

**WHAT IS CLAIMED IS:**

~~1. An isolated monoclonal antibody that competes for binding to human sortilin with antibody 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or 4N2.~~

~~2. The antibody of claim 1 that binds to the same epitope on human sortilin as antibody 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or 4N2.~~

31. A humanized~~An~~ antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of:

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:52 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:58, except that position L54 can be L, G, or I;

~~monoclonal antibody 5E20, wherein 5E20 is~~ a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:4 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:10;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:28 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:34;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:78 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:84;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:90 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:96;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:102 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:108;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:114 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:120;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:126 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:132;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:138 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:144; or

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:150 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:156.

~~4. The antibody of claim 3, wherein the antibody is a humanized antibody.~~

~~5. The humanized antibody of claim 4, wherein the CDRs are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact.~~

~~6. The humanized antibody of claim 5, wherein the humanized mature heavy chain variable region comprises the three Kabat/Chothia Composite heavy chain CDRs of 5E20 (SEQ ID NOS:5-7) and the humanized mature light chain variable region comprises the three Kabat/Chothia Composite light chain CDRs of 5E20 (SEQ ID NOS:11-13).~~

~~7. The humanized antibody of claim 5 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of 5E20 (SEQ ID NO:14, SEQ ID NO:6, and SEQ ID NO:7) and the humanized mature light chain variable region comprises the three Kabat light chain CDRs of 5E20 (SEQ ID NOS:11-13).~~

~~8. The humanized antibody of claim 5 wherein the humanized mature heavy chain variable region comprises the three Chothia heavy chain CDRs of 5E20 (SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:7) and the humanized mature light chain variable region comprises the three Chothia light chain CDRs of 5E20 (SEQ ID NOS:11-13).~~

9. —The humanized antibody of claim 5, wherein the humanized mature heavy chain variable region comprises the three AbM heavy chain CDRs of 5E20 (SEQ ID NO:5, SEQ ID NO:17, and SEQ ID NO:7) and the humanized mature light chain variable region comprises the three AbM light chain CDRs of 5E20 (SEQ ID NOS:11-13).

10. —The humanized antibody of claim 5 wherein the humanized mature heavy chain variable region comprises the three Contact heavy chain CDRs of 5E20 (SEQ ID NOS:18-20) and the humanized mature light chain variable region comprises the three Contact light chain CDRs of 5E20 (SEQ ID NOS:21-23).

11. —The humanized antibody of any one of claims 4-10 comprising a humanized mature heavy chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NOS:163-169, and a humanized mature light chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NOS:173-176.

12. —The humanized antibody of claim 11 wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H5 is occupied by L or V, H40 is occupied by A or T, H42 is occupied by G or D, H44 is occupied by G or R, H49 is occupied by A, H77 is occupied by T or S, H83 is occupied by R or K, H93 is occupied by S, H94 is occupied by R.

13. —The humanized antibody of claim 12, provided positions H49, H93, and H94 in the VH region are occupied by A, S, and R, respectively.

14. —The humanized antibody of claim 12, provided positions H5, H49, H77, H93, and H94 in the VH region are occupied by V, A, S, S, and R, respectively.

15. —The humanized antibody of claim 12, provided positions H5, H44, H49, H77, H93, and H94 in the VH region are occupied by V, R, A, S, S, and R, respectively.

16. —The humanized antibody of claim 12, provided positions H5, H42, H44, H49, H77, H93, and H94 in the VH region are occupied by V, D, R, A, S, S, and R, respectively.

17. — ~~The humanized antibody of claim 12, provided positions H5, H42, H44, H49, H77, H83, H93, and H94 in the VH region are occupied by V, D, R, A, S, K, S, and R, respectively.~~

18. — ~~The humanized antibody of claim 12, provided positions H5, H40, H44, H49, H77, H93, and H94 in the VH region are occupied by V, T, R, A, S, S, and R, respectively.~~

19. — ~~The humanized antibody of claim 12, provided positions H5, H40, H42, H44, H49, H77, H93, and H94 in the VH region are occupied by V, T, D, R, A, S, S, and R, respectively.~~

20. — ~~The humanized antibody of claim 11, wherein at least one of the following positions in the VL region is occupied by the amino acid as specified: L11 is L or V, L36 is L, L44 is F, L46 is G, L69 is A, L85 is T or D, L87 is F, L100 is G or Q, L106 is I or K.~~

21. — ~~The humanized antibody of claim 26, provided positions L36, L44, L46, L69, and L87 in the VL region are occupied by L, F, G, A, and F, respectively.~~

22. — ~~The humanized antibody of claim 26, provided positions L11, L36, L44, L46, L69, and L87 in the VL region are occupied by V, L, F, G, A, and F, respectively.~~

23. — ~~The humanized antibody of claim 26, provided positions L11, L36, L44, L46, L69, L87, L100, and L106 in the VL region are occupied by V, L, F, G, A, F, Q, and K, respectively.~~

24. — ~~The humanized antibody of claim 26, provided positions L11, L36, L44, L46, L69, L85, L87, L100, and L106 in the VL region are occupied by V, L, F, G, A, D, F, Q, and K, respectively.~~

25. — ~~The humanized antibody of claim 11, comprising a mature heavy chain variable region having an amino acid sequence at least 95% identical to at least one of SEQ ID NO: 163–169 and a mature light chain variable region having an amino acid sequence at least 95% identical to at least one of SEQ ID NOS:173–176.~~

~~26. — The humanized antibody of claim 25, comprising a mature heavy chain variable region having an amino acid sequence at least 98% identical to SEQ ID NOS:163-169 and a mature light chain variable region having an amino acid sequence at least 98% identical to SEQ ID NOS:173-176.~~

~~27. — The humanized antibody of claim 26 wherein the mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOS:163-169, and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NOS:173-176.~~

~~28. — The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:163 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:173.~~

~~29. — The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:164 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:173.~~

~~30. — The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:165 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:173.~~

~~31. — The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:166 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:173.~~

~~32. — The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:167 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:173.~~

~~33. — The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:168 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:173.~~

~~34. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:169 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:173.~~

~~35. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:163 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:174.~~

~~36. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:164 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:174.~~

~~37. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:165 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:174.~~

~~38. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:166 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:174.~~

~~39. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:167 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:174.~~

~~40. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:168 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:174.~~

~~41. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:169 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:174.~~

~~42. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO: 163 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:175.~~

~~43. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO: 164 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:175.~~

~~44. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:165 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:175.~~

~~45. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:166 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:175.~~

~~46. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:167 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:175.~~

~~47. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:168 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:175.~~

~~48. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:169 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:175.~~

~~49. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO: 163 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:176.~~

~~50. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO: 164 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:176.~~

~~51. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:165 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:176.~~

~~52. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:166 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:176.~~

~~53. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:167 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:176.~~

~~54. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:168 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:176.~~

~~55. —The humanized antibody of claim 27, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:169 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:176.~~

~~56. —An antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 8H24, wherein 8H24 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:28 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:34.~~

~~57. —The antibody of claim 56, wherein the antibody is a humanized antibody.~~

~~58. —The humanized antibody of claim 57, wherein the CDRs are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact.~~

~~59. —The humanized antibody of claim 58 wherein the humanized mature heavy chain variable region comprises the three Kabat/Chothia Composite heavy chain CDRs of 8H24 (SEQ ID NOS:29-31) and the humanized mature light chain variable region comprises the three Kabat/Chothia Composite light chain CDRs of 8H24 (SEQ ID NOS:35-37).~~

~~60. —The humanized antibody of claim 58 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of 8H24 (SEQ ID NO:38,~~

~~SEQ ID NO:30, and SEQ ID NO:31) and the humanized mature light chain variable region comprises the three Kabat light chain CDRs of 8H24 (SEQ ID NOS:35-37).~~

~~61. — The humanized antibody of claim 58 wherein the humanized mature heavy chain variable region comprises the three Chothia heavy chain CDRs of 8H24 (SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:31) and the humanized mature light chain variable region comprises the three Chothia light chain CDRs of 8H24 (SEQ ID NOS:35-37).~~

~~62. — The humanized antibody of claim 58 wherein the humanized mature heavy chain variable region comprises the three AbM heavy chain CDRs of 8H24 (SEQ ID NO:29, SEQ ID NO:41, and SEQ ID NO:31) and the humanized mature light chain variable region comprises the three AbM light chain CDRs of 8H24 (SEQ ID NOS:35-37).~~

~~63. — The humanized antibody of claim 58 wherein the humanized mature heavy chain variable region comprises the three Contact heavy chain CDRs of 8H24 (SEQ ID NOS:42-44) and the humanized mature light chain variable region comprises the three Contact light chain CDRs of 8H24 (SEQ ID NOS:45-47).~~

~~64. — The humanized antibody of any one of claims 57-63 comprising a humanized mature heavy chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NOS:180-181, and a humanized mature light chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NOS:185-186.~~

~~65. — The humanized antibody of claim 64 wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H2 is occupied by A, H12 is occupied by K or V, H48 is occupied by I, H67 is occupied by A, H71 is occupied by V, H91 is occupied by F, H108 is occupied by T.~~

~~66. — The humanized antibody of claim 65, provided positions H2, H48, H67, H71, H91, and H108 in the VH region are occupied by A, I, A, V, F, and T, respectively.~~

~~67. — The humanized antibody of claim 65, provided H2, H12, H48, H67, H71, H91, and H108 in the VH region are occupied by A, V, I, A, V, F, and T, respectively.~~

~~68. —The humanized antibody of claim 64, wherein at least one of the following positions in the VL region is occupied by the amino acid as specified: L2 is V, L9 is L or S, L74 is K or T.~~

~~69. —The humanized antibody of claim 68, provided position L2 in the VL region is occupied by V.~~

~~70. —The humanized antibody of claim 68, provided positions L2, L9, and L74 in the VL region are occupied by V, S, and T, respectively.~~

~~71. —The humanized antibody of claim 64, comprising a mature heavy chain variable region having an amino acid sequence at least 95% identical to at least one of SEQ ID NO: 180-181 and a mature light chain variable region having an amino acid sequence at least 95% identical to at least one of SEQ ID NOS:185-186.~~

~~72. —The humanized antibody of claim 71, comprising a mature heavy chain variable region having an amino acid sequence at least 98% identical to SEQ ID NOS:180-181 and a mature light chain variable region having an amino acid sequence at least 98% identical to SEQ ID NOS:185-186.~~

~~73. —The humanized antibody of claim 72 wherein the mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOS:180-181, and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NOS:185-186.~~

~~74. —The humanized antibody of claim 73, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:180 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:185.~~

~~75. —The humanized antibody of claim 73, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:180 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:186.~~

~~76. —The humanized antibody of claim 73, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:181 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:185.~~

~~77. — The humanized antibody of claim 73, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:181 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:186.~~

~~782. The humanized~~An antibody ~~specifically binding to sortilin~~of claim 1, ~~wherein the humanized antibody comprises the~~~~comprising~~ three light chain CDRs and ~~the~~ three heavy chain CDRs of ~~monoclonal antibody 11M14, wherein 11M14 is~~ a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:52 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:58), except that position L54 can be L, G, or I.-

~~79. — The antibody of claim 78, wherein the antibody is a humanized antibody.~~

~~80. — The humanized antibody of claim 79, wherein the CDRs are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact.~~

~~813. The humanized antibody of claim 80-2, wherein the~~ humanized antibody comprises a humanized mature heavy chain variable region ~~comprises-comprising~~ the three Kabat/Chothia Composite heavy chain CDRs of ~~11M14 (SEQ ID NOS~~NOs~~: 53-55)~~ and ~~the a~~ humanized mature light chain variable region ~~comprises-comprising~~ the three Kabat/Chothia Composite light chain CDRs of ~~11M14 (SEQ ID NOS~~NOs~~: 59-61)~~, except that position L54 can be L, G, or I.

~~82. — The humanized antibody of claim 80 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of 11M14 (SEQ ID NO:62, SEQ ID NO:54, and SEQ ID NO:55) and the humanized mature light chain variable region comprises the three Kabat light chain CDRs of 11M14 (SEQ ID NOS:59-61), except that position L54 can be L, G, or I.~~

~~83. — The humanized antibody of claim 80 wherein the humanized mature heavy chain variable region comprises the three Chothia heavy chain CDRs of 11M14 (SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:55) and the humanized mature light chain variable region~~

comprises the three Chothia light chain CDRs of 11M14 (SEQ ID NOS:59-61), except that position L54 can be L, G, or I.

~~84. The humanized antibody of claim 80 wherein the humanized mature heavy chain variable region comprises the three AbM heavy chain CDRs of 11M14 (SEQ ID NO:53, SEQ ID NO:65, and SEQ ID NO:55) and the humanized mature light chain variable region comprises the three AbM light chain CDRs of 11M14 (SEQ ID NOS:59-61), except that position L54 can be L, G, or I.~~

~~85. The humanized antibody of claim 80 wherein the humanized mature heavy chain variable region comprises the three Contact heavy chain CDRs of 11M14 (SEQ ID NOS:66-68) and the humanized mature light chain variable region comprises the three Contact light chain CDRs of 11M14 (SEQ ID NOS:69-71), except that position L54 can be L, G, or I.~~

~~864.~~ The humanized antibody of ~~any one of claims 79-85~~claim 2 or 3, comprising a humanized mature heavy chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID ~~NOS~~NOS: 190-192, and a humanized mature light chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID ~~NOS~~NOS: 196-199.

~~875.~~ The humanized antibody of claim ~~864~~875, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H49 is occupied by A, H80 is occupied by L or G, H82c is occupied by L or G.

~~886.~~ The humanized antibody of claim ~~875~~875, provided position H49 in the VH region is occupied by A.

~~897.~~ The humanized antibody of claim ~~875~~875, provided positions H49 and H82c in the VH region are occupied by A and G, respectively.

~~908.~~ The humanized antibody of claim ~~875~~875, provided positions H49 and H80 in the VH region are occupied by A and G, respectively.

[949](#). The humanized antibody of claim [864](#), wherein at least one of the following positions in the VL region is occupied by the amino acid as specified: L43 is A or S, L48 is V, L54 is L, G, or I, L71 is Y, L76 is N or S.

[9210](#). The humanized antibody of claim [949](#), provided positions L48 and L71 in the VL region are occupied by V and Y respectively.

[9311](#). The humanized antibody of claim [949](#), provided positions L43, L48, L71, and L76 in the VL region are occupied by S, V, Y, and S, respectively.

[9412](#). The humanized antibody of claim [949](#), provided positions L43, L48, L54, L71, and L76 in the VL region are occupied by S, V, G, Y, and S, respectively.

[9513](#). The humanized antibody of claim [949](#), provided positions L43, L48, L54, L71, and L76 in the VL region are occupied by S, V, I, Y, and S, respectively.

[9614](#). The humanized antibody of claim [864](#), comprising a [humanized](#) mature heavy chain variable region having an amino acid sequence at least 95% identical to at least one of SEQ ID NOS: 190-192 and a [humanized](#) mature light chain variable region having an amino acid sequence at least 95% identical to at least one of SEQ ID NOS: 196-199.

~~97. The humanized antibody of claim 96, comprising a mature heavy chain variable region having an amino acid sequence at least 98% identical to SEQ ID NOS: 190-192 and a mature light chain variable region having an amino acid sequence at least 98% identical to SEQ ID NOS: 196-199.~~

[9815](#). The humanized antibody of claim [97-14](#), wherein the [humanized](#) mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOS: 190-192, and the [humanized](#) mature light chain variable region has an amino acid sequence of any one of SEQ ID NOS: 196-199.

[9916](#). The humanized antibody of claim [9815](#), wherein:

the [humanized](#) mature heavy chain variable region has an amino acid sequence of SEQ ID NO: 190 and the [humanized](#) mature light chain variable region has an amino acid sequence of SEQ ID NO: 196;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:197;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:198;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:199;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:196;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:197;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO: 191 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO: 198;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:199;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:196;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:197;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:198; or

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:199.

~~100.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:197.~~

~~101.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:198.~~

~~102.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:199.~~

~~103.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:196.~~

~~104.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:197.~~

~~105.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:198.~~

~~106.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:199.~~

~~107.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:196.~~

~~108.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:197.~~

~~109.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:198.~~

~~110.—The humanized antibody of claim 98, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:199.~~

~~111.—An antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 5M13, wherein 5M13 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:78 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:84.~~

~~112.—The antibody of claim 111, wherein the three heavy chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:79-81) and the three light chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:85-87).~~

~~113.—An antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 2F18, wherein 2F18 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:90 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:96.~~

~~114. —The antibody of claim 113, wherein the three heavy chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:91-93) and the three light chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:97-99).~~

~~115. —An antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 2P22, wherein 2P22 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:102 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:108.~~

~~116. —The antibody of claim 115, wherein the three heavy chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:103-105) and the three light chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:109-111).~~

~~117. —An antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 6B15, wherein 6B15 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:114 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:120.~~

~~118. —The antibody of claim 117, wherein the three heavy chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:115-117) and the three light chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:121-123).~~

~~119. —An antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 2C14, wherein 2C14 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:126 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:132.~~

~~120. —The antibody of claim 119, wherein the three heavy chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:127-129) and the three light chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:133-135).~~

~~121. — An antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 9N18, wherein 9N18 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:138 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:144.~~

~~122. — The antibody of claim 121, wherein the three heavy chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:139-141) and the three light chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:145-147).~~

~~123. — An antibody specifically binding to human sortilin comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 4N2, wherein 4N2 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:150 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:156.~~

~~124. — The antibody of claim 123, wherein the three heavy chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:151-153) and the three light chain CDRs are as defined by Kabat Chothia Composite (SEQ ID NOS:157-159).~~

~~125. — The antibody of any one of claims 111-124 that is a humanized antibody.~~

~~126~~17. The humanized antibody of any one of claims 1-~~125~~16 that is an intact antibody.

~~127~~18. The humanized antibody of any one of claims 1-~~125~~16 that is a binding fragment.

~~128~~19. The humanized antibody of any one of ~~the preceding~~ claims 1-18, wherein the humanized antibody has an isotype ~~is of~~ human IgG1.

~~129~~20. The humanized antibody of any one of claims ~~1-125~~14-16, wherein the humanized mature light chain variable region is fused to a light chain constant region and the humanized mature heavy chain variable region is fused to a heavy chain constant region.

~~130~~21. The humanized antibody of claim ~~129~~20, wherein the heavy chain constant region is a mutant form of a natural human heavy chain constant region which has reduced binding to a Fcγ receptor relative to the natural human heavy chain constant region.

~~131~~22. The humanized antibody of claim ~~129~~20, wherein the heavy chain constant region is a mutant form of a natural human heavy chain constant region which has enhanced binding to a neonatal Fcγ receptor relative to the natural human heavy chain constant region.

~~132~~23. The humanized antibody of claim ~~129~~20, comprising:

a heavy chain of SEQ ID NO: ~~244~~ and a light chain of SEQ ID NO: ~~245~~;

a heavy chain of SEQ ID NO: 246 and a light chain of SEQ ID NO: 247;

a heavy chain of SEQ ID NO: 248 and a light chain of SEQ ID NO: 249;

a heavy chain of SEQ ID NO: 250 and a light chain of SEQ ID NO: 245;

a heavy chain of SEQ ID NO:251 and a light chain of SEQ ID NO:247; or

a heavy chain of SEQ ID NO: 252 and a light chain of SEQ ID NO: 249.

~~133. The antibody of claim 129, comprising a heavy chain of SEQ ID NO:246 and a light chain of SEQ ID NO:247.~~

~~134. The antibody of claim 129, comprising a heavy chain of SEQ ID NO:248 and a light chain of SEQ ID NO:249.~~

~~135. The antibody of claim 129, comprising a heavy chain of SEQ ID NO:250 and a light chain of SEQ ID NO:245.~~

~~136. The antibody of claim 129, comprising a heavy chain of SEQ ID NO:251 and a light chain of SEQ ID NO:247.~~

~~137. The antibody of claim 129, comprising a heavy chain of SEQ ID NO:252 and a light chain of SEQ ID NO:249.~~

~~138~~24. The humanized antibody of any one of claims 1-~~127~~18 and ~~129~~20-~~137~~23, wherein the humanized antibody has an isotype of human IgG2 or IgG4 isotype.

~~139~~25. A pharmaceutical composition comprising the humanized antibody ~~as defined in~~ any one of claims 1-~~138~~24 and a pharmaceutically-acceptable carrier.

~~140~~26. A nucleic acid encoding ~~the a~~ heavy chain and/or light chain of the humanized antibody ~~as described in~~ any one of claims 1-~~139~~24.

~~141~~27. A method of humanizing a mouse antibody, the method comprising:

- (a) selecting one or more acceptor antibody sequences;
- (b) identifying amino acid residues of the mouse antibody to be retained;
- (c) synthesizing a nucleic acid encoding a humanized heavy chain comprising CDRs of the mouse antibody heavy chain and a nucleic acid encoding a humanized light chain comprising CDRs of the mouse antibody light chain; and
- (d) expressing the nucleic acids in a host cell to produce a humanized antibody;

wherein the mouse antibody is characterized by:

a mature heavy chain variable region of SEQ ID NO: 52 and a mature light chain variable region of SEQ ID NO: 58;

~~wherein the mouse antibody is 5E20, wherein 5E20 is characterized by~~ a mature heavy chain variable region of SEQ ID NO: 4 and a mature light chain variable region of SEQ ID NO: 10;

~~wherein the mouse antibody is 8H24, wherein 8H24 is characterized by~~ a mature heavy chain variable region of SEQ ID NO: 28 and a mature light chain variable region of SEQ ID NO: 34;

~~wherein the mouse antibody is 11M14, wherein 11M14 is characterized by a mature heavy chain variable region of SEQ ID NO:52 and a mature light chain variable region of SEQ ID NO:58,~~

~~wherein the mouse antibody is 5M13, wherein 5M13 is characterized by a mature heavy chain variable region of SEQ ID NO: 78 and a mature light chain variable region of SEQ ID NO: 84;~~

~~wherein the mouse antibody is 2F18, wherein 2F18 is characterized by a mature heavy chain variable region of SEQ ID NO: 90 and a mature light chain variable region of SEQ ID NO: 96;~~

~~wherein the mouse antibody is 2P22, wherein 2P22 is characterized by a mature heavy chain variable region of SEQ ID NO: 102 and a mature light chain variable region of SEQ ID NO: 108;~~

~~wherein the mouse antibody is 6B15, wherein 6B15 is characterized by a mature heavy chain variable region of SEQ ID NO: 114 and a mature light chain variable region of SEQ ID NO: 120;~~

~~wherein the mouse antibody is 2C14, wherein 2C14 is characterized by a mature heavy chain variable region of SEQ ID NO: 126 and a mature light chain variable region of SEQ ID NO: 132;~~

~~wherein the mouse antibody is 9N18, wherein 9N18 is characterized by a mature heavy chain variable region of SEQ ID NO: 138 and a mature light chain variable region of SEQ ID NO: 144; or~~

~~wherein the mouse antibody is 4N2, wherein 4N2 is characterized by a mature heavy chain variable region of SEQ ID NO: 150 and a mature light chain variable region of SEQ ID NO: 156.~~

14228. A method of producing a humanized, chimeric, or veneered antibody, the method comprising:

(a) culturing cells transformed with nucleic acids encoding the heavy and light chains of the antibody, so that the cells secrete the antibody; and

(b) purifying the antibody from cell culture media;

wherein the antibody is a humanized antibody of any one of claims 1-24,  
~~chimeric, or veneered form of 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or~~  
~~4N2.~~

14329. A method of producing a cell line producing a humanized, chimeric, or veneered antibody, the method comprising:

(a) introducing a vector encoding heavy and light chains of an antibody and a selectable marker into cells;

(b) propagating the cells under conditions to select for cells having increased copy number of the vector;

(c) isolating single cells from the selected cells; and

(d) banking cells cloned from a single cell selected based on yield of antibody;

wherein the antibody is a humanized antibody of any one of claims 1-24,  
~~chimeric, or veneered form of 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or~~  
~~4N2.~~

~~144. — The method of claim 143 further comprising propagating the cells under selective conditions and screening for cell lines naturally expressing and secreting at least 100 mg/L/10<sup>6</sup> cells/24 h.~~

14530. Use of the humanized antibody of any one of claims 1-24 in the manufacture of a medicament for ~~A method of~~ increasing progranulin levels in a subject having or at risk of developing a ~~a~~ disease or disorder associated with changes in progranulin levels, ~~comprising administering to the subject an effective dose of the antibody of any one of claims 1-140, thereby increasing progranulin levels in the subject.~~

~~146~~31. Use of the humanized antibody of any one of claims 1-24 in the manufacture of a medicament for ~~A method of~~ treating or effecting prophylaxis of a disease or disorder associated with changes in progranulin levels in a subject, ~~comprising administering an effective dose of an antibody as defined by any one of claims 1-140 and thereby treating or effecting prophylaxis of the disease or disorder.~~

~~147. — A method of claim 146, further comprising detecting progranulin levels in a subject.~~

~~148. — A method of claim 147, further comprising monitoring progranulin levels in a subject.~~

~~149~~32. ~~A method~~The use of claim ~~146~~31, wherein the disease or disorder associated with changes in progranulin levels is frontotemporal dementia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Batten disease, a neurodegenerative disorder, or a neurodegenerative disorder associated with aging.

~~150. — A method of claim 149, wherein the disease or disorder associated with changes in progranulin levels is frontotemporal dementia.~~

~~151~~33. Use of the humanized antibody of any one of claims 1-24 in the manufacture of a medicament for ~~A method of~~ detecting sortilin in a subject having or at risk of a disease associated with a disease or disorder associated with changes in progranulin levels, ~~comprising administering to a subject an antibody defined by any one of claims 1-140, and detecting the antibody bound to sortilin in the subject.~~

~~152. — An isolated monoclonal antibody that specifically binds to a peptide consisting of residues FTESFLT (SEQ ID NO:202).~~

~~153. — An isolated monoclonal antibody that specifically binds to a peptide consisting of residues ESFL (SEQ ID NO:203).~~

~~154. — An isolated monoclonal antibody that specifically binds to human sortilin at an epitope within a motif of the formula E(S/Q/D)FL (SEQ ID NO:206).~~

~~155.—An isolated monoclonal antibody that specifically binds to a peptide consisting of residues DGCILGYKEQFL (SEQ ID NO:204).~~

~~156.—An isolated monoclonal antibody that specifically binds to a peptide consisting of residues PSICLCSLEDFL (SEQ ID NO:205).~~

~~157.—An isolated monoclonal antibody that specifically binds to a peptide consisting of residues RTEFGMAIGP (SEQ ID NO:213).~~

~~158.—An isolated monoclonal antibody that specifically binds to a peptide consisting of residues WGFTEFLTS (SEQ ID NO:214).~~

~~159.—An isolated monoclonal antibody that specifically binds an epitope defined by amino acid residues D74, R76, F97, K110, Y535, L560, and E557 of SEQ ID NO:215.~~

~~160.—An isolated monoclonal antibody that specifically binds an epitope defined by amino acid residues K110, Y535, E557, T561, Q563, D74, P510, S558, F559, and L560 of SEQ ID NO:215.~~

~~161.—An isolated monoclonal antibody that specifically binds an epitope defined by amino acid residues E557, S558, F559, L560, P510, and Y535 of SEQ ID NO:215.~~

~~162.—A method of treating or effecting prophylaxis of a disease or disorder associated with changes in progranulin levels in a subject comprising administering an immunogen comprising a sortilin peptide of up to 20 contiguous amino acids of SEQ ID NO:1 to which antibody 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or 4N2 specifically binds, wherein the peptide induces formation of antibodies specifically binding to sortilin in the subject.~~