype and the Fc region comprises an amino acid substitution at position P331S, wherein the numbering of the residue position is according to EU numbering;
 - (b) the antibody is an IgG1 isotype and the Fc region comprises amino acid substitutions at positions L234A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering;
 - (c) the antibody is an IgG1, IgG2, or IgG4 isotype and the Fc region comprises an amino acid substitution at position N297A, wherein the numbering of the residue position is according to EU numbering; or
 - (d) the Fc region comprises an amino acid substitution at positions S267E and L328F, wherein the numbering of the residue position is according to EU numbering.

15. The antibody of claim 14, wherein the antibody is an IgG1 isotype and the Fc region comprises amino acid substitutions at positions L234A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering.
16. The antibody of any one of claims 1-15, wherein the Sortilin protein is a human Sortilin protein.
17. The antibody of claim 16, wherein the human Sortilin protein comprises the amino acid sequence of SEQ ID NO: 81.
18. The antibody of any one of claims 1-16, wherein the Sortilin protein is a wild-type protein, a naturally occurring variant, or a disease variant.
19. The antibody of any one of claims 1-18, wherein the antibody is a human antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, or a conjugated antibody.
20. The antibody of claim 19, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen.
21. The antibody of claim 20, wherein the first antigen is Sortilin and the second antigen is an antigen facilitating transport across the blood-brain-barrier.
22. The antibody of claim 21, wherein the second antigen is selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, basigin, Glut1, CD98hc, and ANG1005.
23. The antibody of any one of claims 1-9 and 12-22, wherein the antibody is an antibody fragment that binds to a human Sortilin protein.
24. The antibody of claim 23, wherein the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.
25. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of claims 1-24.
26. A vector comprising the nucleic acid of claim 25.
27. An isolated host cell comprising the vector of claim 26.
28. A method of producing an antibody that binds to Sortilin, comprising culturing the host cell of claim 27 so that the antibody is produced.
29. The method of claim 28, further comprising recovering the antibody produced by the host cell.

30. An isolated antibody that binds to Sortilin produced by the method of claim 28 or 29.
31. A pharmaceutical composition comprising the antibody of any one of claims 1-24 and claim 30 and a pharmaceutically acceptable carrier.
32. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for preventing, reducing risk for, or treating a disease, disorder, or injury in an individual.
33. The use of claim 32, wherein the disease, disorder, or injury is selected from the group consisting of frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, dementia, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis, septic shock, bacterial infection, arthritis, and osteoarthritis.
34. The use of claim 33, wherein the disease, disorder, or injury is selected from frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, and amyotrophic lateral sclerosis.
35. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for inhibiting one or more of neuroinflammation, axonopathy characterized by short axonal outgrowth and aberrant branching, aberrant microglial activation, and inflammatory response in an individual in need thereof.
36. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for promoting one or more of wound healing, autophagy, and clearance of aggregate proteins in an individual in need thereof.
37. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for preventing, reducing risk, or treating arthritis in an individual in need thereof.
38. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for decreasing expression of one or more pro-inflammatory mediators in an individual in need thereof.
39. The use of claim 38, wherein the one or more pro-inflammatory mediators are selected from the group consisting of IL-6, IL12p70, IL12p40, IL-1 β , TNF- α , CXCL1, CCL2, CCL3, CCL4, and CCL5.
40. A method of inhibiting the interaction between Sortilin expressed on a cell and Progranulin, the method comprising exposing a cell expressing Sortilin on the cell surface to the antibody of any

one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31, wherein the cell is *in vitro*.

41. The method of claim 40, further comprising decreasing the level of Sortilin expressed on the cell surface.
42. The method of claim 40 or claim 41, wherein extracellular levels of Progranulin are increased.
43. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for increasing levels of Progranulin in an individual in need thereof.
44. The use of claim 43, wherein levels of Progranulin are increased in plasma.
45. The use of claim 43, wherein levels of Progranulin are increased in cerebrospinal fluid.
46. Use of the antibody of any one of claims 1-24 and claim 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for decreasing levels of Sortilin in an individual in need thereof.
47. The use of claim 46, wherein the levels of Sortilin are decreased in peripheral white blood cells.
48. The use of any one of claims 32-34 and 43-47, wherein the individual has one or more mutations in the gene encoding Progranulin.
49. The use of claim 48, wherein the individual is heterozygous for one or more loss-of-function mutations in the gene encoding Progranulin.
50. The use of claim 48 or claim 49, wherein the individual has or is at risk for frontotemporal dementia, Alzheimer's disease, or amyotrophic lateral sclerosis.
51. The use of any one of claim 32-39 and 43-50, or the method of any one of claims 40-42, wherein the antibody comprises two or more antibodies that bind to a Sortilin protein.