

AL001 completed phase 1 and is currently in phase 2 (See, <https://investors.alector.com/static-files/7418b689-c5b7-43ac-a16a-3c64e1a14e80>). Increased progranulin in plasma and CSF relative to baseline has been reported in healthy volunteers administered an anti-sortilin antibody. Sortilin is also a receptor/transporter for other factors (e.g. neurotensin).

BRIEF SUMMARY ~~OF THE CLAIMED INVENTION~~

[0005] In one ~~aspect~~example, the ~~invention~~disclosure provides an isolated monoclonal antibody that competes for binding to human sortilin with antibody 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or 4N2. Some antibodies bind to the same epitope on human sortilin as antibody 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or 4N2.

[0005a] In one aspect, the disclosure provides a humanized 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;

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.

[0006] In another aspectexample, the inventiondisclosure provides an antibody specifically binding to human sortilin comprising three light chain CDRs and three heavy chain CDRs of 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. For example, the antibody can be a humanized antibody.

[0007] In some antibodies, the CDRs are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact. In some antibodies, 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). In some antibodies, 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). In some antibodies, 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). In some antibodies, 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

sequence of SEQ ID NO:176. In some antibodies, 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. In some antibodies, 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. In some antibodies, 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. In some antibodies, 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. In some antibodies, 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. In some antibodies, 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.

[0017] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. For example, the antibody can be a humanized antibody.

[0018] In some antibodies, the CDRs are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact. In some antibodies, 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). In some antibodies, 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). In some antibodies, the humanized mature heavy chain variable region comprises the three Chothia heavy chain CDRs of 8H24 (SEQ ID NO:39, SEQ ID NO:40,

region having an amino acid sequence at least 98% identical to SEQ ID NOS:185-186. In some antibodies, 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.

[0024] In some antibodies, 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. In some antibodies, 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. In some antibodies, 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. In some antibodies, 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.

[0025] In another [aspectexample](#), the [inventiondisclosure](#) provides an antibody specifically binding to human sortilin comprising three light chain CDRs and 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.. For example, the antibody can be a humanized antibody.

[0026] In some antibodies, the CDRs are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact. In some antibodies, the humanized mature heavy chain variable region comprises the three Kabat/Chothia Composite heavy chain CDRs of 11M14 (SEQ ID NOS:53-55) and the humanized mature light chain variable region comprises the three Kabat/Chothia Composite light chain CDRs of 11M14 (SEQ ID NOS:59-61), except that position L54 can be L, G, or I. In some antibodies, 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. In some antibodies, the humanized mature heavy chain variable

amino acid sequence of SEQ ID NO:197. In some antibodies, 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. In some antibodies, 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.

[0033] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. In some antibodies, 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).

[0034] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. In some antibodies, 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).

[0035] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. In some antibodies, 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).

[0036] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. In some antibodies, 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).

[0037] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. In some antibodies, 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).

[0038] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. In some antibodies, 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).

[0039] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. In some antibodies, 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).

[0040] For example, the antibody can be a humanized antibody.

[0041] The antibody can be an intact antibody or a binding fragment. Some of the antibodies have a human IgG1 isotype, while others may have a human IgG2 or IgG4 isotype. Some

antibodies have the mature light chain variable region fused to a light chain constant region and the mature heavy chain variable region fused to a heavy chain constant region. The heavy chain constant region of some antibodies is a mutant form of a natural human heavy chain constant region which has reduced binding to a Fc γ receptor relative to the natural human heavy chain constant region.

[0042] The heavy chain constant region of some antibodies is a mutant form of a natural human heavy chain constant region which has enhanced binding to a neonatal Fc γ receptor relative to the natural human heavy chain constant region.

[0043] Some antibodies comprise a heavy chain of SEQ ID NO:244 and a light chain of SEQ ID NO:245. Some antibodies comprise a heavy chain of SEQ ID NO:246 and a light chain of SEQ ID NO:247. Some antibodies comprise a heavy chain of SEQ ID NO:248 and a light chain of SEQ ID NO:249. Some antibodies comprise a heavy chain of SEQ ID NO:250 and a light chain of SEQ ID NO:245. Some antibodies comprise a heavy chain of SEQ ID NO:251 and a light chain of SEQ ID NO:247. Some antibodies comprise a heavy chain of SEQ ID NO:252 and a light chain of SEQ ID NO:249.

[0044] In another [aspectexample](#), the [inventiondisclosure](#) provides a pharmaceutical composition comprising any of the antibodies disclosed herein and a pharmaceutically-acceptable carrier. [In one aspect, the disclosure provides a pharmaceutical composition comprising the humanized antibody as disclosed herein and a pharmaceutically-acceptable carrier.](#) In another [aspectexample](#), the [inventiondisclosure](#) provides a nucleic acid encoding the heavy chain and/or light chain of any of the antibodies disclosed herein. [In another aspect, the disclosure provides a nucleic acid encoding a heavy chain and/or light chain of the humanized antibody as disclosed herein.](#)

[0044a] [In one aspect, the disclosure provides 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;
a mature heavy chain variable region of SEQ ID NO: 4 and a mature light chain variable
region of SEQ ID NO: 10;
a mature heavy chain variable region of SEQ ID NO: 28 and a mature light chain variable
region of SEQ ID NO: 34;
a mature heavy chain variable region of SEQ ID NO: 78 and a mature light chain variable
region of SEQ ID NO: 84;
a mature heavy chain variable region of SEQ ID NO: 90 and a mature light chain variable
region of SEQ ID NO: 96;
a mature heavy chain variable region of SEQ ID NO: 102 and a mature light chain
variable region of SEQ ID NO: 108;
a mature heavy chain variable region of SEQ ID NO: 114 and a mature light chain
variable region of SEQ ID NO: 120;
a mature heavy chain variable region of SEQ ID NO: 126 and a mature light chain
variable region of SEQ ID NO: 132;
a mature heavy chain variable region of SEQ ID NO: 138 and a mature light chain
variable region of SEQ ID NO: 144; or
a mature heavy chain variable region of SEQ ID NO: 150 and a mature light chain
variable region of SEQ ID NO: 156.

[0045] In yet another ~~aspect~~example, the ~~invention~~disclosure provides methods of humanizing any non-human antibody described herein, for example mouse antibody 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; mouse antibody 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; mouse antibody 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; mouse antibody 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; mouse antibody 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; mouse antibody 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; mouse antibody 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; mouse antibody 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; mouse antibody 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 mouse antibody 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. Such methods can involve selecting one or more acceptor antibody sequences; identifying amino acid residues of the mouse antibody to be retained; 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 expressing the nucleic acids in a host cell to produce a humanized antibody.

[0046] Methods of producing antibodies, for example humanized, chimeric or veneered form of 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or 4N2, are also provided. In such methods, cells transformed with nucleic acids encoding the heavy and light chains of the antibody are cultured so that the cells secrete the antibody. The antibody can then be purified from the cell culture media.

[0046a] In one aspect, the disclosure provides 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 as disclosed herein.

[0047] Cell lines producing any of the antibodies disclosed herein, for example a humanized, chimeric, or veneered form of 5E20, 8H24, 11M14, 5M13, 2F18, 2P22, 6B15, 2C14, 9N18, or 4N2, can be produced by introducing a vector encoding heavy and light chains of the antibody and a selectable marker into cells, propagating the cells under conditions to select for cells having increased copy number of the vector, isolating single cells from the selected cells; and banking cells cloned from a single cell selected based on yield of antibody.

[0047a] In one aspect, the disclosure provides 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 as disclosed herein.

[0048] Some cells can be propagated under selective conditions and screened for cell lines naturally expressing and secreting at least 100 mg/L/10⁶ cells/24 hours.

[0049] The ~~invention~~[disclosure](#) also provides methods of increasing progranulin levels in a subject having or at risk of developing a disease or disorder associated with changes in progranulin levels, comprising administering to the subject an effective dose of an antibody disclosed herein, thereby increasing progranulin levels in the subject. [In one aspect, the disclosure provides use of the humanized antibody as disclosed herein in the manufacture of a medicament for increasing progranulin levels in a subject having or at risk of developing a disease or disorder associated with changes in progranulin levels.](#)

[0050] The ~~invention~~[disclosure](#) also provides methods 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 disclosed herein, and thereby treating or effecting prophylaxis of the disease or disorder. [In one aspect, the disclosure provides use of the humanized antibody as disclosed herein in the manufacture of a medicament for treating or effecting prophylaxis of a disease or disorder associated with changes in progranulin levels in a subject.](#) Some methods further comprise detecting progranulin levels in a subject. Some methods further comprise comprising monitoring progranulin levels in a subject.

[0051] In some methods, 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. In some methods, the disease or disorder associated with changes in progranulin levels is frontotemporal dementia.

[0052] The ~~invention~~[disclosure](#) also provides methods 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 disclosed herein, and detecting the antibody bound to sortilin in the subject. [In one aspect, the disclosure provides use of the humanized antibody as disclosed herein in the manufacture of a medicament for detecting sortilin in a subject having or at risk of a disease associated with a disease or disorder associated with changes in progranulin levels.](#)

[0053] In another ~~aspect~~[example](#), the ~~invention~~[disclosure](#) provides an isolated monoclonal antibody that specifically binds to a peptide consisting of residues FTESFLT (SEQ ID NO:202). In another ~~aspect~~[example](#), the ~~invention~~[disclosure](#) provides an isolated monoclonal antibody that specifically binds to a peptide consisting of residues ESFL (SEQ ID NO:203). In another ~~aspect~~[example](#), the ~~invention~~[disclosure](#) provides 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). In another ~~aspect~~[example](#), the ~~invention~~[disclosure](#) provides an isolated monoclonal antibody that specifically binds to a peptide consisting of residues DGCILGYKEQFL (SEQ ID NO:204). In another ~~aspect~~[example](#), the ~~invention~~[disclosure](#) provides an isolated monoclonal antibody that specifically binds to a peptide consisting of residues PSICLCSLEDFL (SEQ ID NO:205).

[00510053a] In another [aspectexample](#), the [inventiondisclosure](#) provides an isolated monoclonal antibody that specifically binds to a peptide consisting of residues RTEFGMAIGP (SEQ ID NO:213), In another [aspectexample](#), the [inventiondisclosure](#) provides an isolated monoclonal antibody that specifically binds to a peptide consisting of residues WGFTEFLTS (SEQ ID NO:214).

[00510053b] In another [aspectexample](#), the [inventiondisclosure](#) provides 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. In another [aspectexample](#), the [inventiondisclosure](#) provides an 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. In another [aspectexample](#), the [inventiondisclosure](#) provides an 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.

[0054] The [inventiondisclosure](#) also provides methods 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0055] Figure 1 depicts an alignment of heavy chain variable regions of the mouse 5E20 antibody (5E20VH; SEQ ID NO:4) and humanized versions of the 5E20 antibody (hu5E20VHv1, hu5E20VHv2, hu5E20VHv3, hu5E20VHv4, hu5E20VHv5, hu5E20VHv6, and hu5E20VHv7) with human germline heavy chain variable region sequence IGHV3-21*01 (SEQ ID NO:162), with human acceptor heavy chain variable region sequence AEX29086-VH_huFrwk (AEX29086 VH; SEQ ID NO:161). hu5E20VHv1 (5E20VHv1) is SEQ ID NO:163, hu5E20VHv2 (5E20VHv2) is SEQ ID NO:164, hu5E20VHv3 (5E20VHv3) is SEQ ID NO:165, hu5E20VHv4 (5D20VHv4) is SEQ ID NO:166, hu5E20VHv5 (5E20VHv5) is SEQ ID NO:167, hu5E20VHv6 (5E20VHv6) is SEQ ID NO:168, and hu5E20VHv7 (5E20VHv7) is SEQ