Agents, Uses and Methods for Treatment

Field of The Invention

[0001] The present invention relates to monoclonal anti-Sortilin antibodies useful in correcting a deficient level of progranulin (PGRN). In particular these antibodies can be used in the treatment of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Furthermore, it is anticipated that the monoclonal antibodies may also be useful to treat neurodegenerative disorders such as Alzheimer's Disease (AD).

Reference to Sequence Listing

[0002] This application includes one or more Sequence Listings pursuant to 37 C.F.R. 1.821 et seq., which are disclosed in computer-readable media (file name: 0993_ST25.txt, created on 22 June 2016, and having a size of 144 kB), which file is herein incorporated by reference in its entirety.

Background of the Invention

[0003] Sortilin is a receptor that has been reported to mediate pro-apoptotic effects of pro-neurotrophins and to mediate trafficking and sorting of neurotrophin receptors (Nykjær et al, 2012, Trends Neurosci. 2012;35(4):261-70; Glerup et al, Handb Exp Pharmacol, 2014;220:165-89, Carlo et al, J Mol Med (Berl). 2014 Sep;92(9):905-11). A number of sortilin ligands have been identified including neurotensin for which a high affinity binding site was localized by x-ray crystallography to be inside a beta propeller tunnel in the sortilin molecule (Quistgaard et al, Nat Struct Mol Biol. 2009 Jan; 16(1):96-8; Quistgaard et al, Protein Sci. 2014, Sep;23(9):1291-300). More recently, sortilin was shown to function as a high affinity receptor for the growth factor progranulin (PGRN, Hu *et al*. Neuron. 2010 Nov 18;68(4):654-67.

[0004] PGRN ((proepithelin, granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin)) is a secreted glycosylated protein with anti-inflammatory and neurotrophic-like actions (For a recent review, see Nguyen, Trends Endocrinol Metab. 2013 Dec;24(12):597-606). PGRN is proteolytically

cleaved to granulins, but much remains to be learned regarding the physiological role of PGRN and granulins and the identity of their receptors. PGRN has been implicated in several cellular functions including cell cycle regulation and cell motility (He, Z. & Bateman, A., J. Mol. Med. 57:600-612 (2003); Monami, G., *et al.*, Cancer Res. (5(5:7103-7110 (2006)), wound repair, inflammation (Zhu, J., *et al.*, Cell 777:867-878 (2002)), induction of growth factors such as vascular endothelial growth factor (VEGF) (Tangkeangsiπsin, W. & Serrero, G, Carcinogenesis 25.1587-1592 (2004)), and tumorigenesis (He, Z. & Bateman, A., J. Mol. Med. 81:600- 612 (2003), Monami, G., *et al.*, Cancer Res (5(5:7103-7110 (2006); Serrero, G., Biochem Biophys. Res. Commun. 505-409-413 (2003), Lu, R & Serrero, G., Proc. Natl Acad Sci U.SA 98 142-147 (2001); Liau, L M., et al., Cancer Res. 60:1353-1360 (2000)). PGRN has been reported to bind the TNF receptor (Tang W *et al.*, Science 2011, 332(6028):478-84). but this observation has been challenged by others (Chen *et al.*, J Neurosci. 2013, 33(21):9202-9213).

[0005] The binding of PGRN to sortilin has been mapped to the neurotensin site and reported to be mediated solely through the PGRN C-terminal domain (Zheng *et al.* PLoS One. 2011;6(6):e21023; Lee *et al.* Hum Mol Genet. 2013) in a manner similar to neurotensin and in accordance, neurotensin has been shown to block the interaction of sortilin with PGRN and other ligands. Upon binding, sortilin mediates lysosomal clearance of PGRN and thereby regulates extracellular PGRN levels (Hu *et al.* 2010). Thus, knockdown or overexpression of sortilin have been shown to regulate extracellular PGRN levels in cell culture (Carrasquillo *et al.* Am J Hum Genet. 2010 Dec 10;87(6):890-7) and in mice, sortilin deficiency was reported to increase PGRN levels and to restore plasma and brain PGRN-levels in PGRN +/- mice (Hu *et al.* 2010). Interestingly, a single nucleotide polymorphism (SNP) near sortilin was associated with decreased plasma PGRN and increased sortilin mRNA levels (Carrasquillo *et al.* Am J Hum Genet. 2010 Dec 10;87(6):890-7). These observations suggest that sortilin is a key regulator of extracellular PGRN.

[0006] PGRN has been linked to frontotemporal dementia (FTD), a progressive dementia characterized by behavioral and semantic changes, as well

as frontotemporal lobar degeneration (FTLD) and neuronal inclusions containing TAR DNA Binding Protein-43 (TDP-43) or tau inclusions (Baker et al, 2006, Nature. 2006 Aug 24;442(7105):916-9; Cruts et al, Nature 442: 920-924 (2006); Am J Hum Genet. 2010 Dec 10;87(6):890-7,M et al, Trends in Genetics 24: 186-194 (2008)). The majority of sporadic and familial FTD cases show TDP-43 pathology (~50%) similar to ALS and FTD-TDP43 and ALS are by some considered to constitute a disease spectrum (Ito D Neurology. 2011 Oct 25;77(17):1636-43; Boxer AL et al, Alzheimers Dement. 2013 Mar;9(2):176-88; Rademakers et al, Nat Rev Neurol. 2012 August; 8(8): 423–434) due to common pathologies and genetic factors and some overlap in symptomatology. No disease-modifying treatment options are available for FTD. A subset of frontotemporal dementia patients with TDP-43 pathology have loss of function mutations in the granulin gene (GRN) resulting in PGRN haplo-insufficiency. More than 75 different mutations in the granulin gene, all resulting in reduced PGRN levels and/or function, have been associated with FTD and it is believed that raising extracellular PGRN in plasma and brain would counteract the disease process.

[0007] PGRN mutations have also been linked with Alzheimer's disease (AD) (Sheng *et al.*, 2014, Gene. 2014 Jun 1;542(2):141-5; Brouwers et al., 2008, Neurology. 2008 Aug 26;71(9):656-64) suggesting that PGRN deficiency may play an important role in AD pathogenesis. Furthermore, neuroprotective effects of PGRN in mouse AD models have been observed (Minami et al, 2014, Nat Med. 2014 Oct;20(10):1157-64) providing support for the view that enhanced PGRN may be beneficial in AD and possibly other neurodegenerative conditions.

[0008] The present application describes the generation and identification of anti-human Sortilin antibodies which can regulate PGRN in cellular models and in mice. Those antibodies surprisingly bind to a region on Sortilin which is distant to the previously reported progranulin binding site, the so-called neurotensin-site, and yet are capable of increasing extracellular PGRN.

[0009] The inventors have defined six Sortilin binding regions and identified efficacious antibodies that bind a region ("region E"). These antibodies do not block PGRN binding to sortilin yet influence/increase PGRN levels suggesting a

novel mode of action for these antibodies. As PGRN has neuroprotective and anti-inflammatory effects, the inventors' findings indicate that such antibodies targeting Sortilin are likely to have a beneficial effect in the treatment of a range of neurodegenerative disorders including FTD/FTLD. A subgroup of FTD/FTLD patients with TDP-43 pathology carry a mutation in the gene encoding PGRN leading to PGRN haploinsufficiency. Sortilin antibodies are expected to counteract this PGRN deficiency and likely will have similar therapeutic benefits for patients suffering from other TDP-43 proteinopathies in which PGRN levels may influence TDP43-function and pathology, including ALS and in other neurodegenerative diseases in which increased PGRN function may be neuroprotective including AD.

Summary of invention

[0010] The inventors of the present invention have generated monoclonal antibodies which surprisingly bind to a novel Sortilin region denominated the "E-region" as defined in **SEQ ID NO:146** and is able to modulate the PGRN levels in the brain of a patient.

[0011] The invention also relates to a method of preventing or treating a disease associated with decreased PGRN levels in the brain of a patient, comprising administering an effective dosage of an antibody or an antigen-binding fragment thereof that binds to the E-region of Sortilin. These diseases include *i.a.* FTD, ALS and proteinopathies such as AD, PD.

Brief Description of the Drawings

Figure 1 illustrates steps in the selection of antibodies. A-E refer to the regions to which the respective Sortilin-binding antibodies were assigned based on shuffle constructs as described in **Example 1** and **SEQ ID Nos147-155** "Other" refers to an antibody which could not be assigned to one region, and which may bind at the interface between the A-and B-regions. Tet refers to antibodies binding also tetraodon-Sortilin.

Figure 2 shows the region assignment of antibodies based on binding to Sortilin shuffle constructs.

Panel A shows a linear illustration of the shuffle constructs used for region assignment of antibodies as described in **Example 1**. Sortilin shuffle constructs were generated based on the human Sortilin sequence (**SEQ ID NO:145**) (sections depicted in grey) in which amino acid residues were exchanged to the corresponding amino acid from the tetraodon Sortilin sequence (depicted in black) (**SEQ ID NO:149**) (**Examples 1-3**).

Panel B shows predicted structure of the shuffle constructs illustrated linearly in A. Dark residues indicate residues changed to the corresponding tetraodon sequence in the shuffle constructs.

Panel C illustrates the binding pattern of antibodies assigned to the D-region and the E region classes respectively. A "+" indicates binding to a given shuffle construct and a "-" indicates lack of binding. Based on the binding pattern to the different shuffle constructs, antibodies were assigned to regions. The resultant antibody region classes are indicated by A-E. For the illustrated D and E region antibodies, both bound the human sequences (all grey) as indicated by "+" and neither bound the tetraodon sequence (all black) as indicated by "-", whereas the E region antibody bound the hB45678 shuffle construct while the D Region antibody did not bind resulting in the localisation of binding as illustrated in Panel A. For E Region antibodies, binding to the following shuffle regions was observed: hsort, hB06-10, B12390, hB45678. The antibodies did not bind to hB01-05 and tetraodon constructs.

The antibodies did not bind to the fully tetraodon Sortilin protein, except two. The two antibodies capable of binding the tetraodon sequence were denoted "tet". "Other" refers to an antibody which could not be assigned to one region.

Figure 3 shows binding affinities of human E-domain antibodies. Binding affinities to sortilin constructs by bioLayer interferometry using Octet384RED as described in **example 2** (EC50, ng/ml). NB indicates No Binding. Values between 0.1-10ng/ml and >10 ng/ml indicate binding. Region assignment was based on binding patterns of the antibodies to different sortilin shuffle constructs (**Figure**

2). Lack of binding with sortilin construct hB01-05 and Tetra suggest these antibodies bind to E region.

Figure 4 shows cross-blocking between E-domain antibodies. Each antibody was bound to human wildtype Sortilin to form an antibody-sortilin complex. All other E domain antibodies were tested for binding to the preformed antibody-sortilin complex, **example 8**. Cross blocking between Sortilin antibodies from the same or different domains was determined by analyzing interference with antibody-Sortilin binding. Binding of antibodies to Sortilin-ECD-His was measured by BioLayer Interferometry using Octet 384RED as described previously. The left column indicates primary (immobilized) antibodies and the top row indicates the secondary antibodies (antibodies being tested against the immobilized antibodies). Binding of both the primary and secondary antibodies to Sortilin-ECD-His would results in a response value higher than 0.1 and indicate that both antibodies were binding to different regions of the protein. Response value less than 0.1 shows lack of binding of the secondary antibody and an effective cross blocking by the immobilized (primary) antibody, which suggests that both antibodies bind to the same region of Sortilin. 'x' indicates no binding and hence the antibodies block each other. 'b' indicates binding of both antibodies to sortilin and hence do not cross block each other.

22 out of 26 antibodies from E domain cross block all antibodies from the group and the remaining 4 antibodies cross block 20 out of 26 antibodies suggesting that most of the antibodies bind to the same region or in adjacent regions on sortilin.

Figure 5 shows the effect of Sortilin antibodies on extracellular PGRN in neuronal differentiated induced pluripotent stem cells (iPSCs) generated from an apparently heathy male (18 years). **(Example 9)**

Figure 6 shows plasma PGRN levels in human Sortilin Knock in (KI) mice treated with Sortilin human E-Domain binding antibody **(Example 10)**. Antibody #30 increases plasma PGRN levels as compared to isotype control antibody, anti-HEL, treated mice.

Mice were injected with 10mg/kg of the test antibodies by subcutaneous administration. They were sacrificed after 48hrs and blood samples were collected for analysis. Plasma PGRN was measured by ELISA. Data is presented as mean ± SD. Data was analysed by t-test. ***p<0.001

Figures 7A and B show the effects of Sortilin antibodies on extracellular PGRN in neuronal differentiated induced pluripotent stem cells (iPSCs) generated from an apparently heathy individual as well as from a PGRN R493X patient (**Example 11**)

Figure 8 (A-F) show representative peptides covering the conformational epitope of antibody 30. All of the shown peptides show a protection from exchange larger than 0.5D (**Example 12**).

Detailed Description Of The Invention

[0012] As used herein, the term “Sortilin” is synonymous with the Sortilin protein (identified in for example UniProt as Q99523, 1 and 2). The amino acid numbering of Sortilin is given with respect to **SEQ ID NO:145** as shown below, Methionine (M) being amino acid 1:

MERPWGAADG LSRWPHGLGL LLLQLLPPS TLSQDRLDAP PPPAAPLPRW
SGPIGVSWGL RAAAAGGAFP RGGRWRRSAP GEDEECGRVR DFVAKLANNT
HQHVFDDLRG SVSLSWVGDS TGVILVLTTF HVPLVIMTFG QSKLYRSEDY
GKNFKDITDL INNTFIRTEF GMAIGPENSG KVVLTAEVSG GSRGGRIFRS
SDFAKNFVQT DLPFHPLTQM MYSPQNSDYL LALSTENGLW VSKNFGGKWE
EIHKAVCLAK WGSDNTIFFT TYANGSCKAD LGALELWRTS DLGKSFKTIG
VKIYSFGLGG RFLFASVMAD KDTTRRIHVS TDQGDTWSMA QLPSVGQEQF

YSILAANDDM VFMHVDEPGD TGFGTIFTSD DRGIVYSKSL DRHLYTTTGG
ETDFTNVTSL RGVYITSVLS EDNSIQTMIT FDQGGRWTHL RKPENSECDA
TAKNKNECSL HIHASYSISQ KLNVPMAPLS EPNAVGIVIA HGSVGDAISV
MVPDVYISDD GGYSWTKMLE GPHYYTILDS GGIIVAIEHS SRPINVIKFS
TDEGQCWQTY TFTRDPIYFT GLASEPGARS MNISIWGFTE SFLTSQWVSY
TIDFKDILER NCEEKDYTIW LAHSTDPEDY EDGCILGYKE QFLRLRKSSV
CQNGRDYVVT KQPSICLCSL EDFLCDFGYY RPENDSKCVE QPELKGHDLE
FCLYGREEHL TTNGYRKIPG DKCQGGVNPV REVKDLKKKC TSNFLSPEKQ
NSKSNSVPII LAIVGLMLVT VVAGVLIVKK YVCGGRFLVH RYSVLQQHAE
ANGVDGVDAL DTASHTNKSG YHDDSDEDLLE

[0013] As used herein, the term “E Region” is intended to refer to the region on Sortilin (corresponding to residues 612-753 of **SEQ ID NO:145**) consisting of the amino acids in **SEQ ID NO:146** as shown below:

CEEKDYTIW LAHSTDPEDY EDGCILGYKEQFLRLRKSSVCQNGRDYVVT KQPSICLCSL ED-FLCDFGYY RPENDSKCVE QPELKGHDLEFCLYGREEHL TTNGYRKIPG DKCQGGVNPV REVKDLKKKC TSNFLSPEKQNSKSNS

[0014] For E region antibodies, binding to the following shuffle regions was observed: hsort, hB06-10, B12390, hB45678. The antibodies did not bind to hB01-05, and tetra.

[0015] PGRN gene (proepithelin, granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin) encodes a 68.5 kDa secreted glycoprotein that has 7.5 repeats of smaller granulin motifs, ranging from 6-25 kDa, which can be proteolytically cleaved from the precursor PGRN (He, Z. & Bateman, A., J. Mol. Med. 81:600-6X2 (2003)). In non- neuronal cells, PGRN has been associated with a variety of events, such as cell cycle regulation and cell motility (He, Z. & Bateman, A., J. Mol. Med. 57:600-612 (2003); Monami, G., et ah, Cancer Res. (5(5:7103-7110 (2006)), wound repair, inflammation (Zhu, J., et ah, Cell 777:867-878 (2002)), induction of growth factors such as vascular endothelial growth factor (VEGF) (Tangkeangsiπsin, W. & Serrero, G, Carcinogenesis 25.1587-1592 (2004)), and tumorigenesis (He, Z. & Bateman, A., J. Mol. Med. 81:600-612 (2003), Monami, G., *et al*., Cancer Res (5(5:7103-7110 (2006); Serrero, G., Biochem Biophys. Res. Commun. 505-409-413 (2003), Lu, R & Serrero, G., Proc. Natl Acad Sa U.SA 98 142-147 (2001); Liau, L M., et al., Cancer Res. 60:1353-1360 (2000)).

[0016] PGRN mutations result in haploinsufficiency (Baker, M., et ah, Nature 442:916-919 (2006); Cruts, M., et ah, Nature 442:920-924 (2006)) and are known to be present in nearly 50% of familial FTD cases, making PGRN mutation a major genetic contributor to FTD (Cruts, M. & Van Broeckhoven, C, Trends Genet. 24:186-194 (2008); Le Ber, I., et ah, Brain 129:3051- 3065 (2006)). The loss-of-function heterozygous character of PGRN mutations implies that in healthy individuals, PGRN expression plays a dose-dependent, critical role in protecting healthy individuals from the development of FTD.

[0017] The term "antibody" (Ab) in the context of the present invention refers to an immunoglobulin molecule or according to some embodiments of the invention, a fragment of an immunoglobulin molecule which has the ability to bind to an epitope of a molecule (“antigen”). Naturally occurring antibodies typically comprise a tetramer which is usually composed of at least two heavy (H) chains and at least two light (L) chains. Each heavy chain is comprised of a heavy chain variable domain (abbreviated herein as VH) and a heavy chain constant domain, usually comprised of three domains (CH1, CH2 and CH3). Heavy chains can be of any isotype, including IgG (IgG1, IgG2, IgG3 and IgG4 subtypes). Each light chain is comprised of a light chain variable domain (abbreviated herein as VL) and a light chain constant domain (CL). Light chains include kappa chains and lambda chains. The heavy and light chain variable domain is typically responsible for antigen recognition, while the heavy and light chain constant domain may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system. The VH and VL domains can be further subdivided into regions of hypervariability, termed “complementarity determining regions,” that are interspersed with domains of more conserved sequence, termed “framework regions” (FR). Each VH and VL is composed of three CDR Domains and four FR Domains arranged from amino-terminus to carboxy-terminus in the following order: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. The variable domains of the heavy and light chains contain a binding domain that interacts with an antigen. Of particular relevance are antibodies and their antigen-binding fragments that have been “isolated” so as to exist in a physical

milieu distinct from that in which it may occur in nature or that have been modified so as to differ from a naturally occurring antibody in amino acid sequence.

[0018] The term "epitope" means an antigenic determinant capable of specific binding to an antibody. Epitopes usually consist of surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and linear epitopes are distinguished in that the binding to the former, but not the latter, is always lost in the presence of denaturing solvents. The epitope may comprise amino acid residues directly involved in the binding and other amino acid residues, which are not directly involved in the binding, such as amino acid residues which are effectively blocked by the specifically antigen-binding peptide (in other words, the amino acid residue is within the footprint of the specifically antigen-binding peptide).

[0019] As used herein, the term “antigen-binding fragment of an antibody” means a fragment, portion, region or domain of an antibody (regardless of how it is produced (*e.g.*, via cleavage, recombinantly, synthetically, *etc.*)) that is capable of binding to an epitope, and thus the term “antigen-binding” is intended to mean the same as “epitope-binding” so that, for example, an “antigen-binding fragment of an antibody” is intended to be the same as an “epitope-binding fragment of an antibody”. An antigen-binding fragment may contain 1, 2, 3, 4, 5 or all 6 of the CDR Domains of such antibody and, although capable of binding to such epitope, may exhibit a specificity, affinity or selectivity toward such epitope that differs from that of such antibody. Preferably, however, an antigen-binding fragment will contain all 6 of the CDR Domains of such antibody. An antigen-binding fragment of an antibody may be part of, or comprise, a single polypeptide chain (*e.g.*, an scFv), or may be part of, or comprise, two or more polypeptide chains, each having an amino-terminus and a carboxyl terminus (*e.g.*, a diabody, a Fab fragment, a Fab_2 fragment, *etc.*). Fragments of antibodies that exhibit antigen-binding ability can be obtained, for example, by protease cleavage of intact antibodies. More preferably, although the two domains of the Fv fragment, VL and VH, are naturally encoded by separate genes, or polynucleotides that encode such gene sequences (*e.g.*, their encoding cDNA) can be joined, using

recombinant methods, by a flexible linker that enables them to be made as a single protein chain in which the VL and VH regions associate to form monovalent antigen-binding molecules (known as single-chain Fv (scFv); see e.g., Bird *et al.*, (1988) Science 242:423-426; and Huston *et al.* (1988) Proc. Natl. Acad. Sci. (U.S.A.) 85:5879-5883). Alternatively, by employing a flexible linker that is too short (*e.g.*, less than about 9 residues) to enable the VL and VH domains of a single polypeptide chain to associate together, one can form a bispecific antibody, diabody, or similar molecule (in which two such polypeptide chains associate together to form a bivalent antigen-binding molecule) (see for instance PNAS USA 90(14), 6444-8 (1993) for a description of diabodies). Examples of antigen-binding fragments encompassed within the present invention include (i) a Fab' or Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains, or a monovalent antibody as described in WO2007059782; (ii) F(ab')2 fragments, bivalent fragments comprising two Fab fragments linked by a disulfide bridge at the hinge domain; (iii) an Fd fragment consisting essentially of the VH and CH1 domains; (iv) a Fv fragment consisting essentially of a VL and VH domains, (v) a dAb fragment (Ward et al., Nature 341, 544-546 (1989)), which consists essentially of a VH domain and also called domain antibodies (Holt et al; Trends Biotechnol. 2003 Nov;2i(ll) :484-90); (vi) camelid or nanobodies (Revets et al; Expert Opin Biol Ther. 2005 Jan;5_(l): l ll-24) and (vii) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they may be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH domains pair to form monovalent molecules (known as single chain antibodies or single chain Fv (scFv), see for instance Bird et al., Science 242, 423-426 (1988) and Huston et al., PNAS USA 85, 5879-5883 (1988)). These and other useful antibody fragments in the context of the present invention are discussed further herein. It also should be understood that the term antibody, unless specified otherwise, also includes antibody-like polypeptides, such as chimeric antibodies and humanized antibodies, and antibody fragments retaining the ability to bind to the antigen (antigen-binding fragments) provided by any known technique, such as

enzymatic cleavage, peptide synthesis, and recombinant techniques. An antibody as generated can possess any isotype. As used herein, "isotype" refers to the immunoglobulin class (for instance IgG1, IgG2, IgG3 or IgG4) that is encoded by heavy chain constant domain genes. Such antibody fragments are obtained using conventional techniques known to those of skill in the art; suitable fragments capable of binding to a desired epitope may be readily screened for utility in the same manner as an intact antibody.

[0020] The term “bispecific antibody” refers to an antibody containing two independent antigen-binding fragments that each target independent targets. These targets can be epitopes present on different proteins or different epitopes present on the same target. Bispecific antibody molecules can be made using compensatory amino acid changes in the constant domains of the HCs of the parent monospecific bivalent antibody molecules. The resulting heterodimeric antibody contains one Fabs contributed from two different parent monospecific antibodies. Amino acid changes in the Fc domain leads to increased stability of the heterodimeric antibody with bispecificity that is stable over time. (Ridgway et al., Protein Engineering 9, 617-621 (1996), Gunasekaran et al., JBC 285, 19637-1(2010), Moore et al., MAB 3:6 546-557 (2011), Strop et al., JMB 420, 204-219 (2012), Metz et al., Protein Engineering 25:10 571-580 (2012), Labrijn et al., PNAS 110:113, 5145 -5150 (2013), Spreter Von Kreudenstein et al., MAB 5:5 646-654 (2013)). Bispecific antibodies can also include molecules that are generated using ScFv fusions. Two monospecific scfv are then independently joined to Fc domains able to form stable heterodimers to generate a single bispecific molecule (Mabry et al., PEDS 23:3 115-127 (2010). Bispecific molecules have dual binding capabilities.

[0021] An "anti-Sortilin antibody" or “Sortilin antibody” (used interchangeably herein, depending on the context wherein its written) is an antibody an antigen-binding fragment thereof which binds specifically to Sortilin, and especially to the Sortilin E Region, **SEQ ID NO:146**. An anti-Sortilin antibody that binds to the Sortilin E Region will usually bind to a conformational epitope or a linear epitope of 1, 2, 3, 4, 5, 6 or 7 consecutive amino acids within the E-Region with an affinity

(IC50) at or below 22 nM, such as between 22 nM and 1 nM, between 10 nM and 1 nM or between 5 nM and 1 nM or even higher such as about 1pM or 1 to 5 pM.

[0022] The term "human antibody" (which may be abbreviated to “humAb” or “HuMab”), as used herein, is intended to include antibodies having variable and constant domains derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or during gene rearrangement or by somatic mutation in vivo).

[0023] The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A conventional monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. In certain embodiments a monoclonal antibody can be composed of more than one Fab domain thereby increasing the specificity to more than one target. The terms "monoclonal antibody" or "monoclonal antibody composition" are not intended to be limited by any particular method of production (*e.g.*, recombinant, transgenic, hybridoma, etc.).

The term “antibody XX” is intended to denote an antibody or antigen-binding fragment thereof (for example antibody “6003-056”), comprising or consisting of the Light Chain, the Light Chain Variable domain, or the Light Chain Variable domain CDR1-3, as defined by its respective SEQ ID NO, and the Heavy Chain, Heavy Chain Variable Domain, or Heavy Chain Variable Domain CDR1-3 as defined by its respective SEQ ID NO. In certain embodiments the antibody or antigen-binding fragment thereof are defined by their entire Heavy Chain Variable Domain comprising as defined by their SEQ ID NO and their Light Chain Variable Domain as defined by their SEQ ID NO.

[0024] The numbering of amino acid residues can be performed by IMGT®, the international ImMunoGeneTics information system® or, Kabat, E. A., Wu, T. T., Perry, H. M., Gottesmann, K. S. & Foeller, C. (1991). Sequences of Proteins of Immunological Interest, 5th edit., NIH Publication no. 91-3242 U.S. Department of Health and Human Services; Chothia, C. & Lesk, A. M. (1987), or Canonical

structures For The Hypervariable domains Of Immunoglobulins. J. Mol. Biol. 196, 901-917.

[0025] As used herein, an antibody or an antigen-binding fragment thereof is said to "specifically" bind a region of another molecule (*i.e.*, an epitope) if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity or avidity with that epitope relative to alternative epitopes. In one embodiment, the antibody, or antigen-binding fragment thereof, of the invention binds at least 10-fold more strongly to its target (Sortilin) than to another molecule; preferably at least 50-fold more strongly and more preferably at least 100-fold more strongly. Preferably, the antibody, or antigen-binding fragment thereof, binds under physiological conditions, for example, *in vivo*. Thus, by "specifically binding to Sortilin", we include the ability of the antibody, or antigen-binding fragment thereof, to bind to Sortilin with such specificity and/or under such conditions. Methods suitable for determining such binding will be known to those skilled in the art, and exemplary methods are described in the accompanying Examples. As used herein, the term "binding" in the context of the binding of an antibody to a predetermined antigen typically refers to binding with an affinity corresponding to a KD of about 10^{-7} M or less, such as about 10^{-8} M or less, such as about 10^{-9} M or less when determined by for instance surface plasmon resonance (SPR) technology in either a BIAcore® 3000 or T200instrument using the antigen as the ligand and the antibody as the analyte, and binds to the predetermined antigen with an affinity corresponding to a KD that is at least ten-fold lower, such as at least 100 fold lower, for instance at least 1,000 fold lower, such as at least 10,000 fold lower, for instance at least 100,000 fold lower than its affinity for binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely-related antigen. The amount with which the affinity is lower is dependent on the KD of the antibody, so that when the KD of the antibody is very low (that is, the antibody is highly specific), then the amount with which the affinity for the antigen is lower than the affinity for a non-specific antigen may be at least 10,000 fold. In particular, the invention pertains to anti-Sortilin antibodies that exhibit a binding affinity corresponding to at or below 22 nM, such as between 22 nM and 1 nM, between 10 nM and 1 nM or between 5

nM and 1 nM, when determined by, for instance, bioLayer interferometry using an Octet 384RED (**Example 7**).

[0026] In certain embodiments of the invention the invention relates to an antibody or antigen-binding fragment thereof able to compete with humAb antibody 30 or humAb antibody 900 for binding to Sortilin. In another embodiment the invention relates to an antibody or antigen-binding fragment thereof that is able to compete with antibody 30 for binding to the E region of Sortilin as defined in **SEQ ID NO:146**. Such competitive binding inhibition can be determined using assays and methods well known in the art, for example using BIAcore® chips with immobilised human Sortilin and incubating with a reference antibody (such as antibody “30” or “900”) with and without an antibody polypeptide to be tested. Alternatively, a pair-wise mapping approach can be used, in which a reference antibody (such as antibody “30” or “900”) is immobilised to the surface of the BIAcore® chip, human Sortilin antigen is bound to the immobilised antibody, and then a second antibody is tested for simultaneous binding ability to human Sortilin (see ‘BIAcore® Assay Handbook’, GE Healthcare Life Sciences, 29-0194-00 AA 05/2012; the disclosures of which are incorporated herein by reference). Alternatively, use of Octet 384Red (Example 7 & 8) or a similar approach to demonstrate competitive binding.

[0027] The term "kd" (sec -1 or 1/s), as used herein, refers to the dissociation rate constant of a particular antibody-antigen interaction. Said value is also referred to as the koff value.

[0028] The term "ka" (M-1 x sec-1 or 1/Msec), as used herein, refers to the association rate constant of a particular antibody-antigen interaction.

[0029] The term "KD" (M), as used herein, refers to the dissociation equilibrium constant of a particular antibody-antigen interaction and is obtained by dividing the kd by the ka.

[0030] The term "KA" (M-1 or 1/M), as used herein, refers to the association equilibrium constant of a particular antibody-antigen interaction and is obtained by dividing the ka by the kd.

[0031] In one embodiment, the invention relates to an antibody, or antigen-binding fragment thereof, which exhibits one or more of the following properties:

(i) a binding affinity (K_D) for Sortilin of between 0.5-10 nM, such as 1-5 nM or 1-2 nM;

(ii) capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;

(iii) capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;

(iv) capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice.

[0032] The term "capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells" includes the ability to increase the concentration of PGRN in the medium by at least 20%, such as between 25% and 500%, between 25% and 400% or between 25% and 200% as measured by an ELISA assay as disclosed in **Example 9**.

[0033] The "capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice" includes the ability to increase the concentration of PGRN in the plasma by at least 25% but preferably between 50 and 500 percent as measured by an ELISA assay as disclosed in **Example 10**.

[0034] In some antibodies, only part of a CDR, namely the subset of CDR residues required for binding, termed the SDRs, are needed to retain binding in a humanized antibody. CDR residues not contacting the relevant epitope and not in the SDRs can be identified based on previous studies (for example residues H60-H65 in CDR H2 are often not required), from regions of Kabat CDRs lying outside Chothia hypervariable loops (see, Kabat *et al.* (1992) SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST, National Institutes of Health Publication No. 91-3242; Chothia, C. *et al.* (1987) "*Canonical Structures For The Hypervariable Regions Of Immunoglobulins*," J. Mol. Biol. 196:901-917), by molecular modeling and/or empirically, or as described in Gonzales, N.R. *et al.* (2004) "*SDR Grafting Of A Murine Antibody Using Multiple Human Germline Templates To Minimize Its Immunogenicity*," Mol. Immunol. 41:863-872. In such

humanized antibodies at positions in which one or more donor CDR residues is absent or in which an entire donor CDR is omitted, the amino acid occupying the position can be an amino acid occupying the corresponding position (by Kabat numbering) in the acceptor antibody sequence. The number of such substitutions of acceptor for donor amino acids in the CDRs to include reflects a balance of competing considerations. Such substitutions are potentially advantageous in decreasing the number of mouse amino acids in a humanized antibody and consequently decreasing potential immunogenicity. However, substitutions can also cause changes of affinity, and significant reductions in affinity are preferably avoided. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically.

[0035] The fact that a single amino acid alteration of a CDR residue can result in loss of functional binding (Rudikoff, S. *etc.* (1982) "*Single Amino Acid Substitution Altering Antigen-binding Spec*ificity," Proc. Natl. Acad. Sci. (USA) 79(6):1979-1983) provides a means for systematically identifying alternative functional CDR sequences. In one preferred method for obtaining such variant CDRs, a polynucleotide encoding the CDR is mutagenized (for example via random mutagenesis or by a site-directed method (*e.g.*, polymerase chain-mediated amplification with primers that encode the mutated locus)) to produce a CDR having a substituted amino acid residue. By comparing the identity of the relevant residue in the original (functional) CDR sequence to the identity of the substituted (non-functional) variant CDR sequence, the BLOSUM62.iij substitution score for that substitution can be identified. The BLOSUM system provides a matrix of amino acid substitutions created by analyzing a database of sequences for trusted alignments (Eddy, S.R. (2004) "*Where Did The BLOSUM62 Alignment Score Matrix Come From?*," Nature Biotech. 22(8):1035-1036; Henikoff, J.G. (1992) "Amino acid substitution matrices from protein blocks," Proc. Natl. Acad. Sci. (USA) 89:10915-10919; Karlin, S. *et al.* (1990) "*Methods For Assessing The Statistical Significance Of Molecular Sequence Features By Using General Scoring Schemes*," Proc. Natl. Acad. Sci. (USA) 87:2264-2268; Altschul, S.F. (1991) "*Amino Acid Substitution Matrices From An Information Theoretic Perspective*," J. Mol. Biol. 219, 555-565. Currently, the

most advanced BLOSUM database is the BLOSUM62 database (BLOSUM62.iij). **Table 1** presents the BLOSUM62.iij substitution scores (the higher the score the more conservative the substitution and thus the more likely the substitution will not affect function). If an antigen-binding fragment comprising the resultant CDR fails to bind to Sortilin, for example, then the BLOSUM62.iij substitution score is deemed to be insufficiently conservative, and a new candidate substitution is selected and produced having a higher substitution score. Thus, for example, if the original residue was glutamate (E), and the non-functional substitute residue was histidine (H), then the BLOSUM62.iij substitution score will be 0, and more conservative changes (such as to aspartate, asparagine, glutamine, or lysine) are preferred.

Table 1

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	+4	-1	-2	-2	0	-1	-1	0	-2	-1	-1	-1	-1	-2	-1	+1	0	-3	-2	0
R	-1	+5	0	-2	-3	+1	0	-2	0	-3	-2	+2	-1	-3	-2	-1	-1	-3	-2	-3
N	-2	0	+6	+1	-3	0	0	0	+1	-3	-3	0	-2	-3	-2	+1	0	-4	-2	-3
D	-2	-2	+1	+6	-3	0	+2	-1	-1	-3	-4	-1	-3	-3	-1	0	-1	-4	-3	-3
C	0	-3	-3	-3	+9	-3	-4	-3	-3	-1	-1	-3	-1	-2	-3	-1	-1	-2	-2	-1
Q	-1	+1	0	0	-3	+5	+2	-2	0	-3	-2	+1	0	-3	-1	0	-1	-2	-1	-2
E	-1	0	0	+2	-4	+2	+5	-2	0	-3	-3	+1	-2	-3	-1	0	-1	-3	-2	-2
G	0	-2	0	-1	-3	-2	-2	+6	-2	-4	-4	-2	-3	-3	-2	0	-2	-2	-3	-3
H	-2	0	+1	-1	-3	0	0	-2	+8	-3	-3	-1	-2	-1	-2	-1	-2	-2	+2	-3
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	+4	+2	-3	+1	0	-3	-2	-1	-3	-1	+3
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	+2	+4	-2	+2	0	-3	-2	-1	-2	-1	+1
K	-1	+2	0	-1	-3	+1	+1	-2	-1	-3	-2	+5	-1	-3	-1	0	-1	-3	-2	-2
M	-1	-1	-2	-3	-1	0	-2	-3	-2	+1	+2	-1	+5	0	-2	-1	-1	-1	-1	+1
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	+6	-4	-2	-2	+1	+3	-1
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	+7	-1	-1	-4	-3	-2
S	+1	-1	+1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	+4	+1	-3	-2	-2
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	+1	+5	-2	-2	0
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	+1	-4	-3	-2	+11	+2	-3
Y	-2	-2	-2	-3	-2	-1	-2	-3	+2	-1	-1	-2	-1	+3	-3	-2	-2	+2	+7	-1
V	0	-3	-3	-3	-1	-2	-2	-3	-3	+3	+1	-2	+1	-1	-2	-2	0	-3	-1	+4

[0036] The invention thus contemplates the use of random mutagenesis to identify improved CDRs. In the context of the present invention, conservative substitutions may be defined by substitutions within the classes of amino acids reflected in one or more of the following three tables:

Amino Acid Residue Classes For Conservative Substitutions:

Table 2

Acidic Residues	Asp (D) and Glu (E)
Basic Residues	Lys (K), Arg (R), and His (H)
Hydrophilic Uncharged Residues	Ser (S), Thr (T), Asn (N), and Gln (Q)

Aliphatic Uncharged Residues	Cly (G), Ala (A), Val (V), Leu (L), and Ile (I)
Non-polar Uncharged Residues	Cys (C), Met (M), and Pro (P)
Aromatic Residues	Phe (F), Tyr (Y), and Trp (W)

Alternative Conservative Amino Acid Residue Substitution Classes:

Table 3			
1	A	S	T
2	D	E	
3	N	Q	
4	R	K	
5	I	L	M
6	F	Y	W

Alternative Physical and Functional Classifications of Amino Acid Residues:

Table 4	
Alcohol Group-Containing Residues	S and T
Aliphatic Residues	I, L, V and M
Cycloalkenyl-Associated Residues	F, H, W and Y
Hydrophobic Residues	A, C, F, G, H, I, L, M, R, T, V, W and Y
Negatively Charged Residues	D and E
Polar Residues	C, D, E, H, K, N, Q, R, S and T
Positively Charged Residues	H, K and R
Small Residues	A, C, D, G, N, P, S, T and V
Very Small Residues	A, G and S
Residues Involved In Turn Formation	A, C, D, E, G, H, K, N, Q, R, S, P and T
Flexible Residues	Q, T, K, S, G, P, D, E and R

[0037] More conservative substitutions groupings include: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, and asparagine-glutamine.

[0038] Additional groups of amino acids may also be formulated using the principles described in, e.g., Creighton (1984) Proteins: Structure and Molecular Properties (2d Ed. 1993), W. H. Freeman and Company.

[0039] Phage display technology can alternatively be used to increase (or decrease) CDR affinity. This technology, referred to as affinity maturation, employs mutagenesis or "CDR walking" and re-selection uses the target antigen or an antigenic antigen-binding fragment thereof to identify antibodies having CDRs that bind with higher (or lower) affinity to the antigen when compared with the initial or parental antibody (See, *e.g.* Glaser *et al*. (1992) J. Immunology 149:3903). Mutagenizing entire codons rather than single nucleotides results in a semi-randomized repertoire of amino acid mutations. Libraries can be constructed consisting of a pool of variant clones each of which differs by a single amino acid alteration in a single CDR and which contain variants representing each possible amino acid substitution for each CDR residue. Mutants with increased (or decreased) binding affinity for the antigen can be screened by contacting the immobilized mutants with labeled antigen. Any screening method known in the art can be used to identify mutant antibodies with increased or decreased affinity to the antigen (*e.g.*, ELISA) (See Wu *et al*. 1998, Proc. Natl. Acad. Sci. (U.S.A.) 95:6037; Yelton *et al*., 1995, J. Immunology 155:1994). CDR walking which randomizes the Light Chain may be used possible (see, Schier *et al*., 1996, J. Mol. Bio. 263:551).

[0040] Methods for accomplishing such affinity maturation are described for example in: Krause, J.C. *et al*. (2011) "*An Insertion Mutation That Distorts Antibody Binding Site Architecture Enhances Function Of A Human Antibody*," MBio. 2(1) pii: e00345-10. doi: 10.1128/mBio.00345-10; Kuan, C.T. *et al*. (2010) "*Affinity-Matured Anti-Glycoprotein NMB Recombinant Immunotoxins Targeting Malignant Gliomas And Melanomas*," Int. J. Cancer 10.1002/ijc.25645; Hackel, B.J. *et al*. (2010) "*Stability And CDR Composition Biases Enrich Binder Functionality Landscapes*," J. Mol. Biol. 401(1):84-96; Montgomery, D.L. *et al*.

(2009) "*Affinity Maturation And Characterization Of A Human Monoclonal Antibody Against HIV-1 gp41*," MAntibodies 1(5):462-474; Gustchina, E. *et al.* (2009) "*Affinity Maturation By Targeted Diversification Of The CDR-H2 Loop Of A Monoclonal Fab Derived From A Synthetic Naïve Human Antibody Library And Directed Against The Internal Trimeric Coiled-Coil Of Gp41 Yields A Set Of Fantibodies With Improved HIV-1 Neutralization Potency And Breadth*," Virology 393(1):112-119; Finlay, W.J. *et al.* (2009) "*Affinity Maturation Of A Humanized Rat Antibody For Anti-RAGE Therapy: Comprehensive Mutagenesis Reveals A High Level Of Mutational Plasticity Both Inside And Outside The Complementarity-Determining Regions*," J. Mol. Biol. 388(3):541-558; Bostrom, J. *et al.* (2009) "*Improving Antibody Binding Affinity And Specificity For Therapeutic Development*," Methods Mol. Biol. 525:353-376; Steidl, S. *et al.* (2008) "*In Vitro Affinity Maturation Of Human GM-CSF Antibodies By Targeted CDR-Diversification*," Mol. Immunol. 46(1):135-144; and Barderas, R. *et al.* (2008) "*Affinity Maturation Of Antibodies Assisted By In Silico Modeling*," Proc. Natl. Acad. Sci. (USA) 105(26):9029-9034.

[0041] Thus, the sequence of CDR variants of encompassed antibodies or their antigen-binding fragments may differ from the sequence of the CDR of the parent antibody through substitutions; for instance substituted 4 amino acid residue, 3 amino acid residue, 2 amino acid residue or 1 of the amino acid residues. According to an embodiment of the invention it is furthermore envisaged that the amino acids in the CDR regions may be substituted with conservative substitutions, as defined in the above 3 tables.

[0042] The term "transgenic non-human animal" refers to a non-human animal having a genome comprising one or more human heavy and/or light chain transgenes or trans-chromosomes (either integrated or non-integrated into the animal's natural genomic DNA) and which is capable of expressing fully human antibodies. For example, a transgenic mouse can have a human light chain transgene and either a human heavy chain transgene or human heavy chain trans-chromosome, such that the mouse produces human anti-Sortilin antibody when immunized with Sortilin antigen and/or cells expressing Sortilin. The human heavy chain transgene may be integrated into the chromosomal DNA of the

mouse, as is the case for transgenic mice, for instance HuMAb mice, such as HCo7 or HCo12 mice, or the human heavy chain transgene may be maintained extra-chromosomally, as is the case for trans-chromosomal KM mice as described in WO02/43478. Such transgenic and trans-chromosomal mice (collectively referred to herein as "transgenic mice") are capable of producing multiple isotypes of human monoclonal antibodies to a given antigen (such as IgG, IgA, IgM, IgD and/or IgE) by undergoing V-D-J recombination and isotype switching.

[0043] Transgenic, nonhuman animals can also be used for production of antibodies against a specific antigen by introducing genes encoding such specific antibody, for example by operatively linking the antibody genes to a gene encoding a protein, which is expressed in the milk of the animal.

[0044] The term “treatment” or “treating” as used herein means ameliorating, slowing, attenuating or reversing the progress or severity of a disease or disorder, or ameliorating, slowing, attenuating or reversing one or more symptoms or side effects of such disease or disorder. For purposes of this invention, “treatment” or “treating” further means an approach for obtaining beneficial or desired clinical results, where “beneficial or desired clinical results” include, without limitation, alleviation of a symptom, diminishment of the extent of a disorder or disease, stabilized (i.e., not worsening) disease or disorder state, delay or slowing of the progression a disease or disorder state, amelioration or palliation of a disease or disorder state, and remission of a disease or disorder, whether partial or total detectable or undetectable.

[0045] An "effective amount," when applied to an antibody or antigen-binding fragment thereof of the invention, refers to an amount sufficient, at dosages and for periods of time necessary, to achieve an intended biological effect or a desired therapeutic result including, without limitation, clinical results. The phrase “therapeutically effective amount,” when applied to an antibody or antigen-binding fragment thereof of the invention, is intended to denote an amount of the antibody, or antigen-binding fragment thereof, that is sufficient to ameliorate, palliate, stabilize, reverse, slow, attenuate or delay the progression of a disorder or disease state, or of a symptom of the disorder or disease. In an embodiment,

the method of the present invention provides for administration of the antibody, or antigen-binding fragment thereof, in combinations with other compounds. In such instances, the "effective amount" is the amount of the combination sufficient to cause the intended biological effect.

[0046] A therapeutically effective amount of an anti-Sortilin antibody or antigen-binding fragment thereof of the invention may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the anti-Sortilin antibody or antigen-binding fragment thereof to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects.

[0047] The antibodies of the present invention are preferably a human or humanized antibody.

[0048] The numbering of amino acid residues in this region can be performed using for example IMGT®, the international ImMunoGeneTics information system® or, Kabat, E. A., Wu, T. T., Perry, H. M., Gottesmann, K. S. & Foeller, C. (1991). Sequences of Proteins of Immunological Interest, 5th edit., NIH Publication no. 91-3242 U.S. Department of Health and Human Services; Chothia, C. & Lesk, A. M. (1987), or Canonical structures For The Hypervariable domains Of Immunoglobulins. J. Mol. Biol. 196, 901-917.

Antibody 6003-028:

[0049] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

(a) a heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;

(b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:2**;

(c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;

(d) a light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;

(e) a light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and

(f) a light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.

[0050] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:109** and the light chain variable domain of **SEQ ID NO:110**.

Antibody 6003-056:

[0051] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:7;**
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:8**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:9**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:10**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:11**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:12**.

[0052] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:111** and the light chain variable domain of **SEQ ID NO:112**.

Antibody 6003-1286:

[0053] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:13**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:14**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:15**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:16**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:17**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:18**.

[0054] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:113** and the light chain variable domain of **SEQ ID NO:114**.

Antibody 6003-030:

[0055] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:19**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:20**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:21**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:22**;

e. a light chain variable domain CDR 2 comprising **SEQ ID NO:23**; and

f. a light chain variable domain CDR 3 comprising **SEQ ID NO:24**.

[0056] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:115** and the light chain variable domain of **SEQ ID NO:116**.

Antibody 6003-1277:

[0057] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:25**;

b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:26**;

c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:27**;

d. a light chain variable domain CDR 1 comprising **SEQ ID NO:28**;

e. a light chain variable domain CDR 2 comprising **SEQ ID NO:29**; and

f. a light chain variable domain CDR 3 comprising **SEQ ID NO:30**.

[0058] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:117** and the light chain variable domain of **SEQ ID NO:118**.

Antibody 6003-381:

[0059] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:31**;

b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:32**;

c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:33**;

d. a light chain variable domain CDR 1 comprising **SEQ ID NO:34**;

e. a light chain variable domain CDR 2 comprising **SEQ ID NO:35**; and

f. a light chain variable domain CDR 3 comprising **SEQ ID NO:36**.

[0060] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:119** and the light chain variable domain of **SEQ ID NO:120**.

Antibody 6003-083:

[0061] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:37**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:38**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:39**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:40**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:41**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:42**.

[0062] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:121** and the light chain variable domain of **SEQ ID NO:122**.

Antibody 6003-799:

[0063] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:43**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:44**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:45**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:46**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:47** and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:48**.

[0064] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:123** and the light chain variable domain of **SEQ ID NO:124**.

Antibody 6003-910:

[0065] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:49**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:50**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:51**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:52**;

e. a light chain variable domain CDR 2 comprising **SEQ ID NO:53**; and

f. a light chain variable domain CDR 3 comprising **SEQ ID NO:54**.

[0066] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:125** and the light chain variable domain of **SEQ ID NO:126**.

Antibody 6003-423:

[0067] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:55**;

b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:56**;

c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:57**;

d. a light chain variable domain CDR 1 comprising **SEQ ID NO:58**;

e. a light chain variable domain CDR 2 comprising **SEQ ID NO:59**; and

f. a light chain variable domain CDR 3 comprising **SEQ ID NO:60**.

[0068] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:127** and the light chain variable domain of **SEQ ID NO:128**.

Antibody 6003-822:

[0069] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:61**;

b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:62**;

c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:63**;

d. a light chain variable domain CDR 1 comprising **SEQ ID NO:64**;

e. a light chain variable domain CDR 2 comprising **SEQ ID NO:65**; and

f. a light chain variable domain CDR 3 comprising **SEQ ID NO:66**.

[0070] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:129** and the light chain variable domain of **SEQ ID NO:130**.

Antibody 6003-886:

[0071] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:67**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:68**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:69**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:70**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:71**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:72**.

[0072] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:131** and the light chain variable domain of **SEQ ID NO:132**.

Antibody 6003-072:

[0073] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:73**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:74**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:75**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:76**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:77**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:78**.

[0074] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:133** and the light chain variable domain of **SEQ ID NO:134**.

Antibody 6003-900:

[0075] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:79**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:80**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:81**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:82**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:83**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:84**.

[0076] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:135** and the light chain variable domain of **SEQ ID NO:136**.

Antibody 6003-936:

[0077] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:85**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:86**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:87**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:88**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:89**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:90**.

[0078] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:137** and the light chain variable domain of **SEQ ID NO:138**.

Antibody 6003-408:

[0079] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:91**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:92**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:93**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:94**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:95**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:96**.

[0080] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:139** and the light chain variable domain of **SEQ ID NO:140**.

Antibody 6003-471:

[0081] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:97**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:98**;

c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:99**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:100**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:101**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:102**.

[0082] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:141** and the light chain variable domain of **SEQ ID NO:142**.

Antibody 6003-972:

[0083] Accordingly, the invention relates to an antibody, or an antigen-binding fragment thereof, comprising or consisting of:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:103**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:104**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:105**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:106**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:107**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:108**.

[0084] Preferably, the monoclonal antibody may comprise or consist of the heavy chain variable domain of **SEQ ID NO:143** and the light chain variable domain of **SEQ ID NO:144**.

[0085] The antibodies mentioned above may, according to one embodiment, further comprise a variant with no more than 4 amino acid differences, or no more than 3 amino acid differences, or no more than 2 amino acid differences, or no more than 1 amino acid difference from said CDR1, CDR2, and/or CDR3 (HC and/or VC) sequences.

[0086] Further, the antibodies may be in a composition together with a pharmaceutically acceptable carrier. The antibodies of the invention may be used in therapy. In particular, the antibodies of the invention may be used in treating FTD or ALS or proteinopathies such as Alzheimer's Disease (AD).

[0087] The treatment envisioned by the present invention may be chronic and the patient may be treated at least 2 weeks, such as at least for 1 month, 6, months, 1 year or more.

[0088] The antibodies of the present invention may, for example, be monoclonal antibodies produced by the hybridoma method first described by Kohler et al., Nature 256, 495 (1975), or may be monoclonal antibodies produced by recombinant DNA or other methods. Monoclonal antibodies may also be isolated from phage antibody libraries using the techniques described in, for example, Clackson et al., Nature 352, 624-628 (1991) and Marks et al., J. Mol. Biol. 222, 581-597 (1991). Monoclonal antibodies may be obtained from any suitable source. Thus, for example, monoclonal antibodies may be obtained from hybridomas prepared from murine splenic B lymphocyte cells obtained from mice immunized with an antigen of interest, for instance, in the form of cells expressing the antigen on the surface, or a nucleic acid encoding an antigen of interest. Monoclonal antibodies may also be obtained from hybridomas derived from antibody-expressing cells of immunized humans or from non-human mammals such as rats, rabbits, dogs, sheep, goats, primates, etc.

[0089] In one embodiment, the antibody of the invention is a human antibody. Human monoclonal antibodies directed against Sortilin may be generated using transgenic or transchromosomal mice carrying parts of the human immune system rather than the mouse system. Such transgenic and trans-chromosomic mice include mice referred to herein as HuMAb mice and KM mice, respectively.

[0090] The HuMAb mouse contains a human immunoglobulin gene minilocus that encodes unrearranged human heavy variable and constant (μ and Y) and light variable and constant (κ) chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and K chain loci (Lonberg, N. et al., Nature 368, 856-859 (1994)). Accordingly, the mice exhibit reduced expression of mouse IgM or K and in response to immunization, the introduced human heavy and light chain transgenes, undergo class switching and somatic mutation to generate high affinity human IgG, κ monoclonal antibodies (Lonberg, N. et al. (1994), supra; reviewed in Lonberg, N., Handbook of Experimental Pharmacology 113, 49-101 (1994), Lonberg, N. and Huszar, D., Intern. Rev. Immunol. Vol. 13 65-93 (1995) and Harding, F. and Lonberg, N., Ann. N. Y. Acad. Sci 764 536-546 (1995)). The preparation of HuMAb mice is described in detail in Taylor, L. et al., Nucleic Acids Research 20, 6287-6295 (1992), Chen, J. et al.,

International Immunology 5, 647-656 (1993), Tuaillon et al., J. Immunol. 152, 2912-2920 (1994), Taylor, L. et al., International Immunology 6, 579-591 (1994), Fishwild, D. et al., Nature Biotechnology 14, 845-851 (1996). See also US 5,545,806, US 5,569,825, US 5,625,126, US 5,633,425, US 5,789,650, US 5,877,397, US 5,661,016, US 5,814,318, US 5,874,299, US 5,770,429, US 5,545,807, WO 98/24884, WO 94/25585, WO 93/1227, WO 92/22645, WO 92/03918 and WO 01/09187.

[0091] The HCo7, HCo12, HCo17 and HCo20 mice have a JKD disruption in their endogenous light chain (kappa) genes (as described in Chen et al., EMBO J. 12, 811-820 (1993)), a CMD disruption in their endogenous heavy chain genes (as described in **Example 1** of WO 01/14424), and a KCo5 human kappa light chain transgene (as described in Fishwild et al., Nature Biotechnology 14, 845-851 (1996)). Additionally, the HCo7 mice have a HCo7 human heavy chain transgene (as described in US 5,770,429), the HCo12 mice have a HCo12 human heavy chain transgene (as described in **Example 2** of WO 01/14424), the HCo17 mice have a HCo17 human heavy chain transgene (as described in **Example 2** of WO 01/09187) and the HCo20 mice have a HCo20 human heavy chain transgene. The resulting mice express human immunoglobulin heavy and kappa light chain transgenes in a background homozygous for disruption of the endogenous mouse heavy and kappa light chain loci.

[0092] In the KM mouse strain, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al., EMBO J. 12, 811-820 (1993) and the endogenous mouse heavy chain gene has been homozygously disrupted as described in **Example 1** of WO 01/09187. This mouse strain carries a human kappa light chain transgene, KCo5, as described in Fishwild et al., Nature Biotechnology 14, 845-851 (1996). This mouse strain also carries a human heavy chain transchromosome composed of chromosome 14 fragment hCF (SC20) as described in WO 02/43478. HCo12-Balb/c, HCo17-Balb/c and HCo20-Balb/c mice can be generated by crossing HCo12, HCo17 and HCo20 to KCo5[J/K](Balb) as described in WO 09/097006.

[0093] In the KM mouse strain, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al., EMBO J. 12,

811-820 (1993) and the endogenous mouse heavy chain gene has been homozygously disrupted as described in **Example 1** of WO 01/09187. This mouse strain carries a human kappa light chain transgene, KCo5, as described in Fishwild et al., Nature Biotechnology 14, 845-851 (1996). This mouse strain also carries a human heavy chain trans-chromosome composed of chromosome 14 antigen-binding fragment hCF (SC20) as described in WO 02/43478.

[0094] Splenocytes from these transgenic mice may be used to generate hybridomas that secrete human monoclonal antibodies according to well-known techniques. Human monoclonal or polyclonal antibodies of the present invention, or antibodies of the present invention originating from other species may also be generated transgenically through the generation of another non-human mammal or plant that is transgenic for the immunoglobulin heavy and light chain sequences of interest and production of the antibody in a recoverable form therefrom. In connection with the transgenic production in mammals, antibodies may be produced in, and recovered from, the milk of goats, cows, or other mammals. See for instance US 5,827,690, US 5,756,687, US 5,750,172 and US 5,741,957.

[0095] The antibody of the invention may be of any isotype. The choice of isotype typically will be guided by the desired effector functions, such as ADCC induction. Exemplary isotypes are IgG1, IgG2, IgG3, and IgG4. Either of the human light chain constant domains, kappa or lambda, may be used. If desired, the class of an anti-Sortilin antibody of the present invention may be switched by known methods. For example, an antibody of the present invention that was originally IgM may be class switched to an IgG antibody of the present invention. Further, class switching techniques may be used to convert one IgG subclass to another, for instance from IgGl to IgG2. Thus, the effector function of the antibodies of the present invention may be changed by isotype switching to, e.g., an IgG1, IgG2, IgG3, IgG4 antibody for various therapeutic uses. In one embodiment an antibody of the present invention is an IgG1 antibody, for instance an IgG1, κ. An antibody is said to be of a particular isotype if its amino acid sequence is most homologous to that isotype, relative to other isotypes.

[0096] In one embodiment, the antibody of the invention is a full-length antibody, preferably an IgG antibody, in particular an IgG1, κ antibody. In another embodiment, the antibody of the invention is an antibody antigen-binding fragment or a single-chain antibody.

[0097] Antibodies and antigen-binding fragments thereof may e.g. be obtained by antigen-binding fragmentation using conventional techniques, and antigen-binding fragments screened for utility in the same manner as described herein for whole antibodies. For example, F(ab')2 antigen-binding fragments may be generated by treating antibody with pepsin. The resulting F(ab')2 antigen-binding fragment may be treated to reduce disulfide bridges to produce Fab' antigen-binding fragments. Fab antigen-binding fragments may be obtained by treating an IgG antibody with papain; Fab' antigen-binding fragments may be obtained with pepsin digestion of IgG antibody. An F(ab') antigen-binding fragment may also be produced by binding Fab'-described below via a thioether bond or a disulfide bond. A Fab' antigen-binding fragment is an antibody antigen-binding fragment obtained by cutting a disulfide bond of the hinge domain of the $F(ab')_2$. A Fab'- antigen-binding fragment may be obtained by treating an $F(ab')_2$ antigen-binding fragment with a reducing agent, such as dithiothreitol. Antibody antigen-binding fragment may also be generated by expression of nucleic acids encoding such antigen-binding fragments in recombinant cells (see for instance Evans et al., J. Immunol. Meth. 184, 123-38 (1995)). For example, a chimeric gene encoding a portion of an F(ab')2 antigen-binding fragment could include DNA sequences encoding the CH1 domain and hinge domain of the H chain, followed by a translational stop codon to yield such a truncated antibody antigen-binding fragment molecule.

[0098] In one embodiment, the anti-Sortilin antibody is a monovalent antibody, preferably a monovalent antibody as described in WO2007059782 (which is incorporated herein by reference in its entirety) having a deletion of the hinge region. Accordingly, in one embodiment, the antibody is a monovalent antibody, wherein said anti-Sortilin antibody is constructed by a method comprising : i) providing a nucleic acid construct encoding the light chain of said monovalent antibody, said construct comprising a nucleotide sequence encoding

the VL region of a selected antigen specific anti-Sortilin antibody and a nucleotide sequence encoding the constant CL region of an Ig, wherein said nucleotide sequence encoding the VL region of a selected antigen specific antibody and said nucleotide sequence encoding the CL region of an Ig are operably linked together, and wherein, in case of an IgG1 subtype, the nucleotide sequence encoding the CL region has been modified such that the CL region does not contain any amino acids capable of forming disulfide bonds or covalent bonds with other peptides comprising an identical amino acid sequence of the CL region in the presence of polyclonal human IgG or when administered to an animal or human being; ii) providing a nucleic acid construct encoding the heavy chain of said monovalent antibody, said construct comprising a nucleotide sequence encoding the VH region of a selected antigen specific antibody and a nucleotide sequence encoding a constant CH region of a human Ig, wherein the nucleotide sequence encoding the CH region has been modified such that the region corresponding to the hinge region and, as required by the Ig subtype, other regions of the CH region, such as the CH3 region, does not comprise any amino acid residues which participate in the formation of disulphide bonds or covalent or stable non-covalent inter-heavy chain bonds with other peptides comprising an identical amino acid sequence of the CH region of the human Ig in the presence of polyclonal human IgG or when administered to an animal human being, wherein said nucleotide sequence encoding the VH region of a selected antigen specific antibody and said nucleotide sequence encoding the CH region of said Ig are operably linked together; iii) providing a cell expression system for producing said monovalent antibody; iv) producing said monovalent antibody by co-expressing the nucleic acid constructs of (i) and (ii) in cells of the cell expression system of (iii).

[0099] Similarly, in one embodiment, the anti-Sortilin antibody is a monovalent antibody, which comprises:

(i) a variable domain of an antibody of the invention as described herein or an antigen-binding part of the said domain, and

(ii) a CH domain of an immunoglobulin or a domain thereof comprising the CH2 and CH3 domains, wherein the CH domain or domain thereof has been modified such that the domain corresponding to the hinge domain and, if the immunoglobulin is not an IgG4 subtype, other domains of the CH domain, such as the CH3 domain, do not comprise any amino acid residues, which are capable of forming disulfide bonds with an identical CH domain or other covalent or stable non-covalent inter-heavy chain bonds with an identical CH domain in the presence of polyclonal human IgG.

[00100] In a further embodiment, the heavy chain of the monovalent antibody has been modified such that the entire hinge region has been deleted.

[00101] In another further embodiment, the sequence of the monovalent antibody has been modified so that it does not comprise any acceptor sites for N-linked glycosylation.

[00102] The invention also includes "Bispecific Antibodies," wherein an anti-Sortilin binding region (*e.g.*, a Sortilin-binding region of an anti-Sortilin monoclonal antibody) is part of a bivalent or polyvalent bispecific scaffold that targets more than one epitope, (for example a second epitope could comprise an epitope of an active transport receptor, such that the Bispecific Antibody would exhibit improved transcytosis across a biological barrier, such as the Blood Brain Barrier). Thus, in another further embodiment, the monovalent Fab of an anti-Sortilin antibody may be joined to an additional Fab or scfv that targets a different protein to generate a bispecific antibody. A bispecific antibody can have a dual function, for example a therapeutic function imparted by an anti-sortilin binding domain and a transport function that can bind to a receptor molecule to enhance transfer cross a biological barrier, such as the blood brain barrier.

[00103] Antibodies and antigen-binding fragments thereof of the invention also include single chain antibodies. Single chain antibodies are peptides in which the heavy and light chain Fv domains are connected. In one embodiment, the present invention provides a single-chain Fv (scFv) wherein the heavy and light chains in the Fv of an anti-Sortilin antibody of the present invention are joined with a flexible peptide linker (typically of about 10, 12, 15 or more amino acid residues) in a single peptide chain. Methods of producing such antibodies are described in for

instance US 4,946,778, Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994), Bird et al., Science 242, 423-426 (1988), Huston et al., PNAS USA 85, 5879-5883 (1988) and McCafferty et al., Nature 348, 552-554 (1990). The single chain antibody may be monovalent, if only a single VH and VL are used, bivalent, if two VH and VL are used, or polyvalent, if more than two VH and VL are used.

[00104] The antibodies and antigen-binding fragments thereof described herein may be modified by inclusion of any suitable number of modified amino acids and/or associations with such conjugated substituents. Suitability in this context is generally determined by the ability to at least substantially retain the Sortilin selectivity and/or Sortilin specificity associated with the non-derivatized parent anti-Sortilin antibody. The inclusion of one or more modified amino acids may be advantageous in, for example, increasing polypeptide serum half-life, reducing polypeptide antigenicity, or increasing polypeptide storage stability. Amino acid(s) are modified, for example, co-translationally or post-translationally during recombinant production (e.g., N-linked glycosylation at N-X-S/T motifs during expression in mammalian cells) or modified by synthetic means. Non-limiting examples of a modified amino acid include a glycosylated amino acid, a sulfated amino acid, a prenylated (e. g., farnesylated, geranyl-geranylated) amino acid, an acetylated amino acid, an acylated amino acid, a PEGylated amino acid, a biotinylated amino acid, a carboxylated amino acid, a phosphorylated amino acid, and the like. References adequate to guide one of skill in the modification of amino acids are replete throughout the literature. Example protocols are found in Walker (1998) Protein Protocols On CD-Rom, Humana Press, Totowa, NJ. The modified amino acid may, for instance, be selected from a glycosylated amino acid, a PEGylated amino acid, a farnesylated amino acid, an acetylated amino acid, a biotinylated amino acid, an amino acid conjugated to a lipid moiety, or an amino acid conjugated to an organic derivatizing agent.

[00105] The antibodies and antigen-binding fragments thereof of the invention, may also be chemically modified by covalent conjugation to a polymer to for instance increase their circulating half-life. Exemplary polymers, and methods to

attach them to peptides, are illustrated in for instance US 4,766,106; US 4,179,337; US 4,495,285 and US 4,609,546. Additional illustrative polymers include polyoxyethylated polyols and polyethylene glycol (PEG) (e.g., a PEG with a molecular weight of between about 1,000 and about 40,000, such as between about 2,000 and about 20,000, e.g., about 3,000-12,000 g/mol).

[00106] The antibodies and antigen-binding fragments thereof of the present invention may further be used in a diagnostic method or as a diagnostic imaging ligand.

[00107] In one embodiment, antibodies and antigen-binding fragments thereof of the invention comprising one or more radiolabeled amino acids are provided. A radiolabeled anti-Sortilin antibody may be used for both diagnostic and therapeutic purposes (conjugation to radiolabeled molecules is another possible feature). Non-limiting examples of such labels include, but are not limited to bismuth (^{213}Bi), carbon (^{11}C, ^{13}C, ^{14}C), chromium (^{51}Cr), cobalt (^{57}Co, ^{60}Co), copper (^{64}Cu), dysprosium (^{165}Dy), erbium (^{169}Er), fluorine (^{18}F), gadolinium (^{153}Gd, ^{159}Gd), gallium (^{68}Ga, ^{67}Ga), germanium (^{68}Ge), gold (^{198}Au), holmium (^{166}Ho), hydrogen (^{3}H), indium (^{111}In, ^{112}In, ^{113}In, ^{115}In), iodine (^{121}I, ^{123}I, ^{125}I, ^{131}I), iridium (^{192}Ir), iron (^{59}Fe), krypton (^{81m}Kr), lanthanium (^{140}La), lutelium (^{177}Lu), manganese (^{54}Mn), molybdenum (^{99}Mo), nitrogen (^{13}N, ^{15}N), oxygen (^{15}O), palladium (^{103}Pd), phosphorus (^{32}P), potassium (^{42}K), praseodymium (^{142}Pr), promethium (^{149}Pm), rhenium (^{186}Re, ^{188}Re), rhodium (^{105}Rh), rubidium (^{81}Rb, ^{82}Rb), ruthenium (^{82}Ru, ^{97}Ru), samarium (^{153}Sm), scandium (^{47}Sc), selenium (^{75}Se), sodium (^{24}Na), strontium (^{85}Sr, ^{89}Sr, ^{92}Sr), sulfur (^{35}S), technetium (^{99}Tc), thallium (^{201}Tl), tin (^{113}Sn, ^{117}Sn), xenon (^{133}Xe), ytterbium (^{169}Yb, ^{175}Yb, ^{177}Yb), yttrium (^{90}Y) and zinc (^{65}Zn). Methods for preparing radiolabeled amino acids and related peptide derivatives are known in the art (see for instance Junghans et al., in Cancer Chemotherapy and Biotherapy 655-686 (2nd edition, Chafner and Longo, eds., Lippincott Raven (1996)) and US 4,681,581, US 4,735,210, US 5,101,827, US 5,102,990 (US RE35,500), US 5,648,471 and US 5,697,902. For example, a radioisotope may be conjugated by a chloramine T method (Lindegren, S. *et al.* (1998) "*Chloramine-T In High-Specific-Activity Radioiodination Of Antibodies Using N-Succinimidyl-3-*

(Trimethylstannyl)Benzoate As An Intermediate," Nucl. Med. Biol. 25(7):659-665; Kurth, M. *et al.* (1993) "*Site-Specific Conjugation Of A Radioiodinated Phenethylamine Derivative To A Monoclonal Antibody Results In Increased Radioactivity Localization In Tumor*," J. Med. Chem. 36(9):1255-1261; Rea, D.W. *et al.* (1990) "Site-specifically radioiodinated antibody for targeting tumors," Cancer Res. 50(3 Suppl):857s-861s).

[00108] The invention also provides anti-Sortilin antibodies and antigen-binding fragments thereof that are detectably labeled using a fluorescent label (such as a rare earth chelate (*e.g.*, a europium chelate)), a fluorescein-type label (*e.g.*, fluorescein, fluorescein isothiocyanate, 5-carboxyfluorescein, 6-carboxy fluorescein, dichlorotriazinylamine fluorescein), a rhodamine-type label (*e.g.*, ALEXA FLUOR® 568 (Invitrogen), TAMRA® or dansyl chloride), VIVOTAG 680 XL FLUOROCHROME™ (Perkin Elmer), phycoerythrin; umbelliferone, Lissamine; a cyanine; a phycoerythrin, Texas Red, BODIPY FL-SE® (Invitrogen) or an analogue thereof, all of which are suitable for optical detection. Chemiluminescent labels may be employed (*e.g.*, luminol, luciferase, luciferin, and aequorin). Such diagnosis and detection can also be accomplished by coupling the diagnostic molecule of the present invention to detectable substances including, but not limited to, various enzymes, enzymes including, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase, or to prosthetic group complexes such as, but not limited to, streptavidin/biotin and avidin/biotin.

[00109] Chemiluminescent labels may be employed (*e.g.*, luminol, luciferase, luciferin, and aequorin). Such diagnosis and detection can also be accomplished by coupling the diagnostic molecule of the present invention to detectable substances including, but not limited to, various enzymes, enzymes including, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase, or to prosthetic group complexes such as, but not limited to, streptavidin/biotin and avidin/biotin. Paramagnetic labels can also be employed, and are preferably detected using Positron Emission Tomography (PET) or Single-Photon Emission Computed Tomography (SPECT). Such paramagnetic labels include, but are not limited to compounds containing

paramagnetic ions of Aluminum (Al), Barium (Ba), Calcium (Ca), Cerium (Ce), Dysprosium (Dy), Erbium (Er), Europium (Eu), Gandolinium (Gd), Holmium (Ho), Iridium (Ir), Lithium (Li), Magnesium (Mg), Manganese (Mn), Molybdenum (M), Neodymium (Nd), Osmium (Os), Oxygen (O), Palladium (Pd), Platinum (Pt), Rhodium (Rh), Ruthenium (Ru), Samarium (Sm), Sodium (Na), Strontium (Sr), Terbium (Tb), Thulium (Tm), Tin (Sn), Titanium (Ti), Tungsten (W), and Zirconium (Zi), and particularly, Co^{+2}, CR^{+2}, Cr^{+3}, Cu^{+2}, Fe^{+2}, Fe^{+3}, Ga^{+3}, Mn^{+3}, Ni^{+2}, Ti^{+3}, V^{+3}, and V^{+4}, positron emitting metals using various positron emission tomographies, and non-radioactive paramagnetic metal ions.

[00110] Thus in one embodiment the anti-Sortilin antibody or Sortilin-binding fragment thereof of the invention may be labelled with a fluorescent label, a chemiluminescent label, a paramagnetic label, a radioisotopic label or an enzyme label. The labelled antibody of fragment may be used in detecting or measuring the presence or amount of said Sortilin in the brain of a subject. This method may comprise the detection or measurement of in vivo imaging of anti-Sortilin antibody or Sortilin-binding fragment bound to said Sortilin and may comprises ex vivo imaging of said anti-Sortilin antibody or Sortilin-binding fragment bound to such Sortilin.

[00111] In a further aspect, the invention relates to an expression vector encoding one or more polypeptide chains of an antibody of the invention or an antigen-binding-domain thereof. Such expression vectors may be used for recombinant production of the antibodies and antigen-binding fragments of the invention.

[00112] An expression vector in the context of the present invention may be any suitable DNA or RNA vector, including chromosomal, non-chromosomal, and synthetic nucleic acid vectors (a nucleic acid sequence comprising a suitable set of expression control elements). Examples of such vectors include derivatives of SV40, bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA, and viral nucleic acid (RNA or DNA) vectors. In one embodiment, an anti-Sortilin antibody-encoding nucleic acid is comprised in a naked DNA or RNA vector, including, for example, a linear expression element (as described in, for instance, Sykes and Johnston,

Nat Biotech 12, 355-59 (1997)), a compacted nucleic acid vector (as described in for instance US 6,077,835 and/or WO 00/70087), a plasmid vector such as pBR322, pUC 19/18, or pUC 118/119, a "midge" minimally-sized nucleic acid vector (as described in, for instance, Schakowski et al., Mol Ther 3, 793-800 (2001)), or as a precipitated nucleic acid vector construct, such as a $CaPO_4$-precipitated construct (as described in, for instance, WO 00/46147, Benvenisty and Reshef, PNAS USA 83, 9551-55 (1986), Wigler et al., Cell 14, 725 (1978), and Coraro and Pearson, Somatic Cell Genetics 2, 603 (1981)). Such nucleic acid vectors and the usage thereof are well known in the art (see for instance US 5,589,466 and US 5,973,972).

[00113] In one embodiment, the vector is suitable for expression of anti-Sortilin antibodies or antigen-binding fragments thereof in a bacterial cell. Examples of such vectors include expression vectors such as BlueScript (Stratagene), pIN vectors (Van Heeke & Schuster, J Biol Chem 264, 5503-5509 (1989), pET vectors (Novagen, Madison, WI) and the like).

[00114] An expression vector may also or alternatively be a vector suitable for expression in a yeast system. Any vector suitable for expression in a yeast system may be employed. Suitable vectors include, for example, vectors comprising constitutive or inducible promoters such as alpha factor, alcohol oxidase and PGH (reviewed in: F. Ausubel *et al.*, ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley InterScience New York (1987), Grant *et al.*, Methods in Enzymol 153, 516-544 (1987), Mattanovich, D. *et al.* Methods Mol. Biol. 824, 329-358 (2012), Celik, E. *et al.* Biotechnol. Adv. 30(5), 1108-1118 (2012), Li, P. *et al.* Appl. Biochem. Biotechnol. 142(2), 105-124 (2007), Böer, E. *et al.* Appl. Microbiol. Biotechnol. 77(3), 513-523 (2007), van der Vaart, J.M. Methods Mol. Biol. 178, 359-366 (2002), and Holliger, P. Methods Mol. Biol. 178, 349-357 (2002)).

[00115] In an expression vector of the invention, anti-Sortilin antibody-encoding nucleic acids may comprise or be associated with any suitable promoter, enhancer, and other expression-facilitating elements. Examples of such elements include strong expression promoters (e. g., human CMV IE promoter/enhancer as well as RSV, SV40, SL3-3, MMTV, and HIV LTR

promoters), effective poly (A) termination sequences, an origin of replication for plasmid product in E. coli, an antibiotic resistance gene as selectable marker, and/or a convenient cloning site (e.g., a polylinker). Nucleic acids may also comprise an inducible promoter as opposed to a constitutive promoter such as CMV IE (the skilled artisan will recognize that such terms are actually descriptors of a degree of gene expression under certain conditions).

[00116] In an even further aspect, the invention relates to a recombinant eukaryotic or prokaryotic host cell, such as a transfectoma, which produces an antibody or antigen-binding fragment thereof of the invention as defined herein or a bispecific molecule of the invention as defined herein. Examples of host cells include yeast, bacteria, and mammalian cells, such as CHO or HEK cells. For example, in one embodiment, the present invention provides a cell comprising a nucleic acid stably integrated into the cellular genome that comprises a sequence coding for expression of an anti-Sortilin antibody of the present invention or an antigen-binding fragment thereof. In another embodiment, the present invention provides a cell comprising a non-integrated nucleic acid, such as a plasmid, cosmid, phagemid, or linear expression element, which comprises a sequence coding for expression of an anti-Sortilin antibody or antigen-binding fragment thereof of the invention.

[00117] In a further aspect, the invention relates to a method for producing an anti-Sortilin antibody of the invention, said method comprising the steps of a) culturing a hybridoma or a host cell of the invention as described herein above, and b) purifying the antibody of the invention from the culture media.

[00118] In one embodiment, the invention relates to a preparation that, as such term is used herein, comprises an anti-Sortilin antibody as defined herein, and that is substantially free of naturally-arising antibodies that are either not capable of binding to sortilin or that do not materially alter the anti-Sortilin functionality of the preparation. Thus, such a preparation does not encompass naturally-arising serum, or a purified derivative of such serum, that comprises a mixture of an anti-Sortilin antibody and another antibody that does not alter the functionality of the anti-Sortilin antibody of the preparation, wherein such functionality is:

(i) a binding affinity (K_D) for Sortilin;

(ii) a;

(iii) a capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;

(iv) a capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;

(v) a capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice; a capability to increase the amount and/or concentration of PGRN in the brain and/or

(vi) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS).

[00119] The invention particularly relates to preparations of such an anti-Sortilin antibody having a structural change in its amino acid sequence (in any of its CDRs, variable domains, framework residues and/or constant domains) relative to the structure of a naturally-occurring anti-Sortilin antibody, wherein said structural change causes the anti-Sortilin antibody monoclonal antibody to exhibit a markedly altered functionality (i.e., more than a 20% difference, more than a 40% difference, more than a 60% difference, more than an 80% difference, more than a 100% difference, more than a 150% difference, more than a 2-fold difference, more than a 4-fold difference, more than a 5-fold difference, or more than a 10-fold difference in functionality) relative to the functionality exhibited by said naturally-occurring anti-Sortilin antibody; wherein such functionality is:

(i) a binding affinity (K_D) for Sortilin;

(ii) a capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;

(iii) a capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;

(iv) a capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice;

(v) a capability to increase the amount and/or concentration of PGRN in the brain and/or

(vi) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and/or Alzheimer's Disease (AD).

especially wherein such altered functionality is a result of the structural change and thus is inseparable from it.

[00120] The term "substantially free" of naturally-arising antibodies refers to the complete absence of such naturally-arising antibodies in such preparations, or of the inclusion of a concentration of such naturally-arising antibodies in such preparations that does not materially affect the Sortilin-binding properties of the preparations. An antibody is said to be "isolated" if it has no naturally-arising counterpart or has been separated or purified from components which naturally accompany it.

[00121] The term "naturally-arising antibodies," as it relates to such preparations, refers to antibodies (including naturally-arising autoantibodies) elicited within living humans or other animals, as a natural consequence to the functioning of their immune systems.

[00122] Thus, the preparations of the present invention do not exclude, and indeed explicitly encompass, such preparations that contain an anti-Sortilin antibody and a deliberately added additional antibody capable of binding to an epitope that is not possessed by Sortilin. Such preparations particularly include embodiments thereof wherein the preparation exhibits enhanced efficacy in treating frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS).

[00123] The antibodies of antigen-binding fragments thereof of the present invention may be produced in different cell lines, such as a human cell line, a mammal non-human cell line, and insect cell line, for example a CHO cell line, HEK cell line, BHK-21 cell line, murine cell line (such as a myeloma cell line), fibrosarcoma cell line, PER.C6 cell line, HKB-11 cell line, CAP cell line and HuH-7 human cell line (Dumont et al, 2015, Crit Rev Biotechnol. Sep 18:1-13., the contents which is included herein by reference).

[00124] In an even further aspect, the invention relates to a pharmaceutical composition comprising:

(i) an anti-Sortilin antibody or antigen-binding fragment thereof, both as defined herein, or a preparation, as such term is defined herein, that comprises such an anti-Sortilin antibody or antigen-binding fragment thereof; and

(ii) a pharmaceutically-acceptable carrier.

[00125] The pharmaceutical compositions may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 22nd Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 2013.

[00126] The pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients should be suitable for the chosen compound of the present invention and the chosen mode of administration. Suitability for carriers and other components of pharmaceutical compositions is determined based on the lack of significant negative impact on the desired biological properties of the chosen compound or pharmaceutical composition of the present invention (e.g., less than a substantial impact (10% or less relative inhibition, 5% or less relative inhibition, etc.)) on epitope binding.

[00127] A pharmaceutical composition of the present invention may also include diluents, fillers, salts, buffers, detergents (e.g., a non-ionic detergent, such as Tween-20 or Tween- 80), stabilizers (e.g., sugars or protein-free amino acids), preservatives, tissue fixatives, solubilizers, and/or other materials suitable for inclusion in a pharmaceutical composition. The diluent is selected to not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, or non-toxic, nontherapeutic, non-immunogenic stabilizers and the like. The compositions may also include large, slowly metabolized macromolecules, such as proteins, polysaccharides like chitosan, polylactic acids, polyglycolic acids and copolymers (e.g., latex functionalized sepharose, agarose, cellulose, and the like), polymeric amino acids, amino acid copolymers, and lipid aggregates (e.g., oil droplets or liposomes).

[00128] The actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[00129] The pharmaceutical composition may be administered by any suitable route and mode, including: parenteral, topical, oral or intranasal means for prophylactic and/or therapeutic treatment. In one embodiment, a pharmaceutical composition of the present invention is administered parenterally. The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and include epidermal, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, intratendinous, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, intracranial, intrathoracic, epidural and intrasternal injection and infusion. Additional suitable routes of administering a compound of the present invention in vivo and in vitro are well known in the art and may be selected by those of ordinary skill in the art. In one embodiment that pharmaceutical composition is administered by intravenous or subcutaneous injection or infusion.

[00130] Pharmaceutically acceptable carriers include any and all suitable solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonicity agents, antioxidants and absorption delaying agents, and the like that are physiologically compatible with a compound of the present invention.

[00131] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the present invention include water, saline, phosphate buffered saline, ethanol, dextrose, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, corn oil, peanut oil, cottonseed oil, and sesame oil, carboxymethyl cellulose colloidal solutions, tragacanth gum and injectable organic esters, such as ethyl oleate, and/or various buffers. Other carriers are well known in the pharmaceutical arts.

[00132] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the present invention is contemplated.

[00133] Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00134] Pharmaceutical compositions of the present invention may also comprise pharmaceutically acceptable antioxidants for instance (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha- tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[00135] Pharmaceutical compositions of the present invention may also comprise isotonicity agents, such as sugars, polyalcohols, such as mannitol, sorbitol, glycerol or sodium chloride in the compositions.

[00136] The pharmaceutical compositions of the present invention may also contain one or more adjuvants appropriate for the chosen route of administration such as preservatives, wetting agents, emulsifying agents, dispersing agents,

preservatives or buffers, which may enhance the shelf life or effectiveness of the pharmaceutical composition. The compounds of the present invention may be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Such carriers may include gelatin, glyceryl monostearate, glyceryl distearate, biodegradable, biocompatible polymers such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid alone or with a wax, or other materials well known in the art. Methods for the preparation of such formulations are generally known to those skilled in the art. See, e.g., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

[00137] In one embodiment, the compounds of the present invention may be formulated to ensure proper distribution in vivo. Pharmaceutically acceptable carriers for parenteral administration include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the present invention is contemplated. Supplementary active compounds may also be incorporated into the compositions.

[00138] Pharmaceutical compositions for injection must typically be sterile and stable under the conditions of manufacture and storage. The composition may be formulated as a solution, micro-emulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier may be an aqueous or non-aqueous solvent or dispersion medium containing for instance water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many

cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as glycerol, mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions may be brought about by including in the composition an agent that delays antibody absorption, for example, monostearate salts and gelatin. Sterile injectable solutions may be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients e.g. as enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients e.g. from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, examples of methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00139] Sterile injectable solutions may be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, examples of methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00140] Dosage regimens in the above methods of treatment and uses described herein are adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. Parenteral compositions may be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers

to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the present invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

[00141] The effective dosages and the dosage regimens for the anti-Sortilin antibodies depend on the disease or condition to be treated and may be determined by the persons skilled in the art. An exemplary, non-limiting range for a therapeutically effective amount of an antibody of the present invention is about 0.1-10 mg/kg/body weight, such as about 0.1-5 mg/kg/body weight, for example about 0.1-2 mg/kg/body weight, such as about 0.1-1 mg/kg/body weight, for instance about 0.15, about 0.2, about 0.5, about 1, about 1.5 or about 2 mg/kg/body weight.

[00142] A physician or veterinarian having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the anti-Sortilin antibody employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, a suitable daily dose of a composition of the present invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Administration may e.g. be intravenous, intramuscular, intraperitoneal, or subcutaneous, and for instance administered proximal to the site of the target. If desired, the effective daily dose of a pharmaceutical composition may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. While it is possible for a compound of the present invention to be

administered alone, it is preferable to administer the compound as a pharmaceutical composition as described above.

[00143] The labelled antibodies or antigen-binding fragments thereof of the invention can be used for diagnostic purposes to detect, diagnose, or monitor diseases or disorders. The invention provides for the detection or diagnosis of a neurodegenerative or cognitive disease or disorder, including but not limited to FTD, ALS or - proteinopathies such as Alzheimer's Disease (AD), comprising: (a) assaying the existence of pyroglutamated Aβ fragments in cells or tissue samples of a subject using one or more antibodies that specifically bind to Sortilin; and (b) comparing the level of the antigen with a control level, e.g. levels in normal tissue samples, whereby an increase in the assayed level of antigen compared to the control level of antigen is indicative of the disease or disorder, or indicative of the severity of the disease or disorder.

[00144] The antibodies or antigen-binding fragments thereof of the invention can be used to assay Sortilin or antigen-binding fragments of Sortilin in a biological sample using immuno-histochemical methods well-known in the art. Other antibody-based methods useful for detecting protein include immunoassays such as the enzyme linked immunoassay (ELISA) and the radioimmunoassay assay (RIA) and mesoscale discovery platform based assays (MSD). Suitable antibody labels may be used in such kits and methods, and labels known in the art include enzyme labels, such as alkaline phosphatase and glucose oxidase; radioisotope labels, such as iodine (^{125}I, ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{121}In), and technetium (^{99m}Tc); and luminescent labels, such as luminol and luciferase; and fluorescent labels, such as fluorescein and rhodamine.

[00145] The presence of labeled anti-Sortilin antibodies or their Sortilin-binding fragments may be detected in vivo for diagnostic purposes. In one embodiment, diagnosis comprises: a) administering to a subject an effective amount of such labeled molecule; b) waiting for a time interval following administration to allow the labeled molecule to concentrate at sites (if any) of Aβ deposition and to allow for unbound labeled molecule to be cleared to background level; c) determining a background level; and d) detecting the labeled molecule in the subject, such

that detection of labeled molecule above the background level is indicative that the subject has the disease or disorder, or is indicative of the severity of the disease or disorder. In accordance with such embodiment, the molecule is labeled with an imaging moiety suitable for detection using a particular imaging system known to those skilled in the art. Background levels may be determined by various methods known in the art, including comparing the amount of labeled antibody detected to a standard value previously determined for a particular imaging system. Methods and systems that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as positron emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[00146] In a further aspect, the invention relates to an antibody, or antigen-binding fragment thereof, of the invention, for use in medicine.

[00147] In a further aspect, the invention relates to an antibody, or antigen-binding fragment thereof, of the invention, for use in treating a disease associated with decreased PGRN levels in the brain of a patient,

[00148] In a further aspect, the invention relates to the use of the antibody, or antigen-binding fragment thereof, of the invention, in the manufacture of a medicament for treating a disease associated with decreased PGRN levels in the brain of a patient,

[00149] In a further aspect, the invention relates to a method of preventing or treating a disease associated with decreased PGRN or decreased functional PGRN levels in the brain of a patient, comprising administering an effective dosage of an antibody of the invention, or an antigen-binding fragment thereof.

[00150] It is preferred that in the uses and methods of those aspects of the invention the disease is: FTD; ALS; or proteinopathies, such as AD.

[00151] Preferably, in the uses and methods of those aspects of the invention, the treatment is chronic, and is preferably for at least 2 weeks, such as at least for 1 month, 6, months, 1 year or more.

[00152] In a further aspect, the invention provides a kit comprising the antibody, or antigen-binding fragment thereof, of the invention.

Table 5 - Sequences

Antibody	**6003-028**			
Seq ID No	1	CDR	1	Heavy Chain
Seq ID No	2	CDR	2	Heavy Chain
Seq ID No	3	CDR	3	Heavy Chain
Seq ID No	4	CDR	1	Light Chain
Seq ID No	5	CDR	2	Light Chain
Seq ID No	6	CDR	3	Light Chain
Antibody	**6003-056**			
Seq ID No	7	CDR	1	Heavy Chain
Seq ID No	8	CDR	2	Heavy Chain
Seq ID No	9	CDR	3	Heavy Chain
Seq ID No	10	CDR	1	Light Chain
Seq ID No	11	CDR	2	Light Chain
Seq ID No	12	CDR	3	Light Chain
Antibody	**6003-1286**			
Seq ID No	13	CDR	1	Heavy Chain
Seq ID No	14	CDR	2	Heavy Chain
Seq ID No	15	CDR	3	Heavy Chain
Seq ID No	16	CDR	1	Light Chain
Seq ID No	17	CDR	2	Light Chain
Seq ID No	18	CDR	3	Light Chain
Antibody	**6003-030**			
Seq ID No	19	CDR	1	Heavy Chain
Seq ID No	20	CDR	2	Heavy Chain
Seq ID No	21	CDR	3	Heavy Chain
Seq ID No	22	CDR	1	Light Chain
Seq ID No	23	CDR	2	Light Chain
Seq ID No	24	CDR	3	Light Chain
Antibody	**6003-1277**			
Seq ID No	25	CDR	1	Heavy Chain
Seq ID No	26	CDR	2	Heavy Chain

Seq ID No	27	CDR	3	Heavy Chain
Seq ID No	28	CDR	1	Light Chain
Seq ID No	29	CDR	2	Light Chain
Seq ID No	30	CDR	3	Light Chain
Antibody	**6003-381**			
Seq ID No	31	CDR	1	Heavy Chain
Seq ID No	32	CDR	2	Heavy Chain
Seq ID No	33	CDR	3	Heavy Chain
Seq ID No	34	CDR	1	Light Chain
Seq ID No	35	CDR	2	Light Chain
Seq ID No	36	CDR	3	Light Chain
Antibody	**6003-083**			
Seq ID No	37	CDR	1	Heavy Chain
Seq ID No	38	CDR	2	Heavy Chain
Seq ID No	39	CDR	3	Heavy Chain
Seq ID No	40	CDR	1	Light Chain
Seq ID No	41	CDR	2	Light Chain
Seq ID No	42	CDR	3	Light Chain
Antibody	**6003-799**			
Seq ID No	43	CDR	1	Heavy Chain
Seq ID No	44	CDR	2	Heavy Chain
Seq ID No	45	CDR	3	Heavy Chain
Seq ID No	46	CDR	1	Light Chain
Seq ID No	47	CDR	2	Light Chain
Seq ID No	48	CDR	3	Light Chain
Antibody	**6003-910**			
Seq ID No	49	CDR	1	Heavy Chain
Seq ID No	50	CDR	2	Heavy Chain
Seq ID No	51	CDR	3	Heavy Chain
Seq ID No	52	CDR	1	Light Chain
Seq ID No	53	CDR	2	Light Chain
Seq ID No	54	CDR	3	Light Chain

Antibody	**6003-423**			
Seq ID No	55	CDR	1	Heavy Chain
Seq ID No	56	CDR	2	Heavy Chain
Seq ID No	57	CDR	3	Heavy Chain
Seq ID No	58	CDR	1	Light Chain
Seq ID No	59	CDR	2	Light Chain
Seq ID No	60	CDR	3	Light Chain
Antibody	**6003-822**			
Seq ID No	61	CDR	1	Heavy Chain
Seq ID No	62	CDR	2	Heavy Chain
Seq ID No	63	CDR	3	Heavy Chain
Seq ID No	64	CDR	1	Light Chain
Seq ID No	65	CDR	2	Light Chain
Seq ID No	66	CDR	3	Light Chain
Antibody	**6003-886**			
Seq ID No	67	CDR	1	Heavy Chain
Seq ID No	68	CDR	2	Heavy Chain
Seq ID No	69	CDR	3	Heavy Chain
Seq ID No	70	CDR	1	Light Chain
Seq ID No	71	CDR	2	Light Chain
Seq ID No	72	CDR	3	Light Chain
Antibody	**6003-072**			
Seq ID No	73	CDR	1	Heavy Chain
Seq ID No	74	CDR	2	Heavy Chain
Seq ID No	75	CDR	3	Heavy Chain
Seq ID No	76	CDR	1	Light Chain
Seq ID No	77	CDR	2	Light Chain
Seq ID No	78	CDR	3	Light Chain
Antibody	**6003-900**			
Seq ID No	79	CDR	1	Heavy Chain
Seq ID No	80	CDR	2	Heavy Chain
Seq ID No	81	CDR	3	Heavy Chain

Seq ID No	82	CDR	1	Light Chain
Seq ID No	83	CDR	2	Light Chain
Seq ID No	84	CDR	3	Light Chain
Antibody	**6003-936**			
Seq ID No	85	CDR	1	Heavy Chain
Seq ID No	86	CDR	2	Heavy Chain
Seq ID No	87	CDR	3	Heavy Chain
Seq ID No	88	CDR	1	Light Chain
Seq ID No	89	CDR	2	Light Chain
Seq ID No	90	CDR	3	Light Chain
Antibody	**6003-408**			
Seq ID No	91	CDR	1	Heavy Chain
Seq ID No	92	CDR	2	Heavy Chain
Seq ID No	93	CDR	3	Heavy Chain
Seq ID No	94	CDR	1	Light Chain
Seq ID No	95	CDR	2	Light Chain
Seq ID No	96	CDR	3	Light Chain
Antibody	**6003-471**			
Seq ID No	97	CDR	1	Heavy Chain
Seq ID No	98	CDR	2	Heavy Chain
Seq ID No	99	CDR	3	Heavy Chain
Seq ID No	100	CDR	1	Light Chain
Seq ID No	101	CDR	2	Light Chain
Seq ID No	102	CDR	3	Light Chain
Antibody	**6003-972**			
Seq ID No	103	CDR	1	Heavy Chain
Seq ID No	104	CDR	2	Heavy Chain
Seq ID No	105	CDR	3	Heavy Chain
Seq ID No	106	CDR	1	Light Chain
Seq ID No	107	CDR	2	Light Chain
Seq ID No	108	CDR	3	Light Chain
Seq ID No	109	HC		6003-028

Seq ID No	110	LC	6003-028
Seq ID No	111	HC	6003-056
Seq ID No	112	LC	6003-056
Seq ID No	113	HC	6003-1286
Seq ID No	114	LC	6003-1286
Seq ID No	115	HC	6003-030
Seq ID No	116	LC	6003-030
Seq ID No	117	HC	6003-1277
Seq ID No	118	LC	6003-1277
Seq ID No	119	HC	6003-381
Seq ID No	120	LC	6003-381
Seq ID No	121	HC	6003-083
Seq ID No	122	LC	6003-083
Seq ID No	123	HC	6003-799
Seq ID No	124	LC	6003-799
Seq ID No	125	HC	6003-910
Seq ID No	126	LC	6003-910
Seq ID No	127	HC	6003-423
Seq ID No	128	LC	6003-423
Seq ID No	129	HC	6003-822
Seq ID No	130	LC	6003-822
Seq ID No	131	HC	6003-886
Seq ID No	132	LC	6003-886
Seq ID No	133	HC	6003-072
Seq ID No	134	LC	6003-072
Seq ID No	135	HC	6003-900
Seq ID No	136	LC	6003-900
Seq ID No	137	HC	6003-936
Seq ID No	138	LC	6003-936
Seq ID No	139	HC	6003-408
Seq ID No	140	LC	6003-408
Seq ID No	141	HC	6003-471

Seq ID No	142	LC	6003-471
Seq ID No	143	HC	6003-972
Seq ID No	144	LC	6003-972
Seq ID No	145	Full human Sortilin sequence isoform 1	
Seq ID No	146	"**E** Region" as identified by present invention	
Seq ID No	147	Sortilin "hSORTECDBAP"	
Seq ID No	148	Sortilin SORTECDBAP_hBACK	
Seq ID No	149	Sortilin SORTECDBAP_tetra	
Seq ID No	150	Sortilin SORTECDBAP_hB01-05	
Seq ID No	151	Sortilin SORTECDBAP_hRIM	
Seq ID No	152	Sortilin SORTECDBAP_hB06-10	
Seq ID No	153	Sortilin SORTECDBAP_hB12390	
Seq ID No	154	Sortilin SORTECDBAP_hB45678	
Seq ID No	155	Sortilin SORTECD_HIS	
Seq ID No	156	HDX-MS construct	

The listing or discussion in this specification of an apparently prior-published document should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

5

EMBODIMENTS

[00153] As would be apparent from the text and the Examples the invention further relates to the below embodiments:

1. An antibody, or an antigen-binding fragment thereof, capable of specifically binding to Sortilin and inhibiting binding of PGRN to Sortilin.
2. The antibody, or antigen-binding fragment thereof, according to Embodiment 1, wherein the antibody comprises or consists of an intact antibody.
3. The antibody, or antigen-binding fragment thereof, according to Embodiment 1 or 2, wherein the antigen-binding fragment comprises or consists of an antigen-binding fragment selected from the group consisting of: an Fv fragment (*e.g.* single chain Fv or a disulphide-bonded Fv); a Fab-like fragment (*e.g.* Fab fragment or $F(ab')_2$ fragment); and a domain antibody (*e.g.* a single V_H variable domain or V_L variable domain).
4. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, wherein the antibody is selected from the group consisting of: an antibody of subtype IgG1, IgG2, IgG3 or IgG4**.**
5. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, wherein said antibody or antigen-binding fragment thereof binds specifically to the E region of Sortilin as defined in **SEQ ID NO:146**.
6. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, wherein said antibody or fragment thereof binds specifically to at least 3 consecutive amino acids, such as 4, 5, 6 or 7 consecutive amino acids, of the E region of Sortilin as defined in **SEQ ID NO:146**.
7. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, wherein the antibody or antigen-binding fragment exhibits one or more of the following properties:

(i) a binding affinity (K_D) for Sortilin of between 0.5-10 nM, such as 1-5 nM or 1-2 nM, or even higher such as between 0.5 pM and 500 pM

(ii) capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;

(iii) capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;

(iv) capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice.

8. The antibody, or antigen-binding fragment thereof, according to Embodiment 5, which is human or humanized.

9. The antibody, or antigen-binding fragment thereof, according to Embodiment 6, which is human or humanized.

10. The antibody, or antigen-binding fragment thereof, according to any previous Embodiment, wherein the antibody or antigen-binding fragment thereof is human or is humanized.

11. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, comprising a light chain variable domain comprising one or more of the CDR 1-3 Light Chain as listed for each of the antibodies defined in Table 5, or an amino acid sequence having no more than 4 amino acid differences, or no more than 3 amino acid differences, or no more than 2 amino acid differences, or no more than 1 amino acid difference.

12. The antibody, or antigen-binding fragment thereof, according to Embodiment 11, comprising a light chain variable domain comprising the CDR 1-3 Light Chain as listed for each of the antibodies defined in Table 5.

13. The antibody, or antigen-binding fragment thereof, according to Embodiment 11 or 12, comprising a light chain variable domain comprising or consisting of the amino acid sequence VL as listed for each of the antibodies defined in Table 5.

14. The antibody, or antigen-binding fragment thereof, according to any of Embodiments 11 to 13, comprising a light chain comprising or consisting of the amino acid sequence of VL as listed for each of the antibodies defined in Table 5.

15. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, comprising a heavy chain variable domain comprising one or more CDR 1-3 Heavy Chain as listed for each of the antibodies defined in Table 5, or an amino acid sequence having no more than 4 amino acid differences, or no more than 3 amino acid differences, or no more than 2 amino acid differences, or no more than 1 amino acid difference.

16. The antibody, or antigen-binding fragment thereof, according to Embodiment 15, comprising a heavy chain variable domain comprising the CDR 1-3 Heavy Chain as listed for each of the antibodies defined in Table 5.

17. An antibody, or antigen-binding fragment thereof, according to Embodiment 15 or 16 comprising a heavy chain variable domain comprising or consisting of the amino acid sequence of VH as listed for each of the antibodies defined in Table 5.

18. The antibody, or antigen-binding fragment thereof, according to any of Embodiments 15 to 17, comprising a heavy chain comprising or consisting of the amino acid sequence VL as listed for each of the antibodies defined in Table 5.

19. The antibody, or antigen-binding fragment thereof, according to any preceding embodiment, comprising a light chain variable domain comprising or consisting of the amino acid sequence of VL as listed for each of the antibodies defined in Table 5, and a heavy chain variable domain comprising or consisting of the amino acid sequence of VH as listed for each of the antibodies defined in Table 5.

20. The antibody, or antigen-binding fragment thereof, according to any preceding embodiment, comprising a light chain comprising or consisting of the amino acid sequence of VL as listed for each of the antibodies defined in Table 5, and a heavy chain comprising or consisting of the amino acid sequence of VH as listed for each of the antibodies defined in Table 5.

21. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, wherein said antibody or antigen-binding fragment thereof competes with the antibody or antigen-binding fragment thereof defined in Embodiment 20 for binding to Sortilin.

22. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, wherein the antibody or antigen-binding fragment comprises an Fc region.

23. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, wherein the antibody or antigen-binding fragment further comprises a moiety for increasing *in vivo* half-life.

24. The antibody, or antigen-binding fragment thereof, according to Embodiment 22, wherein the moiety for increasing the *in vivo* half-life is selected from the group consisting of polyethylene glycol (PEG), human serum albumin, glycosylation groups, fatty acids and dextran.

25. The antibody, or antigen-binding fragment thereof, according to any preceding Embodiment, wherein the antibody or antigen-binding fragment further comprises a detectable moiety.

26. The antibody, or antigen-binding fragment thereof, according to Embodiment 25, wherein the detectable moiety is selected from the group consisting of: a fluorescent label; a chemiluminescent label; a paramagnetic label; a radio-isotopic label; or an enzyme label.

27. The antibody, or antigen-binding fragment thereof, according to Embodiment 25 or 26, wherein the detectable moiety comprises or consists of a radioisotope.

28. The antibody, or antigen-binding fragment thereof, according to Embodiment 26 or 27, wherein the radioisotope is selected from the group consisting of ^{99m}Tc, ^{111}In, ^{67}Ga, ^{68}Ga, ^{72}As,^{89}Zr, ^{123}I and ^{201}Tl.

29. The antibody, or antigen-binding fragment thereof, according to Embodiment 25, wherein the detectable moiety comprises or consists of a paramagnetic isotope.

30. The antibody, or antigen-binding fragment thereof, according to Embodiment 29 wherein the paramagnetic isotope is selected from the group consisting of ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Cr and ^{56}Fe.

31. The antibody, or antigen-binding fragment thereof, according to any of Embodiments 25 to 30, wherein the detectable moiety is detectable by an imaging technique such as SPECT, PET, MRI, optical or ultrasound imaging.

32. The antibody, or antigen-binding fragment thereof, according to any of Embodiments 25 to 31, wherein the detectable moiety is joined to the antibody or antigen-binding fragment thereof indirectly, via a linking moiety.

33. The antibody, or antigen-binding fragment thereof, according to Embodiment 32 wherein the linking moiety is selected from the group consisting of: derivatives of 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA); deferoxamine (DFO); derivatives of diethylenetriaminepentaacetic avid (DTPA); derivatives of S-2-(4-Isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA); and derivatives of 1,4,8,11-tetraazacyclodocedan-1,4,8,11-tetraacetic acid (TETA).

34. An isolated nucleic acid molecule encoding an antibody or antigen-binding fragment thereof as defined in any of Embodiments 1-33.

35. A nucleic acid molecule according to Embodiment 34 wherein the molecule is a cDNA molecule.

36. A vector comprising a nucleic acid molecule as defined in Embodiment 34 or 35.

37. A recombinant host cell comprising a nucleic acid molecule as defined in any of Embodiments 34-36.

38. A method for producing an antibody or antigen-binding fragment as defined in any of Embodiments 1-33, the method comprising culturing a host cell as defined in Embodiment 37 under conditions which permit expression of the encoded antibody or antigen-binding fragment thereof.

39. A preparation comprising the antibody or antigen-binding fragment thereof according to any one of the previous Embodiments, wherein said preparation is substantially free of naturally-arising antibodies that are either not capable of binding to Sortilin or that do not materially alter an anti-Sortilin functionality of the preparation, said functionality being selected from the group consisting of:

(i) a binding affinity (K_D) for Sortilin;

(ii) a capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;

(iii) a capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;

(iv) a capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice; and/or

(v) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS).

40. A preparation comprising the monoclonal antibody or antigen-binding fragment thereof according to any one of the previous Embodiments, wherein said monoclonal antibody possesses a structural change in its amino acid sequence, relative to the structure of a naturally-occurring anti-Sortilin antibody, wherein said structural change causes said monoclonal antibody to exhibit an altered functionality relative to the functionality exhibited by said naturally-occurring anti-Sortilin antibody, wherein said functionality is:

(i) a binding affinity (KD) for Sortilin;

(ii) a capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;

(iii) a capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;

(iv) a capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice; and/or

(v) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS).

41. A pharmaceutical composition comprising an antibody, or antigen-binding fragment thereof, as defined in any of Embodiments 1-33, or the preparation of any one of embodiments 39-40, and a pharmaceutically-acceptable carrier.

42. The antibody, or antigen-binding fragment thereof, as defined in any of Embodiments 1-33, or the preparation of any one of embodiments 39-40, for use in medicine.

43. The antibody, or antigen-binding fragment thereof, as defined in any of Embodiments 1-33, or the preparation of any one of embodiments 39-40, for use in preventing and/or treating a disease associated with decreased PGRN or decreased functional PGRN levels in the brain of a patient.

44. Use of an antibody, or antigen-binding fragment thereof, as defined in any of Embodiments 1-33, or the preparation of any one of embodiments 39-40, in the manufacture of a medicament for preventing and/or treating a disease associated with decreased PGRN levels in the brain of a patient.

45. The antibody or antigen-binding fragment thereof for use according to Embodiment 43, or the use according to Embodiment 44, wherein the disease is selected from the group consisting of: FTD; ALS; proteinopathies, such as AD, PD.

46. A method of preventing or treating a disease associated with decreased PGRN levels in the brain of a patient, comprising administering an effective dosage of an antibody or a fragment thereof as defined in any of Embodiments 1-33, the preparation of any one of Embodiments 39-40, or the pharmaceutical composition of Embodiment 41.

47. The antibody, or antigen-binding fragment thereof, for use according to Embodiment 43, or the use according to Embodiment 44, or the method according to Embodiment 46, wherein the disease is selected from the group consisting of: FTD; ALS; or proteinopathies, such as AD, PD.

48. The antibody, or antigen-binding fragment thereof, for use; or the use; or the method according to Embodiment 46 or 47, wherein the treatment is chronic.

49. The antibody, or antigen-binding fragment thereof, for use; or the use; or the method, according to Embodiment 48, wherein the chronic treatment is for at least 2 weeks, such as at least for 1 month, 6, months, 1 year or more

50. The antibody, or antigen-binding fragment thereof, as defined in any of Embodiments 1-33, the preparation of any one of Embodiments 39-40, or the pharmaceutical composition of Embodiment 41, which is capable of specifically binding to Sortilin, but which binding does not inhibit or substantially inhibit the binding of neurotensin or AF38469 (Schrøder TJ et al., Bioorg Med Chem Lett. 2014 Jan 1;24(1):177-80) to Sortilin.

51. A kit comprising the antibody, or antigen-binding fragment thereof, as defined in any of Embodiments 1-33, the preparation, as defined in any one of Embodiments 39-40, or the pharmaceutical composition as defined in Embodiment 41.

[00154] Preferred, non-limiting examples which embody certain aspects of the invention will now be described, with reference to the accompanying figures.

EXAMPLES

[00155] Examples 1-3 describe the generation of sortilin constructs

Example 1 discloses the shuffle constructs. **Example 2** discloses the expression of sortilin constructs. **Example 3** discloses the purification of sortilin constructs.

Examples 4-6 describe the generation of sortilin antibodies

Example 4 discloses the immunization and the hybridomas. **Example 5** discloses the sequence analysis. **Example 6** discloses the purification of antibodies.

Examples 7-11 describe the characterization of sortilin antibodies

Example 7 discloses the binding to sortilin. **Example 8** discloses the cross blocking ability of Sortilin antibodies. **Example 9** discloses extracellular PGRN levels **in iPSCs Example 10** discloses plasma PGRN levels

Example 1

For use in both the hybridoma screening process and as a diversification of the panel of antibodies, so called 'shuffle constructs" were designed, constructed and produced, making a set of chimeric sortilin molecules containing amino acid sequences derived from both human sortilin and a distantly related species (tetraodon) with significantly reduced sequence homology. The rationale being that the overall sortilin structure and functionality of these chimeric constructs would be retained but that loss of binding of antibodies to certain chimeric constructs would indicate the involvement of the specific exchanged regions in binding. Soluble extracellular region (ECD, aa 1-755) constructs were tagged with either a BAP tag (biotin acceptor peptide), enabling the "in vitro" biotinylation of the proteins by co-expression of biotin ligase or a His tag, enabling easy purification. Expression vectors encoding the following proteins were prepared: SORT-ECDBAP, SORT-ECDBAP-hB01-05, SORT-ECDBAP-hB06-10, SORT-ECDBAP-hB12390, SORT-ECDBAP-hB45678, SORT-ECDBAP-tetra, SORT, SORT-tetra.

The Sortilin sequences can be found in **SEQ ID NOs:147-155** and **Figure 2** shows schematic presentation of the region assignment of antibodies based on binding to Sortilin shuffle constructs.

Example 2

In the case of antibody expression, the appropriate heavy chain and light chain vectors, as described in **Examples 4, 5 and 6**, were co-expressed in HEK-293F cells.

Example 3: Purification of His-tagged Sortilin

SORTECDHis was expressed in HEK-293F cells. The His-tag in the proteins enables purification with immobilized metal affinity chromatography. In this process NiNTA Superflow Cartridge (Qiagen) is equilibrated with 50mM NAH_2PO_4, 300 mM NaCl and 10mM Imidazole pH 8.0. Column is loaded with His tagged protein with a residence time of 1 minute. Column is washed with 50mM NAH_2PO_4, 300 mM NaCl and 20mM Imidazole pH 8.0. Protein is eluted with 50mM NAH_2PO_4, 300 mM NaCl and 250mM Imidazole pH 8.0. Subsequently the protein is dialyzed to PBS using a Slide-A-Lyzer with a cut off of 10.000 mwco (Thermo Scientific). After dialyzing the protein is sterile filtered using a 0.2 micron SFCA filter(Thermo Scientific).

Clones were characterized for sortilin mRNA expression using qPCR. Highest expressing clones were than analyzed by FACS (Guava, Millipore) using an anti-sortilin polyclonal antibody (Polyclonal Goat Sortilin Biotinylated Ab, Cat.No: BAF2934_(R&D Systems)) to determine the surface expressed levels of Sortilin.

Example 4

A - Immunization procedure of transgenic mice

Antibodies HuMab Sortilin were derived from the immunizations of HuMAb mouse strains HCo12, HCo17, HCo20, HCo12-BALB/c, HCo17-BALB/c and HCo20-BALB/c (human monoclonal antibody; Medarex Inc., San Jose, CA, USA), These mice are double knock out for the mouse immunoglobulin (Ig) heavy and mouse kappa light chain, which substantially inactivate the expression of antibodies that

are completely murine. The various mouse strains were made transgenic by the insertion of human Ig heavy and human Ig kappa light chain loci and differ in the number of human VH (variable domain of heavy chain) and VL (variable domain of light chain) genes. HCo12-BALB/c mice were derived by crossbreeding with KCo5-BALB/c (kappa light chain transgenic) mice.

48 mice were immunized alternating intraperitoneally (IP) with 20 µg SORTECDHis (SEQ ID NO: 155) and subcutaneously (SC, at the tail base) with the same protein, with an interval of 14 days. A maximum of eight immunizations were performed, 4 IP and 4 SC.

In one protocol, the first immunization was performed with SORTECDHis in complete Freund's adjuvant (CFA; Difco Laboratories, Detroit, MI, USA), the following immunizations in incomplete Freund's adjuvant (IFA). A second protocol used SAS as an adjuvant in all immunization steps. When serum titers were found to be sufficient (dilution of serum of 1/50 or lower found positive in antigen specific screening assay on at least two sequential, biweekly, screening events), mice were additionally boosted twice intravenously (IV) with 10 µg SORTECDHis protein in 100 µL PBS, four and three days before fusion.

B - HuMab hybridoma-generation

HuMAb mice with sufficient antigen-specific titer development as defined above were sacrificed and the spleen and lymph nodes flanking the abdominal aorta and caval vein were collected. Fusion of splenocytes and lymph node cells with a mouse myeloma cell line was done by electrofusion using a CEEF 50 Electrofusion System (Cyto Pulse Sciences, Glen Burnie, MD, USA), essentially according to the manufacturer's instructions. Fused cells were seeded in fusion medium containing 10% Fetal Clone I Bovine serum (Perbio), 1 mM sodium pyruvate (Cambrex), 0.5 U/mL penicillin, 0.5 U/mL streptomycin (Cambrex), 50 µM 2-mercaptoethanol (Invitrogen), 600 ng/mL interleukin 6 (IL-6) (Strathmann), 1 x HAT (Sigma) and 0.5 mg/mL kanamycin (Invitrogen) in HyQ mADCF-Mab (Perbio). After ten days, supernatant was harvested and cells were refreshed with harvest medium, containing 10 % Fetal Clone I Bovine serum, 0.5 U/mL penicillin, 0.5 U/mL streptomycin, 600 ng/mL IL-6 and 1 x proHT (Cambrex) in HyQ

mADCF-Mab. Supernatants of the hybridoma cultures were screened by primary screening assays and streptavidin beads coupled to SORTECDBAP (**SEQ ID NO 147**), SORTECDBAPhB06-10 (**SEQ ID NO 152**), SORTECDBAPhB12390 (**SEQ ID NO 153**), to detect hybridomas producing human (or chimeric) anti-Sortilin antibodies. Hybridoma cells from the best primary wells were seeded in semisolid medium made from 40% CloneMedia (Genetix, Hampshire, UK) and 60% HyQ 2x complete medium (Hyclone, Waltham, USA). For each primary well, a well of a Genetix black 6-well plate was seeded. From each well, 25 sub clones were picked, using the ClonePix system (Genetix). The sub clones were picked in harvest medium. After seven days, the supernatants of the sub clones were screened again for Sortilin-specific human IgG binding and the human IgG concentration was measured using Octet 384red (Fortebio, Menlo Park, USA). From each primary well, the best sub clone was selected and expanded in expansion medium containing only 600 ng/mL IL-6, 0.5 U/mL penicillin, 0.5 U/mL streptomycin and 1 x proHT. The sub clones were expanded from one 96-well plate well to one 24-well plate well to four 24-well plate wells to six 6-well plate wells. Clones derived by this process were designated as primary clones (PC).

The anti-sortilin HuMab antibodies of the invention were identified and subjected to sequence analysis.

Example 5: Sequence analysis of the Sortilin-specific HuMab variable domains and cloning in expression vectors

Total RNA was prepared from 0.2 to 5x106 hybridoma cells and 5'-RACE-Complementary DNA (cDNA) was prepared from 100 ng total RNA, using the SMART RACE cDNA Amplification kit (Clontech), according to the manufacturer's instructions. VH and VL coding regions were amplified by PCR and cloned directly, in frame, in the p33G1f and p33Kappa expression vectors (containing the human IgG1./ kappa constant domain encoding sequences), by ligation independent cloning (Aslanidis, C. and P.J. de Jong, Nucleic Acids Res 1990;18(20): 6069-74). For each antibody, 16 VL clones and 16 VH clones were sequenced. Clones with a correct Open Reading Frame (ORF) were selected for further study and

expression. Vectors of all combinations of heavy chains and light chains were transiently co-expressed in FreestyleTM 293-F cells using 293fectin.

The resulting sequences are shown in the Sequence Listing (**SEQ ID NOs:1-144**) herein. CDR sequences were defined according to the pub-lished guidelines.

Example 6: Purification of antibodies

Culture supernatant was filtered over 0.2 µm dead-end filters, loaded on 5 mL Protein A columns (rProtein A FF, Amersham Bioscience) and eluted with 0.1 M citric acid-NaOH, pH 3. The eluate was immediately neutralized with 2M Tris-HCl, pH 9 and dialyzed to 12.6 mM NaH_2PO_4, 140 mM NaCl, pH 7.4 (B.Braun), O/N (over night). After dialysis, samples were sterile-filtered over 0.2 µm dead-end filters. Purity was determined by SDS-PAGE and concentration was measured by nephelometry and absorbance at 280 nm. Purified antibodies were aliquoted and stored at -80°C. Once thawed, purified antibody aliquots were kept at 4°C. Mass spectrometry was performed to identify the molecular mass of the antibody heavy and light chains expressed by the hybridomas.

Example 7: Affinity of Sortilin specific HuMab to recombinant extracellular region of Sortilin

Binding kinetics of anti-Sortilin HuMab antibodies to Sortilin were determined using Octet 384RED (Fortebio, Menlo Park, USA). HuMab solutions of 2 µg/ml were made by dilution in sample diluent (ForteBio, art. No. 18-5028). Prot A sensors (ForteBio, art.no. 18-0004) were prewetted with kinetics buffer (1:10 sample diluent in PBS) for at least 600 seconds. Subsequently sensors were immobilized with HuMab solution for 600 seconds. A baseline response was obtained by dipping in kinetics buffer for 120 seconds. Association of SORTECD constructs was performed during a 1000 seconds incubation. This was followed by dissociation in kinetics buffer for 100 seconds. After dissociation, sensors were regenerated (10 mM Glycine pH 1.0) and neutralized (kinetics buffer) 3 times for 5 seconds. All HuMab were analysed using four concentrations of SORTECD constructs (10,

5, 2.5 and 1.25 µg/ml). A molecular weight of 76.8 kDA was used for SORTECDHis. Data was fitted with ForteBio Analysis 6.4 software, using a global full fit. Results are shown in **Figure 3**.

Example 8: Antibody cross block of anti-Sortilin HuMantibodies

Antibody cross-block studies were performed using Octet 384RED (Fortebio, Menlo Park, USA). HuMab antibody solutions of 2 µg/ml were made by dilution in sample diluent (ForteBio, art. No. 18-5028). Amine reactive sensors (ForteBio, art.no. 18-0008) were used for immobilization of HuMantibodies. Prior to coupling to amine reactive sensors, HuMantibodies were diluted in MES pH 6.0 buffer (18-5027). Coupling was performed at 30°C and 1000 rpm as follows: Amine reactive sensors were prewet in PBS and subsequently activated with EDC/NHS (ForteBio. Art.no. 18-1033/18-1034) activation solution (according to manufacturer's instruction) for 300 seconds. Activated sensors were immobilized with HuMantibodies during 600 seconds. Immobilized sensors were quenched for remaining amine reactivity with Ethanolamine (ForteBio, cat no. 18-1039). After quenching sensors were placed in PBS until use. Cross block analysis starts with establishing a baseline response at 30°C and 1000 rpm. Baseline response was obtained by dipping in sample diluent for 120 seconds. Association of SORTECDHis was performed during 300 seconds directly followed by association of HuMab for 300 seconds. After association of HuMab, sensors were regenerated (10 mM Glycine pH 1.0) and neutralized (sample diluent) 3 times for 5 seconds. Data was processed using ForteBio Analysis 6.4 software.

Antibodies were grouped based on their binding profiles on the different Sortilin shuffle constructs (**Figure 2 and Figure 3)**. To confirm that all the antibodies from Region E bind to the same region on human wild type Sortilin ECD, their ability to block each other's binding to the wild type human Sortilin ECD was characterised in a cross blocking study using the Octet384 red. For example, when antibodies from the same region were tested, the primary antibody would block binding of the secondary antibody and vice versa. Whereas, when antibodies from different regions were tested, there would be no cross blocking as only one region

is blocked by the primary antibody and the remaining regions are available for the secondary antibody to bind. **Figure 4** shows that 22 out of 26 antibodies from E domain cross block all antibodies from the group and the remaining 4 antibodies cross block 20 out of 26 antibodies which confirms that most of these antibodies bind in the same region on sortilin and rest of them have overlapping binding sites and/or bind in close proximity in the E region. This confirms classification of the antibodies to Region E based on shuffle constructs. Further, these data also confirm that the chimeric Sortilin constructs retain similarity to the native human wild type Sortilin ECD.

Example 9:

ELISA assay for extracellular PGRN in iPSCs

[00156] The sortilin E-region antibody 900 increased PGRN levels whereas the control antibody B12 did not affect extracellular progranulin levels. The assay was performed with growth factor matured iPSC neurons plated into 96 wells plate. Antibodies were added to the cell media. The culture media was collected after 72 hrs exposure and analysed by human PGRN ELISA (Biovendor) and samples analysed according to the manufacturer's instructions. Sortilin human antibody 900 increased PGRN levels in the media collected from the iPSC neurons, whereas no effect was seen of the control antibody B12 (Figure 5). Media with antibodies not exposed to the cells showed no signal in the PGRN ELISA. CellTiter-Glo Luminescent cell viability assay (Promega) showed no effect on viability of antibody applications. Data is presented as mean ± SD. Data was analyzed by one-way Anova followed by Dunnett's analysis ***$p<0.001$.

[00157] The iPSC line was generated from human fibroblasts sampled from an apparently heathy male (18 years) by reprogramming according to a non-integrative method as described in Rasmussen *et al.* (Stem Cell Reports. 2014 Sep 9;3(3):404-13.). The clone named NHDF K1_shp53 (deposited in the European Bank of induced Pluripotent Stem Cells as BIONi010-A) was used. The iPSCs

were cultured in monolayer in mTeSR1 media (Stemcell Technologies) on matrigel (BD Biosciences). Neuronal differentiation was initiated day 0 by dual SMAD inhibition (100 nM LDN and 10 µM SB431542 in N3 media (50% DMEM/F12 + 50% Neurobasal media supplemented with 0.5% N2, 1% B27 with RA, 0,5 mM GlutaMAX-I, 0.5% NEA, 50 µM 2-mercaptoethanol and 2.5 µg/mL insulin) of iPSCs plated at high density. The cells were split at day 12 and from now on plated on poly-L-ornithine/laminin. LDN and SB431542 were withdrawn from day 13. From this time point, the cells were split approximately every 5 day until the neuronal progenitor cells (NPCs) were frozen day 21 to generate a NPC bank. These NPCs were thawed, allowed to proliferate for approximately 4 days before re-plating day 25 and subjecting to day final maturation medium (N3 with 20 ng/mL BDNF, 10 ng/mLGDNF, 500 µM db-cAMP, 200 µM ascorbic acid) from day 26. Day 32, the cells were subjected to final re-plating into assay plates in maturation medium. FACS studies have confirmed surface expression of the sortilin receptor on iPSC neurons from other lines generated in a similar way. Antibodies were applied day 56 and samples collected day 59.

Example 10 Effect of antibodies on plasma PGRN levels in mice

To analyze the effect of antibodies on PGRN levels in plasma, humanized Sortilin KI mice were given a single injection (10mg/kg) of the sortilin antibody or isotype control by subcutaneous injections. The animals were anaesthetized and sacrificed 48hrs time points after dosing and plasma PGRN levels determined by ELISA.

Mice were anaesthetized with 0,4 ml Avertin IP and heart blood was collected and transferred to a 500 ul kEDTA vial. Samples were kept on ice until centrifuged at 3600G for 15 min at 4C. The plasma was pipetted in to a micronic vial and frozen at -20C. PGRN in the samples was measured using PGRN ELISA kit (Adipogen) as per the manufacturer's instructions.

Mice treated with Sortilin humab, #30, showed an increase in plasma PGRN levels after 48hrs compared to Anti-HEL, isotype control antibody. Results can be seen in **Figure 6**.

Example 11

[00158] **Figures 7A and B** show the effects of Sortilin antibodies on extracellular PGRN in neuronal differentiated induced pluripotent stem cells (iPSCs) generated from an apparently heathy individual as well as from a PGRN R493X patient.

[00159] The anti-sortilin human antibodies #72, #1277, #83, #900, #799, #886, #28, #471, #1286, #822, #423, #56, #381, #936 increased extracellular PGRN levels whereas the control antibody B12 did not. The assay was performed with growth factor matured iPSC neurons plated into 96 wells plate. Antibodies were added to the cell media. The culture media from the iPSC neurons was collected after 72 hrs exposure and analysed by human PGRN ELISA (Biovendor) according to the manufacturer's instructions. Media with antibodies not exposed to the cells showed no signal in the PGRN ELISA. CellTiter-Glo Luminescent cell viability assay (Promega) showed no effect on viability (quantification of intracellular ATP levels) of antibody applications. Data is presented as mean ± SEM of three experimental runs with six replicates in each run. Data was analyzed by one-way ANOVA followed by Dunnett's analysis *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

[00160] The iPSC lines were reprogramming according to non-integrative methods from human fibroblasts sampled from an apparently heathy individual (18y male) as well as from PGRN R493X patient (65y male). The clones used are named BIONi010-A (apparently heathy individual) and LUBi001-A (PGRN R493X patient). They are deposited in the European Bank of induced Pluripotent Stem Cells and distributed by European Collection of Authenticated Cell Cultures. The iPSCs were cultured in monolayer on matrigel (BD Biosciences) in mTeSR1 media (Stemcell Technologies) and Essential 8 madia (Gibco), respectively. Neuronal differentiation was initiated day 0 by dual SMAD inhibition (100 nM LDN and 10 µM SB431542) in N3 media (50% DMEM/F12 + 50% Neurobasal media supplemented with 0.5% N2, 1% B27 with RA, 0,5 mM GlutaMAX-I, 0.5% NEA, 50 µM 2-mercaptoethanol and 2.5 µg/mL insulin) of iPSCs plated at high density. The cells were split at day 12 and from now on plated on poly-L-ornithine/laminin.

LDN and SB431542 were replaced by 20 ng/ml of FGF2 from day 13. From this time point, the cells were split approximately every 5 day until the neuronal progenitor cells (NPCs) were frozen day 21 to generate a NPC bank. These NPCs were thawed, allowed to proliferate before re-plating day 25 and subjecting to maturation medium (N3 with 20 ng/mL BDNF, 10 ng/mL GDNF, 500 µM db-cAMP, 200 µM ascorbic acid) from day 26. Day 32, the cells were final re-plated into assay plates in maturation medium. FACS studies on BIONi010-A iPSC neurons confirmed surface expression of the sortilin receptor. Antibodies were applied day 57 and samples collected after 72 hours, i.e. day 60.

Example 12: Epitope mapping of antibodies targeting the progranulin-sortilin interaction by hydrogen/deuterium exchange followed by mass spectrometry

In hydrogen/deuterium exchange followed by mass spectrometry (HDX-MS) the exchange rate of backbone amide hydrogens in a protein is measured. Hereby, it is possible to probe the conformational dynamics of the entire protein backbone except at proline residues. The rate of the exchange reaction is determined by the hydrogen bonding status of the backbone amide and to a lesser extent its solvent accessibility. Subtle changes in these two parameters e.g. caused by the presence of a ligand can be observed as a change in deuterium incorporation.

To sub-localize the changes in deuterium incorporation the protein is treated with an acid stable protease (e.g. pepsin), which generates local regions of typically ten to fifteen amino acids. Regions that shows a perturbation in the presence of a ligand is either directly involved in the binding interface or allosterically affected by the binding event.

Epitope mapping of antibodies

The deuterium incorporation of the extra cellular region of Sortilin (**SEQ ID NO:156**) was measured in the -absence and presence of mAb30 which binds the E region. To secure that the measurements were conducted at steady-state conditions the complexes were equilibrated for 15min at 25ºC before the exchange reaction was initiated. The exchange reaction was initiated by dilution of the protein samples 1:9 (v/v) into deuterated buffer (99% D2O, 20mM tris, 150mM NaCl,

pDread = 7.6). After various time points (15s, 1min, 10min, 1h and 8h) the exchange reaction was quenched by 1:1 (v/v) dilution with ice-cold quench buffer (2M glycine, 0.8M tris-(2-carboxyethyl)phosphine (TCEP), pH = 2.3), thereby decreasing the pH to 2.46. The quenched samples were immediately placed inside a -80º freezer and stored until analysis. Fully deuterated control samples were prepared by diluting sortilin samples 1:9 (v/v) into a deuterated denaturation buffer (6M guanidinium chloride, 99% D2O, 20mM tris, 150mM NaCl, pDread = 7.6) followed by incubation at 25ºC for 16h before they were quenched and handled as described above.

The quenched samples were thawed and injected into a cooled (0ºC) reverse-phase UPLC-HDX-system (Waters Inc., USA) equipped with a home-packed pepsin column (internal volume of 60µL, pepsin beads acquired from Thermo Scientific Inc.). Here, the deuterated protein samples were subjected to online pepsin digestion at 20ºC, and the resulting peptic peptides were separated by reverse-phase UPLC. The peptides were ionized by electrospray ionization into a mass spectrometer (Synapt G2 mass spectrometer, Waters Inc, UK), where the peptides were further separated by ion mobility before final mass determination. The Identification of peptides was performed on fully reduced and non-deuterated samples by tandem mass spectrometry using a combination of data independent (MSe) and data dependent acquisition.

Data analysis

Identification of peptides

The acquired mass spectra were lock mass corrected against GFP and analyzed in PLGS 3.0, which matched precursor and fragment ions to a local protein database. All peptide identifications were carefully assessed manually.

Determination of deuterium incorporation: The acquired mass spectra were lock mass corrected against GFP and the software DynamX 3.0 (Waters Inc., USA) was used to determine the deuterium incorporation for all peptides of sortilin either in absence or presence of antibodies.

A peptide was considered to be a part of the binding epitope if a protection from exchange larger than 0.5D was observed in presence of an antibody.

Table 1 – Table of identified conformational epitopes by HDX-MS.

Antibody	Epitope mapping by HDX-MS relative to SEQ ID NO:145				
30	617-642	657-672	715-728		

CLAIMS

1. An antibody, or an antigen-binding fragment thereof, capable of binding specifically within the E Region of Sortilin as defined by **SEQ ID NO:146**

2. The antibody, or antigen-binding fragment thereof, according to claim 1, wherein the antigen-binding fragment is selected from the group consisting of: an Fv fragment (e.g. single chain Fv or a disulphide-bonded Fv); a Fab-like fragment (e.g. Fab fragment, Fab' fragment or a F(ab)2 fragment); and a domain antibody (e.g. a single VH variable domain or VL variable domain).

3. The antibody according to any preceding claims, wherein the antibody consists of an intact antibody.

4. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody is selected from the group consisting of: an antibody of subtype IgG1, IgG2, IgG3 or IgG4.

5. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein said antibody or antigen-binding fragment thereof binds to the E Region of Sortilin as defined by **SEQ ID NO:146**.

6. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein said antibody or antigen-binding fragment thereof binds to at least 1 or more consecutive amino acids, such as 1,2,3, 4, 5, 6 or 7 consecutive amino acids, within the E Region of Sortilin as defined in **SEQ ID NO:146**.

7. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody or antigen-binding fragment exhibits one or more of the following properties:

   a. a binding affinity (KD) for Sortilin between 0.5-10 nM, such as 1-5 nM or 1-2 nM or even higher such as between 0.5 pM and 500 pM
   b. capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;
   c. capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;
   d. a capability to increase the amount and/or concentration of PGRN in the brain, and/or

e. capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice.

8. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims 1-7, wherein the capability of said antibody or antigen-binding fragment thereof to reduce and/or inhibit clearance of PGRN comprises reducing and/or inhib clearance of PGRN with an IC50 at or below 22 nM, such as between 22 nM and 1 nM, or between 10 nM and 1 nM, or between 5 nM and 1 nM.

9. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody or antigen-binding fragment thereof is a human, humanized, recombinant or chimeric antibody.

10. An antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:1**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:2**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:3**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:4**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:5**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:6**.

11. An antibody, or antigen-binding fragment thereof, according to claim 10, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:109.**

12. The antibody, or antigen-binding fragment thereof, according to claim 10, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:110**.

13. The antibody, or antigen-binding fragment thereof, according to claim 10, wherein said antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 11 and 12.

14. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a heavychain variable domain CDR1 comprising **SEQ ID NO:7**;
    b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:8**;
    c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:9**;
    d. a light chain variable domain CDR 1 comprising **SEQ ID NO:10**;
    e. a light chain variable domain CDR 2 comprising **SEQ ID NO:11**; and
    f. a light chain variable domain CDR 3 comprising **SEQ ID NO:12**.

15. The antibody, or antigen-binding fragment thereof, according to claim 14, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:111**.

16. The antibody, or antigen-binding fragment thereof, according to claim 14, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:112**.

17. The antibody, or antigen-binding fragment thereof, according to claim 14, wherein said antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 15 and 16.

18. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:13**;
    b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:14**;
    c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:15**;
    d. a light chain variable domain CDR 1 comprising **SEQ ID NO:16**;
    e. a light chain variable domain CDR 2 comprising **SEQ ID NO:17**; and
    f. a light chain variable domain CDR 3 comprising **SEQ ID NO:18**.

19. The antibody, or antigen-binding fragment thereof, according to claim 18, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:113**.

20. The antibody, or antigen-binding fragment thereof, according to claim 18, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:114**.

21. The antibody, or antigen-binding fragment thereof, according to of claim 18, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 19 and 20.

22. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:19**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:20**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:21**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:22**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:23**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:24**.

23. The antibody, or antigen-binding fragment thereof, according to claim 22, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:115**.

24. The antibody, or antigen-binding fragment thereof, according to claim 22, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:116**.

25. The antibody, or antigen-binding fragment thereof, according to claim 22, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 23 and 24.

26. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:25**;
    b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:26**;
    c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:27**;
    d. a light chain variable domain CDR 1 comprising **SEQ ID NO:28**;
    e. a light chain variable domain CDR 2 comprising **SEQ ID NO:29**; and
    f. a light chain variable domain CDR 3 comprising **SEQ ID NO:30**.

27. The antibody, or antigen-binding fragment thereof, according to claim 26, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:117**.

28. The antibody, or antigen-binding fragment thereof, according to claim 26, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:118**.

29. The antibody or antigen-binding fragment thereof according to claim 26, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 27 and 28.

30. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:31**;
    b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:32**;
    c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:33**;
    d. a light chain variable domain CDR 1 comprising **SEQ ID NO:34**;
    e. a light chain variable domain CDR 2 comprising **SEQ ID NO:35**; and
    f. a light chain variable domain CDR 3 comprising **SEQ ID NO:36**.

31. The antibody, or antigen-binding fragment thereof, according to claim 30, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:119**.

32. The antibody, or antigen-binding fragment thereof, according to claim 30, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:120**.

33. The antibody, or antigen-binding fragment thereof, according to claim 30, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 31 and 32.

34. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:37**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:38**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:39**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:40**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:41**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:42**.

35. The antibody, or antigen-binding fragment thereof, according to claim 34, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:121**.

36. The antibody, or antigen-binding fragment thereof, according to claim 34, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:122**.

37. The antibody, or antigen-binding fragment thereof, according to claim 34, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 35 and 36.

38. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:43**;
    b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:44**;
    c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:45**;
    d. a light chain variable domain CDR 1 comprising **SEQ ID NO:46**;
    e. a light chain variable domain CDR 2 comprising **SEQ ID NO:47** and
    f. a light chain variable domain CDR 3 comprising **SEQ ID NO:48**.

39. The antibody, or antigen-binding fragment thereof, according to claim 38, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:123**.

40. The antibody, or antigen-binding fragment thereof, according to claim 38, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:124**.

41. The antibody, or antigen-binding fragment thereof, according to claim 38, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 39 and 40.

42. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:49**;
    b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:50**;
    c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:51**;
    d. a light chain variable domain CDR 1 comprising **SEQ ID NO:52**;
    e. a light chain variable domain CDR 2 comprising **SEQ ID NO:53**; and
    f. a light chain variable domain CDR 3 comprising **SEQ ID NO:54**.

43. The antibody or antigen-binding fragment thereof according to claim 42, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:125**.

44. The antibody or antigen-binding fragment thereof according to claim 42, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:126**.

45. The antibody or antigen-binding fragment thereof according to claim 42, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 43 and 44.

46. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:55**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:56**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:57**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:58**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:59**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:60**.

47. The antibody or antigen-binding fragment thereof according to claim 46, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:127**.

48. The antibody or antigen-binding fragment thereof according to claim 46, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:128**.

49. The antibody or antigen-binding fragment thereof according to claim 46, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 47 and 48.

50. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:61**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:62**;

c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:63**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:64**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:65**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:66**.

51. The antibody or antigen-binding fragment thereof according to claim 50, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:129**.

52. The antibody or antigen-binding fragment thereof according to claim 50, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:130**.

53. The antibody or antigen-binding fragment thereof according to claim 50, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 51 and 52.

54. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:67**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:68**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:69**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:70**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:71**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:72**.

55. The antibody or antigen-binding fragment thereof according to claim 54, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:131.**

56. The antibody or antigen-binding fragment thereof according to claim 54, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:132**.

57. The antibody or antigen-binding fragment thereof according to claim 54, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 55 and 56.

58. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:73**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:74**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:75**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:76**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:77**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:78**.

59. The antibody or antigen-binding fragment thereof according to claim 58, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:133**.

60. The antibody or antigen-binding fragment thereof according to claim 58, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:134.**

61. The antibody or antigen-binding fragment thereof according to claim 58, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 59 and 60.

62. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:79**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:80**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:81**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:82**;

e. a light chain variable domain CDR 2 comprising **SEQ ID NO:83**; and

f. a light chain variable domain CDR 3 comprising **SEQ ID NO:84**.

63. The antibody or antigen-binding fragment thereof according to claim 62, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:135**.

64. The antibody or antigen-binding fragment thereof according to claim 62, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:136**.

65. The antibody or antigen-binding fragment thereof according to claim 62, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 63 and 64.

66. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:85**;

b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:86**;

c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:87**;

d. a light chain variable domain CDR 1 comprising **SEQ ID NO:88**;

e. a light chain variable domain CDR 2 comprising **SEQ ID NO:89**; and

f. a light chain variable domain CDR 3 comprising **SEQ ID NO:90**.

67. The antibody or antigen-binding fragment thereof according to claim 66, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:137**.

68. The antibody or antigen-binding fragment thereof according to claim 66, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:138**.

69. The antibody or antigen-binding fragment thereof according to claim 66, wherein the antibody or antigen-binding fragment thereof comprises both

the heavy chain variable domain and light chain variable domain as defined in claims 67 and 68.

70. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:91**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:92**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:93**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:94**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:95**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:96**.

71. The antibody or antigen-binding fragment thereof according to claim 70, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:139**.

72. The antibody or antigen-binding fragment thereof according to claim 70, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:140**.

73. The antibody or antigen-binding fragment thereof according to claim 70, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 71 and 72.

74. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:97**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:98**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:99**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:100**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:101**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:102**.

75. The antibody or antigen-binding fragment thereof according to claim 74, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:141**.

76. The antibody or antigen-binding fragment thereof according to claim 74, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:142**.

77. The antibody or antigen-binding fragment thereof according to claim 74, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 75 and 76.

78. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:103**;
b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:104**;
c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:105**;
d. a light chain variable domain CDR 1 comprising **SEQ ID NO:106**;
e. a light chain variable domain CDR 2 comprising **SEQ ID NO:107**; and
f. a light chain variable domain CDR 3 comprising **SEQ ID NO:108**.

79. The antibody or antigen-binding fragment thereof according to claim 78, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:143**.

80. The antibody or antigen-binding fragment thereof according to claim 78, wherein said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:144**.

81. The antibody or antigen-binding fragment thereof according to claim 78, wherein the antibody or antigen-binding fragment thereof comprises both the heavy chain variable domain and light chain variable domain as defined in claims 79 and 80.

82. A preparation comprising the antibody or antigen-binding fragment thereof according to any one of the previous claims, wherein said preparation is

substantially free of naturally-arising antibodies that are either not capable of binding to Sortilin or that do not materially alter an anti-Sortilin functionality of the preparation, said functionality being selected from the group consisting of:

(i) a binding affinity (K_D) for Sortilin;

(ii) a capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;

(iii) a capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;

(iv) a capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice; and/or

(v) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) or Alzheimer's Disease (AD).

83. A preparation comprising the monoclonal antibody or antigen-binding fragment thereof according to any one of the previous claims, wherein said monoclonal antibody possesses a structural change in its amino acid sequence, relative to the structure of a naturally-occurring anti-Sortilin antibody, wherein said structural change causes said monoclonal antibody to exhibit an altered functionality relative to the functionality exhibited by said naturally-occurring anti-Sortilin antibody, wherein said functionality being selected from the group consisting of:

(i) a binding affinity (KD) for Sortilin;

(ii) a capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;

(iii) a capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;

(iv) a capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice;

(v) a capability to increase the amount and/or concentration of PGRN in the brain, or

(vi) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and/or Alzheimer's Disease (AD).

84. A pharmaceutical composition comprising an antibody, or an antigen-binding fragment thereof, as defined in any of claims 1 to 81, or the preparation of any one of claims 82-83, and a pharmaceutically-acceptable carrier.

85. The antibody, or antigen-binding fragment thereof, as defined in any of claims 1 to 81, or the preparation of any one of claims 82-83, or the pharmaceutical composition of claim 84, for use in medicine.

86. The antibody, or antigen-binding fragment thereof, as defined in any of claims 1 to 81, or the preparation of any one of claims 82-83 or the pharmaceutical composition of claim 84 for use in treating a disease associated with decreased PGRN levels or decreased functional PGRN in the brain of a patient.

87. Use of the antibody, or antigen-binding fragment thereof, as defined in any of claims 1 to 81, or the preparation of any one of claims 82-83, or the pharmaceutical composition of claim 84 in the manufacture of a medicament for treating a disease associated with decreased PGRN or decreased functional PGRN levels in the brain of a patient.

88. A method of preventing or treating a disease associated with decreased PGRN or decreased functional PGRN levels in the brain of a patient, comprising administering an effective dosage of an antibody, or an antigen-binding fragment thereof, as defined in any of claims 1-81, or the preparation of any one of claims 82-83, or the pharmaceutical composition of claim 84.

89. The antibody, or antigen-binding fragment thereof, for use according to claim 86, or the use according to claim 87, or the method according to claim 88, wherein the disease is: FTD; ALS; or proteinopathies, such as AD.

90. The antibody, or antigen-binding fragment thereof, for use according to claim 86, or the use according to claim 87, or the method according to

claim 88, wherein the treatment is chronic, and is preferably for at least 2 weeks, such as at least for 1 month, or at least for 6 months, or at least for 1 year.

91. A kit comprising the antibody, or antigen-binding fragment thereof, as defined in any of claims 1-81, or the preparation of any one of claims 82-83, or the pharmaceutical composition of claim 84.

92. An antibody, or antigen-binding fragment thereof, as defined in any of claims 1-81 which has been produced or manufactured in a cell line such as a human cell line, a mammal non-human cell line, an insect, yeast or bacterial cell line.

93. The antibody, or antigen binding fragment thereof, according to claim 92 produced in a CHO cell line, HEK cell line, BHK-21 cell line, murine cell line (such as a myeloma cell line), fibrosarcoma cell line, PER.C6 cell line, HKB-11 cell line, CAP cell line and HuH-7 human cell line.