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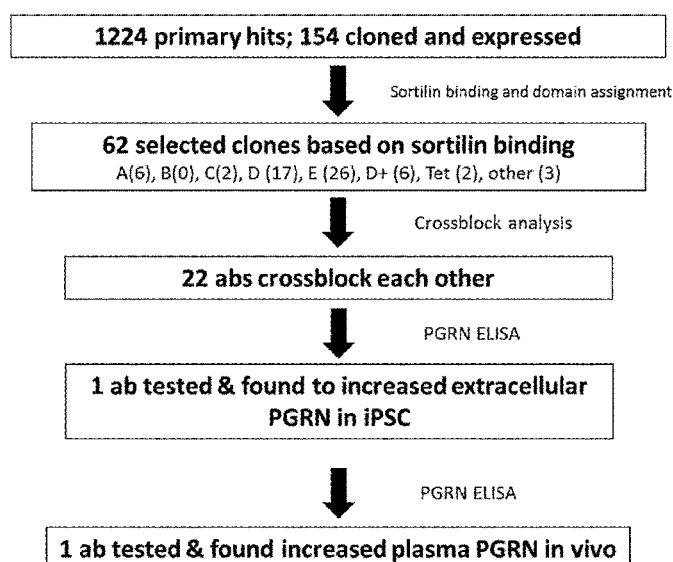
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Figure 1



(57) Abstract: The present invention relates to monoclonal anti-Sortilin antibodies which have been found 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) and other neurodegenerative disorders such as Alzheimers disease (AD).





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Agents, Uses and Methods for Treatment

Field of The Invention

[0001] The present invention relates to monoclonal anti-Sortilin antibodies
5 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).

10

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),
15 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
20 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
25 (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
30 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) (Tangkeangsinsin, 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.S.A 98 142-147 (2001); Liao, 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] In a first aspect, the present invention provides 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**, wherein the antibody, is selected from the group consisting of antibodies (1)-(3), (5)-(8), (10)-(15), and (17) wherein:

antibody (1) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (2) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (3) comprises:

- 5 a. a heavy chain variable domain CDR 1 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
- 10 f. a light chain variable domain CDR 3 comprising **SEQ ID NO:18**;

antibody (5) comprises:

- a. a heavy chain variable domain CDR 1 comprising **SEQ ID NO:25**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:26**;
- 15 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**;

20 antibody (6) comprises:

- a. a heavy chain variable domain CDR 1 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**;
- 25 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**;

antibody (7) comprises:

- a. a heavy chain variable domain CDR 1 comprising **SEQ ID NO:37**;
- 30 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**;

antibody (8) comprises:

- 5 a. a heavy chain variable domain CDR 1 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
- 10 f. a light chain variable domain CDR 3 comprising **SEQ ID NO:48**;

antibody (10) comprises:

- a. a heavy chain variable domain CDR 1 comprising **SEQ ID NO:55**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:56**;
- 15 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**;

20 antibody (11) comprises:

- a. a heavy chain variable domain CDR 1 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**;
- 25 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**;

antibody (12) comprises:

- a. a heavy chain variable domain CDR 1 comprising **SEQ ID NO:67**;
- 30 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**;

antibody (13) comprises:

- 5 a. a heavy chain variable domain CDR 1 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
- 10 f. a light chain variable domain CDR 3 comprising **SEQ ID NO:78**;

antibody (14) comprises:

- a. a heavy chain variable domain CDR 1 comprising **SEQ ID NO:79**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:80**;
- 15 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**;

20 antibody (15) comprises:

- a. a heavy chain variable domain CDR 1 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**;
- 25 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**;

antibody (17) comprises:

- a. a heavy chain variable domain CDR 1 comprising **SEQ ID NO:97**;
- 30 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**.

5 **[0010a]** In a second aspect, the present invention provides a pharmaceutical composition comprising an antibody, or an antigen-binding fragment thereof, as defined in the first aspect.

[0010b] In a third aspect, the present invention provides the antibody, or antigen-binding fragment thereof, as defined in the first aspect for use in medicine.

10 **[0010c]** In a fourth aspect, the present invention provides the antibody, or antigen-binding fragment thereof, as defined in the first aspect for use in treating a disease associated with decreased PGRN levels or decreased functional PGRN in the brain of a patient.

[0010d] In a fifth aspect, the present invention provides use of the antibody, or antigen-binding fragment thereof, as defined in the first aspect in the manufacture
15 of a medicament for treating a disease associated with decreased PGRN or decreased functional PGRN levels in the brain of a patient.

[0010e] In a sixth aspect, the present invention provides 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
20 effective dosage of an antibody, or an antigen-binding fragment thereof, as defined in the first aspect or the pharmaceutical composition of the second aspect.

[0010f] In a seventh aspect, the present invention provides an antibody, or antigen-binding fragment thereof, as defined in the first aspect which has been
25 produced or manufactured in a cell line such as a human cell line, a mammal non-human cell line, an insect, a yeast, or a bacterial cell line.

[0010g] 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
30 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.

5 **Brief Description of the Drawings**

10 **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 healthy 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.

5

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 \pm SD. Data was analysed by t-test. *** $p < 0.001$

10

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 healthy individual as well as from a PGRN R493X patient (**Example 11**)

15

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**).

20

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,

25

Methionine (M) being amino acid 1:

30
 MERPWGAADG LSRWPHGLGL LLLLQLLPSS TLSQDRLDAP PPPAAPLPRW
 SGPIGVSWGL RAAAAGGAFP RGGRWRRSAP GEDEECGRVR DFVAKLANNT
 HQHVFDLLRG SVLSWVGDS TGVILVLTTF HVPLVIMTFG QSKLYRSEDY
 GKNFKDITDL INNTFIRTEF GMAIGPENSG KVVLTAEVSG GSRGGRIFRS
 SDFAKNFVQT DLPFHPLTQM MYSPQNSDYL LALSTENGLW VSKNFGGKWE
 EIHKAVCLAK WGSNTIFFT TYANGSCKAD LGALELWRTS DLGKSFKTIG
 VKIYSFGLGG RFLFASVMAD KDTTRRIHVS TDQGDWWSMA QLPSVGQEQF

YSILAANDDM VFMHVDEPGD TGFGTIFTSD DRGIVYSKSL DRHLYTTTGG
 ETDFTNVTSL RGVYITSVLS EDNSIQTMIT FDQGGRWTHL RKPENSECDA
 TAKNKNECSL HIHASYSISQ KLNVPMAPLS EPNAVGVIA HGSVGDAISV
 MVPDVYISDD GGYSWTKMLE GPHYTYLDS GGIIVAEHS SRPINVIKFS
 5 TDEGQCWQTY TFTRDPIYFT GLASEPGARS MNISIWGFTE SFLTSQWVSY
 TIDFKDILER NCEEKDYTIW LAHSTDPEY EDGCILGYKE QFLRLRKSSV
 CQNGRDYVVT KQPSICLCSL EDFLCDFGYR RPENDSKCVE QPELKGHDLE
 FCLYGREEHL TTNGYRKIPG DKCQGGVNPV REVKDLKKKC TSNFLSPEKQ
 NSKSNSVPII LAIVGLMLVT VVAGVLIVKK YVCGGRFLVH RYSVLQQHAE
 10 ANGVGDVDAL DTASHTNKSG YHDDSDLEDLLE

[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:

15 CEEKDYTIW LAHSTDPEY EDGCILGYKEQFLRLRKSSVCQNGRDYVVT KQPSICLCSL ED-
 FLCDFGYR RPENDSKCVE QPELKGHDLEFCLYGREEHL TTNGYRKIPG DKCQGGVNPV
 REVKDLKKKC TSNFLSPEKQNSKNS

[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 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) (Tangkeangsinsin, 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.S.A 98 142-147 (2001); Liao, L M., et al., Cancer Res. 60:1353-1360 (2000)).

[0016] PGRN mutations result in haploinsufficiency (Baker, M., et al, Nature 442:916-919 (2006); Cruts, M., et al, 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 al, 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 Fab₂ 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;21(11) :484-90); (vi) camelid or nanobodies (Revets *et al.*; Expert Opin Biol Ther. 2005 Jan;5(1): 11-24) 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 IMG T®, 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
5 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
10 100-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
15 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
20 resonance (SPR) technology in either a BIAcore® 3000 or T200 instrument 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
25 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
30 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
5 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
10 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
15 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.

20

[0027] The term " k_d " (sec^{-1} or $1/\text{s}$), as used herein, refers to the dissociation rate constant of a particular antibody-antigen interaction. Said value is also referred to as the k_{off} value.

[0028] The term " k_a " ($\text{M}^{-1} \times \text{sec}^{-1}$ or $1/\text{Msec}$), as used herein, refers to the
25 association rate constant of a particular antibody-antigen interaction.

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

[0030] The term " K_A " (M^{-1} or $1/\text{M}$), as used herein, refers to the association
30 equilibrium constant of a particular antibody-antigen interaction and is obtained by dividing the k_a by the k_d .

[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;
- 5 (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;
- 10 (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 25 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 30 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 Specificity*," 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.ijj 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.ijj). **Table 1** presents the BLOSUM62.ijj 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

5 fails to bind to Sortilin, for example, then the BLOSUM62.ijj 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.ijj substitution score will be 0, and more

10 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:

5 **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:

5

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
 5 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
 10 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
 20 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
 25 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
 30 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
5 (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
10 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,
15 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,
20 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
25 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
30 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.

5 **[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
10 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
15 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
20 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**;
- 25 (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**.

30 **[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**;
 - 5 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**.
- 10 [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
15 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**;
- 20 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**.

25 **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**;
- 30 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
5 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:

10

- 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**;
- 15 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**.

20

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**;
- 25 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**.

30

[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:

- 5 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
- 10 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:

15 [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**;
- 20 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:

25 [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**;
- 30 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**;
- 10 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**.

15 [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:

20 [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**;
- 25 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**.

30 **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**;
- 5 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**.

10 **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**;
- 15 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:

- 25 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
- 30 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:

5 [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**;
- 10 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
15 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**;
- 20 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**.

25 [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
30 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**.

5 **[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:

10 **[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**;
- 15 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**.

20 **[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.

25 **[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).

30 **[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-chromosomal 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), Tuailon 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
5 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,
10 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
15 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
20 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.
25 Further, class switching techniques may be used to convert one IgG subclass to another, for instance from IgG1 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
30 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.

5 **[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.

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[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

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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, Rosenberg 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).

5 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
10 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,
15 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
20 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
25 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.

30 **[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
 5 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
 10 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),
 15 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 (^3H), 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 ($^{81\text{m}}\text{Kr}$), lanthanum (^{140}La), lutetium (^{177}Lu), manganese (^{54}Mn), molybdenum (^{99}Mo), nitrogen (^{13}N , ^{15}N), oxygen (^{15}O),
 20 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),
 25 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
 30 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 (10 *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) 15 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 20 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 25 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 30 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), Gadolinium (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 (Zr), 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.

10 **[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 or fragment may be used in detecting or measuring the presence or amount of said Sortilin in the brain of a subject. This method may
15 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
20 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
25 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
30 (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
5 (2001)), or as a precipitated nucleic acid vector construct, such as a CaPO₄-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
10 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
15 (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
20 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
25 (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
30 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
5 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
10 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
15 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)
20 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
25 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-
30 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.

5 [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
10 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)
15 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
20 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
25 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
30 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.

5 **[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.

10 **[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
15 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.

20 **[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,
25 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
30 (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,
5 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
10 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
15 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
20 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
25 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
30 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
5 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 A β fragments in cells or tissue samples of a subject using one or more antibodies that specifically bind to Sortilin; and (b)
10 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
15 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
20 (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 (^3H), indium (^{121}In), and technetium ($^{99\text{m}}\text{Tc}$); and luminescent labels, such as luminol and luciferase; and fluorescent labels, such as fluorescein
25 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
30 the labeled molecule to concentrate at sites (if any) of A β 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.

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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.

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;
 - 5 (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
- 10 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
- 15 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
- 20 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.
- 25 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
- 30 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.
- 5 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.
- 10 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.
- 15 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.
- 20 27. The antibody, or antigen-binding fragment thereof, according to Embodiment 25 or 26, wherein the detectable moiety comprises or consists of a radioisotope.
- 25 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

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 acid (DTPA); derivatives of S-2-(4-Isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA); and derivatives of 1,4,8,11-tetraazacyclododecane-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;
 - 10 (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
 - 15 (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 (K_D) for Sortilin;
 - 25 (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;
 - 30 (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
5 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,
10 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.
- 15 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
20 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
25 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
30 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 (Schröder 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

5 **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.

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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

15 **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
20 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
25 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-
30 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.

5 **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.

10 **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
15 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
20 Scientific).

Clones were characterized for sortilin mRNA expression using qPCR. Highest expressing clones were then 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.

25

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
30 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
5 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.

10 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
15 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

20 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
25 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).
30 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.

20

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

30

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

The resulting sequences are shown in the Sequence Listing (**SEQ ID NOs:1-144**)
5 herein. CDR sequences were defined according to the published 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
10 citric acid-NaOH, pH 3. The eluate was immediately neutralized with 2M Tris-HCl, pH 9 and dialyzed to 12.6 mM NaH₂PO₄, 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
15 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.

20 **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
25 (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
30 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**.

5 **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
10 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 Hu-
15 Mantibodies 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
20 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.

25 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 anti-
30 bodies 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.

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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 \pm 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 healthy 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

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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 μ M 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 μ M 2-mercaptoethanol and 2.5 μ g/mL insulin) of iP-SCs 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/mL GDNF, 500 μ M db-cAMP, 200 μ M 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 μ l 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 healthy individual as well as from a PGRN R493X patient.

5 **[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
10 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 \pm SEM of three
15 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 healthy individual (18y male)
20 as well as from PGRN R493X patient (65y male). The clones used are named BIONi010-A (apparently healthy 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
25 (Stemcell Technologies) and Essential 8 media (Gibco), respectively. Neuronal differentiation was initiated day 0 by dual SMAD inhibition (100 nM LDN and 10 μ M 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 μ M 2-mercaptoethanol and 2.5 μ g/mL insulin) of iPSCs plated at high density.
30 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 μ M db-cAMP, 200 μ M 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.

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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 25°C 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,

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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
5 a -80° 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 25°C for 16h before they were quenched and handled as described above.

10 The quenched samples were thawed and injected into a cooled (0°C) 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 20°C, and the resulting peptic peptides were separated by
15 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
20 (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 data-
25 base. 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.

30 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**, wherein the antibody, is selected from the group consisting of antibodies (1)-(3), (5)-(8), (10)-(15), and (17), wherein:

antibody (1) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (2) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (3) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (5) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (6) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (7) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (8) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (10) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (11) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (12) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (13) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (14) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (15) comprises:

- a. a heavy chain variable domain CDR 1 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**;

antibody (17) comprises:

- a. a heavy chain variable domain CDR 1 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**.

2. The antibody according to claim 1, wherein the antibody, is selected from the group consisting of antibodies (1)-(3), (5)-(8), (10)-(15), and (17), wherein the antibodies comprises a heavy chain variable domain and light chain variable domain, wherein

antibody (1) comprises a heavy chain variable domain comprising **SEQ ID NO:109** and a light chain variable domain comprising **SEQ ID NO:110**;

antibody (2) comprises a heavy chain variable domain comprising **SEQ ID NO:111** and a light chain variable domain comprising **SEQ ID NO:112**;

antibody (3) comprises a heavy chain variable domain comprising **SEQ ID NO:113** and a light chain variable domain comprising **SEQ ID NO:114**;

antibody (5) comprises a heavy chain variable domain comprising **SEQ ID NO:117** and a light chain variable domain comprising **SEQ ID NO:118**;

antibody (6) comprises a heavy chain variable domain comprising **SEQ ID NO:119** and a light chain variable domain comprising **SEQ ID NO:120**;

antibody (7) comprises a heavy chain variable domain comprising **SEQ ID NO:121** and a light chain variable domain comprising **SEQ ID NO:122**;

antibody (8) comprises a heavy chain variable domain comprising **SEQ ID NO:123** and a light chain variable domain comprising **SEQ ID NO:124**;

antibody (10) comprises a heavy chain variable domain comprising **SEQ ID NO:127** and a light chain variable domain comprising **SEQ ID NO:128**;

antibody (11) comprises a heavy chain variable domain comprising **SEQ ID NO:129** and a light chain variable domain comprising **SEQ ID NO:130**;

antibody (12) comprises a heavy chain variable domain comprising **SEQ ID NO:131** and a light chain variable domain comprising **SEQ ID NO:132**;

antibody (13) comprises a heavy chain variable domain comprising **SEQ ID NO:133** and a light chain variable domain comprising **SEQ ID NO:134**;

antibody (14) comprises a heavy chain variable domain comprising **SEQ ID NO:135** and a light chain variable domain comprising **SEQ ID NO:136**;

antibody (15) comprises a heavy chain variable domain comprising **SEQ ID NO:137** and a light chain variable domain comprising **SEQ ID NO:138**;

antibody (17) comprises a heavy chain variable domain comprising **SEQ ID NO:141** and a light chain variable domain comprising **SEQ ID NO:142**.

3. The antibody, or antigen-binding fragment thereof, according to claim 1, wherein the antigen-binding fragment is selected from the group consisting of: a Fab-like fragment (e.g. Fab fragment, Fab' fragment or a F(ab)₂ fragment).

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

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

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

7. A pharmaceutical composition comprising an antibody, or an antigen-binding fragment thereof, as defined in any one of claims 1 to 6.

8. The antibody, or antigen-binding fragment thereof, as defined in any one of claims 1 to 6 for use in medicine.

9. The antibody, or antigen-binding fragment thereof, as defined in any one of claims 1 to 6 for use in treating a disease associated with decreased PGRN levels or decreased functional PGRN in the brain of a patient.

10. Use of the antibody, or antigen-binding fragment thereof, as defined in any one of claims 1 to 6 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.

11. 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 one of claims 1 to 6 or the pharmaceutical composition of claim 7.

12. The antibody, or antigen-binding fragment thereof, for use according to claim 9, or the use according to claim 10, or the method according to claim 11, wherein the disease is: FTD; ALS; or proteinopathies, such as AD.

13. An antibody, or antigen-binding fragment thereof, as defined in any one of claims 1 to 6 which has been produced or manufactured in a cell line such as a human cell line, a mammal non-human cell line, an insect, a yeast, or a bacterial cell line.

14. The antibody, or antigen binding fragment thereof, according to claim 13 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 or HuH-7 human cell line.

H. Lundbeck A/S

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

Figure 1

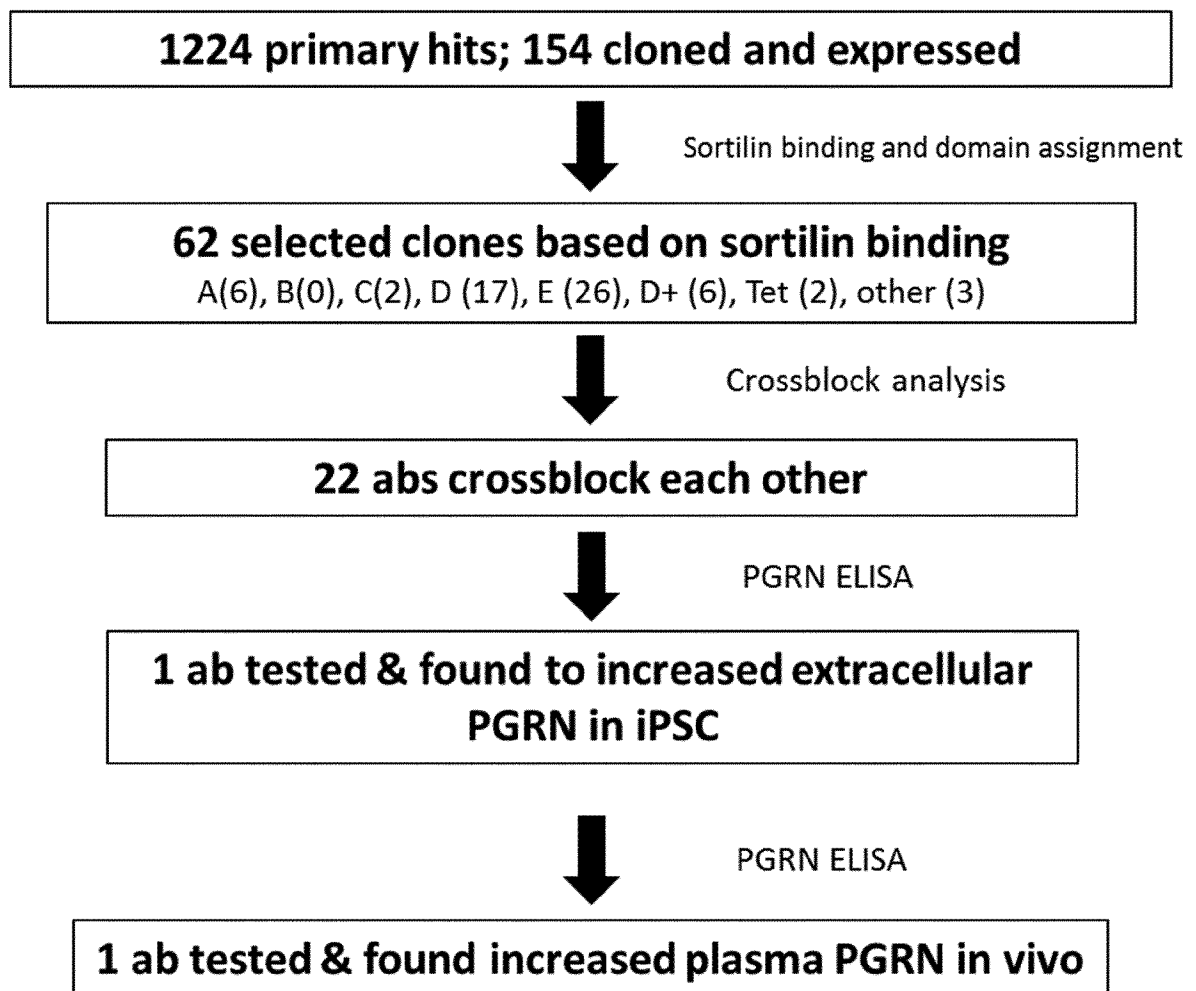


Figure 2A




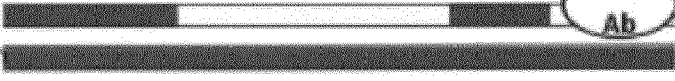

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Sort-human	<hr/>					+	+
hB01-05						-	-
hB06-10						+	+
hB12390						+	+
hB45678						+	-
Sort-tetradon						-	-
Sort-human	<hr/>					+	+

Figure 2B

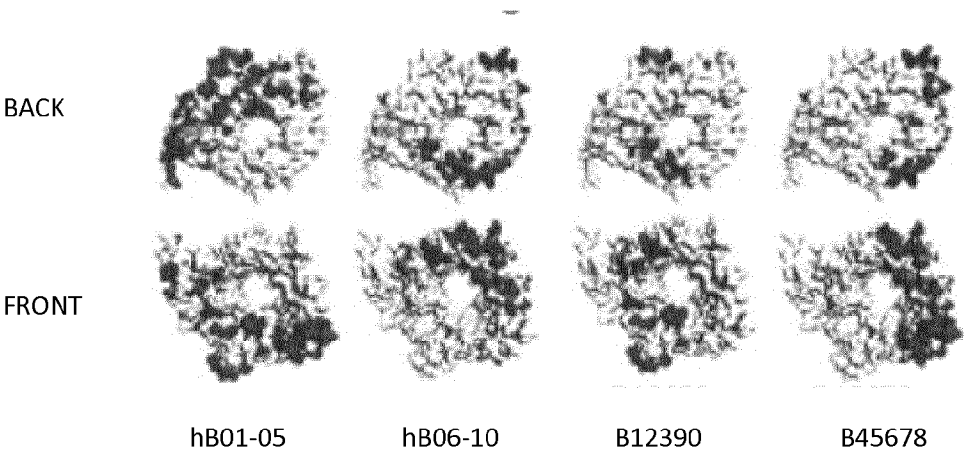


Figure 2C

mAbs	Domain	hSort	hB01-05	hB06-10	B12390	B45678	Tet
6	A	+	+	-	+	-	-
0	B	+	+	-	-	+	-
2	C	+	-	+	-	+	-
17	D	+	-	+	+	-	-
26	E	+	-	+	+	+	-
6	D+	+	-	-	+	-	-
2	Tet	+	+	+	+	+	+
3	Other	+	+/-	+/-	+/-	+	-

Figure 3

Antibody	Sort WT	hB01- 05	hB06- 10	hB12390	hB45678	hBack	hRim	Tetra
IgG1-6003-030	0.89	NB	0.74	0.82	0.85	0.85	0.86	NB
IgG1-6003-010	2.45	NB	2.29	3.00	4.39	2.85	3.77	NB
IgG1-6003-028	1.75	NB	1.56	1.86	1.96	1.87	2.04	NB
IgG1-6003-056	1.26	NB	0.97	1.42	1.10	1.14	1.24	NB
IgG1-6003-072	2.03	NB	1.96	6.29	4.41	2.63	4.93	NB
IgG1-6003-083	0.77	NB	0.76	0.86	0.92	1.34	0.99	NB
IgG1-6003-1277	3.03	NB	2.62	3.63	4.30	4.07	4.34	NB
IgG1-6003-1286	1.02	NB	0.87	0.86	1.02	1.02	1.05	NB
IgG1-6003-1342	1.79	NB	1.49	2.08	2.51	1.84	2.44	NB
IgG1-6003-381	1.82	NB	1.34	1.93	2.00	1.60	2.28	NB
IgG1-6003-408	1.93	NB	1.68	2.21	2.58	2.37	2.78	NB
IgG1-6003-423	3.47	NB	2.96	3.55	4.45	4.00	4.24	NB
IgG1-6003-471	2.63	NB	2.06	3.16	2.93	2.54	3.65	NB
IgG1-6003-530	4.77	NB	5.77	8.37	14.89	8.01	11.99	NB
IgG1-6003-532	1.30	NB	1.01	1.23	1.35	1.25	1.42	NB

Figure 3 (continued)

IgG1-6003-784	2.14	NB	2.33	4.27	6.50	3.25	5.86	NB
IgG1-6003-799	3.49	NB	2.63	3.36	4.16	3.20	5.02	NB
IgG1-6003-822	1.97	NB	1.49	1.89	2.08	2.59	2.31	NB
IgG1-6003-826	6.54	NB	6.95	15.40	18.06	9.36	18.27	NB
IgG1-6003-886	3.40	NB	2.44	3.36	3.45	2.72	4.42	NB
IgG1-6003-899	3.06	NB	2.32	17.70	5.55	4.54	5.35	NB
IgG1-6003-900	1.06	NB	0.91	1.06	1.19	1.16	1.26	NB
IgG1-6003-910	1.34	NB	1.16	1.84	2.23	1.54	2.59	NB
IgG1-6003-936	2.18	NB	1.85	11.40	2.86	2.62	3.20	NB
IgG1-6003-995	2.03	NB	1.42	10.21	2.99	2.03	3.31	NB
IgG1-6003-972	1.35	NB	1.12	2.36	2.57	1.49	3.08	NB

Figure 3 (continued)

Homogenous binding legend	
+	EC50 0.1-10 ng/ml
+	EC50 >10 ng/ml
NB	no binding

Figure 4

		E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
Domain	Antibody	530	784	010	471	532	910	072	972	826.0	028	030	056	083				
E	530	0.00	0.00	-0.01	-0.01	-0.01	0.00	0.00	-0.01	0.01	-0.04	-0.04	-0.04	-0.03				
E	784	-0.01	-0.01	0.00	-0.01	0.00	0.00	-0.01	0.00	0.00	-0.01	-0.01	-0.03	-0.01				
E	010	0.00	0.01	0.01	0.02	0.01	0.03	0.00	0.02	0.03	0.02	0.01	0.00	0.01				
E	471	0.01	0.02	0.00	0.01	0.02	0.02	0.01	0.02	0.02	0.01	0.01	0.01	0.02				
E	532	0.01	0.01	0.00	0.02	0.01	0.03	0.01	0.01	0.03	0.00	0.01	0.01	0.01				
E	910	0.02	0.03	0.01	0.02	0.03	0.04	0.02	0.04	0.05	0.01	0.02	0.00	0.02				
E	072	0.00	0.00	0.00	0.00	0.00	0.02	0.00	0.01	0.01	-0.01	0.00	0.00	0.00				
E	972	x	x	0.01	0.10	x	x	0.06	x	x	0.00	0.00	0.06	0.06				
E	826	0.00	0.00	0.00	-0.01	-0.01	0.00	0.00	0.00	0.01	-0.03	-0.03	-0.05	-0.03				
E	028	0.03	0.04	0.00	0.02	0.04	0.07	0.01	0.04	0.06	0.00	0.00	0.01	0.02				
E	030	0.03	0.03	0.00	0.02	0.04	0.06	0.01	0.05	0.06	0.00	0.01	0.01	0.02				
E	056	0.01	0.01	0.01	0.00	0.01	0.02	-0.07	0.01	0.02	0.01	0.01	0.00	0.01				
E	083	0.02	0.02	0.00	0.02	0.02	0.03	0.02	0.03	0.05	0.00	0.01	0.01	0.02				

Figure 4 - continued

E	381	0.01	0.02	0.00	0.01	0.01	0.02	0.02	0.03	0.03	0.00	0.01	0.00	0.01	0.00	0.01
E	408	0.01	0.02	0.00	0.01	0.01	0.02	0.05	0.00	0.03	0.01	0.01	0.01	0.00	0.01	0.01
E	423	0.01	0.02	0.01	0.01	0.01	0.01	0.03	0.01	0.02	-0.01	-0.01	-0.01	-0.02	0.00	0.00
E	799	0.02	0.01	0.01	0.01	0.01	0.01	0.05	0.00	0.02	0.00	0.05	0.00	0.00	0.01	0.01
E	822	0.00	0.01	0.01	0.01	0.01	0.00	0.01	0.00	0.01	0.00	0.02	0.00	0.00	0.01	0.01
E	1286	0.04	0.04	0.00	0.05	0.04	0.04	0.05	0.03	0.04	0.01	0.01	0.01	0.03	0.04	0.04
E	1342	0.01	0.02	0.02	0.00	0.03	0.03	0.03	0.02	0.03	0.01	-0.04	-0.01	-0.01	0.01	0.01
E	900	0.02	0.03	0.00	0.02	0.02	0.02	0.05	0.01	0.03	-0.01	-0.02	-0.01	-0.01	0.00	0.00
E	1277	0.02	0.01	0.00	0.08	0.02	0.02	0.04	0.01	0.02	0.01	0.01	0.01	0.01	0.02	0.02
E	899*	b	b	b	b	b	b	B	x	ND	x	x	x	x	x	x
E	995	b	b	0.21	b	b	b	b	x	x	-0.03	-0.03	x	x	x	x
E	936	b	b	0.71	0.33	b	b	b	x	x	-0.22	-0.20	-0.07	x	x	x
E	886	0.34	0.39	0.37	0.57	0.58	0.37	0.37	0.02	0.02	0.00	0.00	0.01	0.01	0.01	0.01

Figure 4 - continued

		E	E	E	E	E	E	E	E	E	E	E	E	E
Domain	Antibody	381	408	423	799	822	1286	1342	900	1277	899	995	936	886
E	530	-0.01	-0.02	-0.01	0.00	0.00	-0.03	-0.01	-0.03	-0.01	b	b	b	b
E	784	-0.01	0.00	0.00	0.00	0.00	-0.02	-0.01	-0.01	-0.01	b	b	b	b
E	010	0.00	0.01	0.01	0.02	0.03	0.01	0.03	0.02	0.01	0.52	0.60	0.53	0.44
E	471	0.01	0.02	0.01	0.02	0.01	0.01	0.02	0.02	0.01	0.54	0.62	0.58	0.54
E	532	0.01	0.01	0.01	0.02	0.03	0.02	0.03	0.01	0.01	0.64	0.71	0.64	0.51
E	910	0.01	0.02	0.04	0.03	0.03	0.02	0.04	0.03	0.02	0.23	0.31	0.35	0.51
E	072	0.00	0.00	0.00	0.01	0.01	0.00	0.02	0.00	0.00	0.01	0.02	0.01	0.05
E	972	x	x	0.10	x	x	x	x	x	x	ND	ND	ND	x
E	826	0.00	-0.01	0.00	0.00	0.00	-0.03	0.00	-0.03	-0.01	-0.02	-0.02	-0.03	0.00
E	028	0.02	0.02	0.03	0.05	0.07	0.04	0.07	0.04	0.04	0.02	0.02	-0.11	0.04
E	030	0.02	0.03	0.03	0.04	0.05	0.03	0.05	0.04	0.03	0.01	0.01	-0.10	0.03
E	056	0.00	0.01	0.01	0.01	0.01	0.01	0.03	0.01	0.01	0.01	0.00	-0.04	0.01
E	083	0.01	0.02	0.02	0.02	0.04	0.02	0.03	0.02	0.02	0.01	-0.02	-0.07	0.02

Figure 4 - continued

E	381	0.01	0.01	0.01	0.02	0.02	0.02	0.01	0.01	0.03	0.02	0.01	0.01	0.01	0.01	-0.07	0.01
E	408	0.00	0.01	0.01	0.02	0.02	0.06	0.02	0.02	0.03	0.02	0.02	0.02	0.02	0.05	0.02	0.01
E	423	0.00	0.01	0.01	0.00	0.02	0.02	0.02	0.00	0.03	0.01	0.01	0.01	0.01	0.00	-0.03	0.01
E	799	0.01	0.01	0.01	0.01	0.01	0.03	0.02	0.02	0.03	0.01	0.02	0.01	0.01	0.02	-0.09	0.02
E	822	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.01	0.00	-0.03	0.00
E	1286	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.03	-0.01	0.04
E	1342	0.00	0.02	0.01	0.01	0.03	0.01	0.01	0.01	0.03	0.02	0.01	0.01	0.00	-0.03	-0.09	0.01
E	900	0.01	0.01	0.01	0.03	0.03	0.03	0.02	0.02	0.05	0.02	0.04	0.03	0.04	0.04	0.03	0.02
E	1277	0.01	0.02	0.01	0.01	0.02	0.03	0.03	0.02	0.04	0.02	0.02	0.02	0.02	0.03	0.02	0.02
E	899*	x	x	x	x	x	x	x	x	x	x	x	x	ND	ND	ND	x
E	995	x	x	x	x	x	x	x	x	x	x	x	x	ND	ND	ND	x
E	936	x	x	x	x	x	x	x	x	x	x	x	x	ND	ND	ND	x
E	886	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.01	0.01	0.01	0.02	0.01	0.01	0.02	0.01	0.01

0	response < 0.1	b = binding - no cross block	ND= not done
0.2	response > 0.1	x = no binding - cross block	

Figure 5

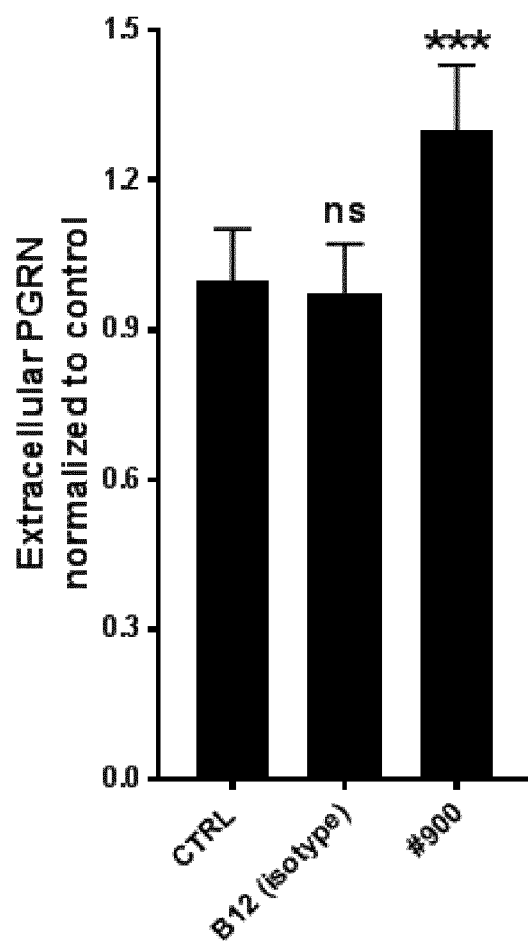


Figure 6

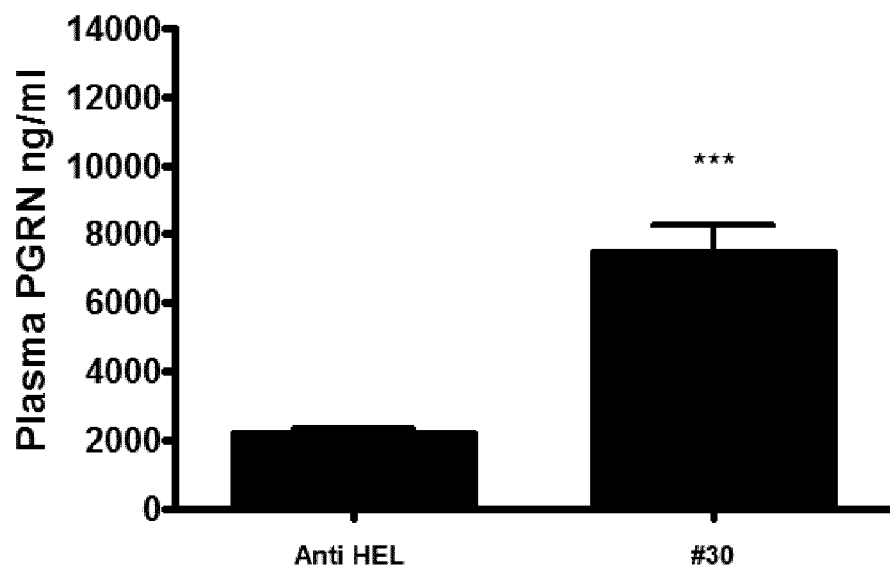


Fig 7 A

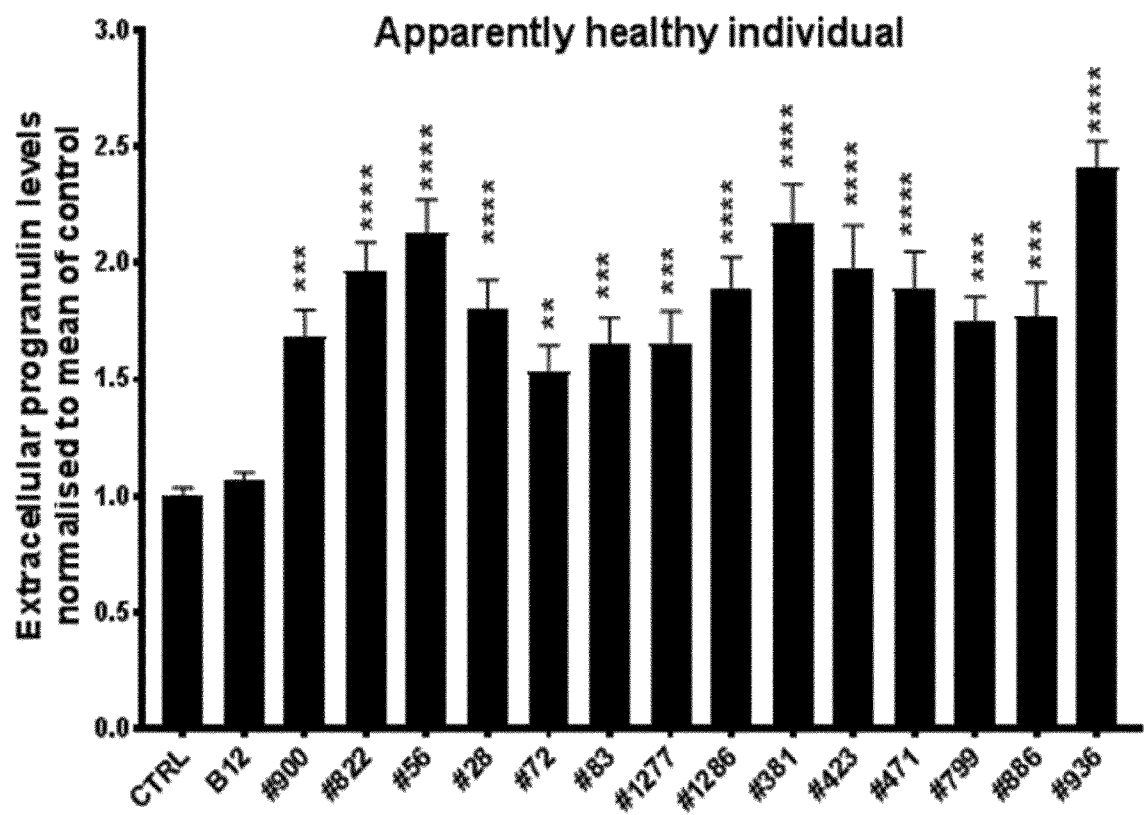


Fig 7 B

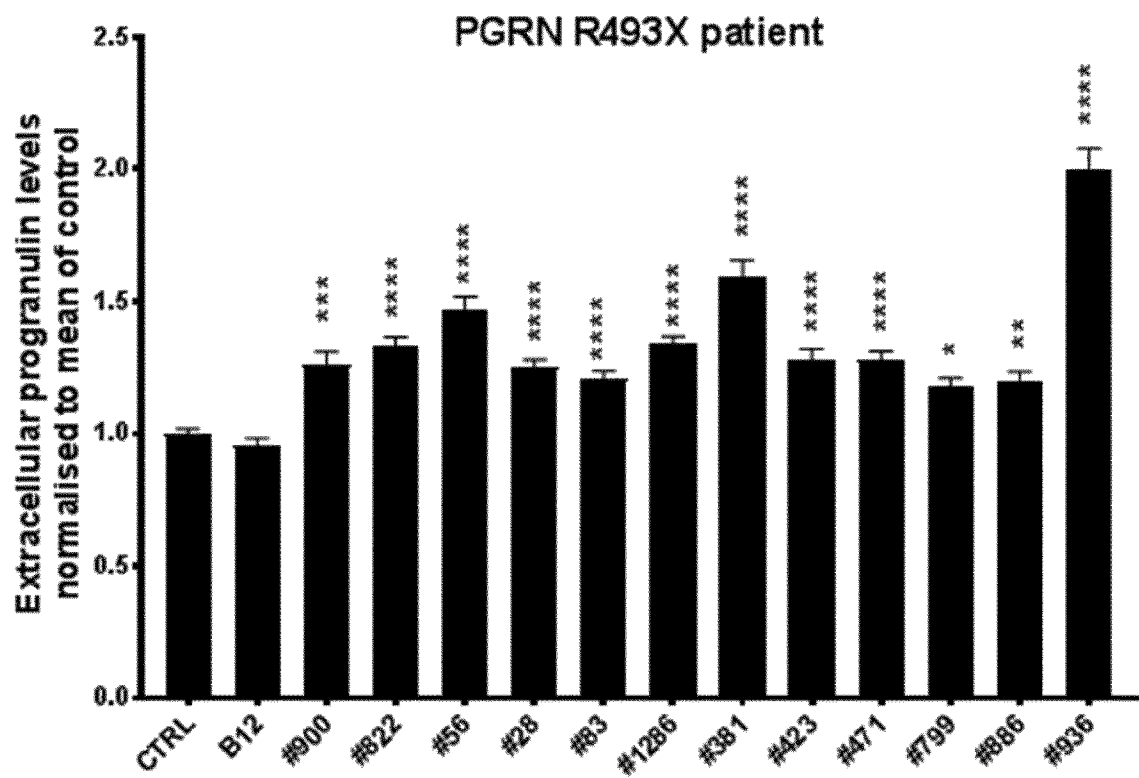
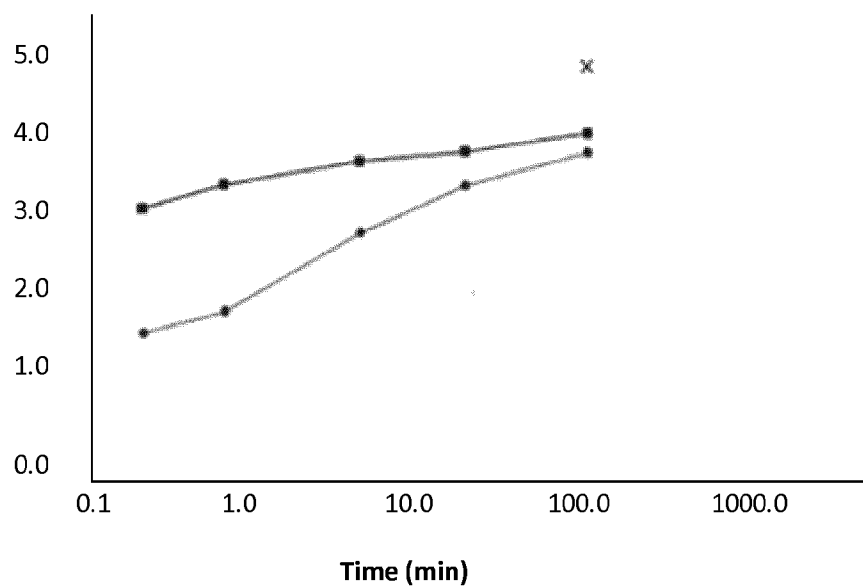


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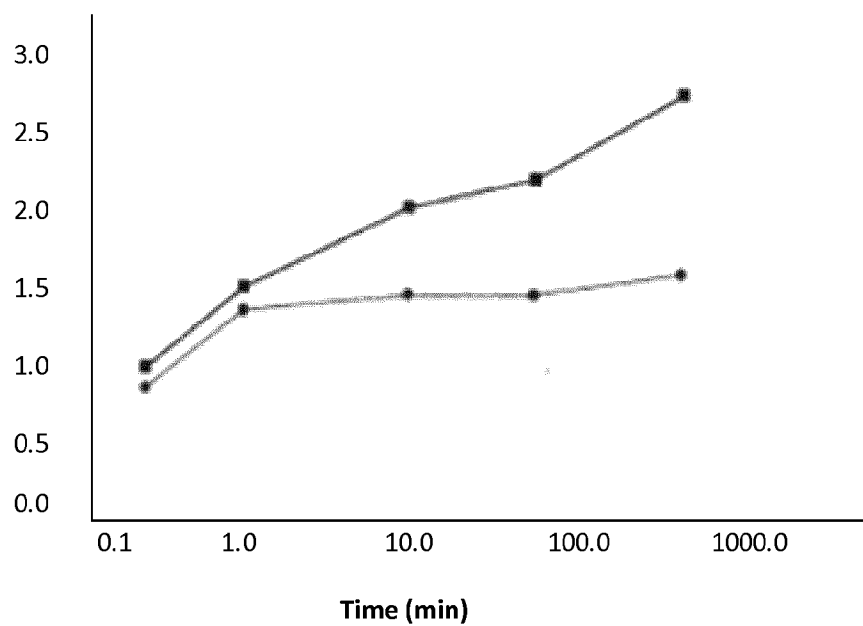
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Relative deuterium
uptake (D)

■	Sortilin
●	Sortilin + mAb30

Figure 8 B

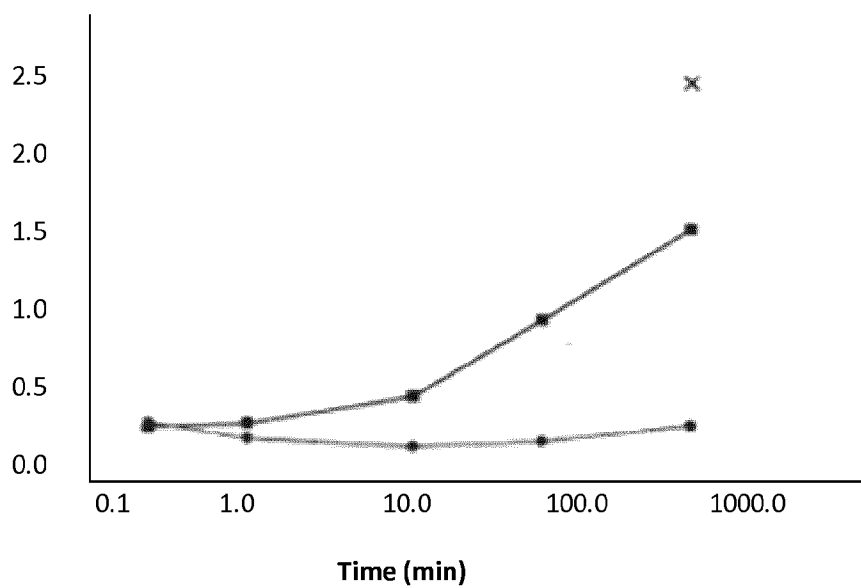
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Figure 8 C

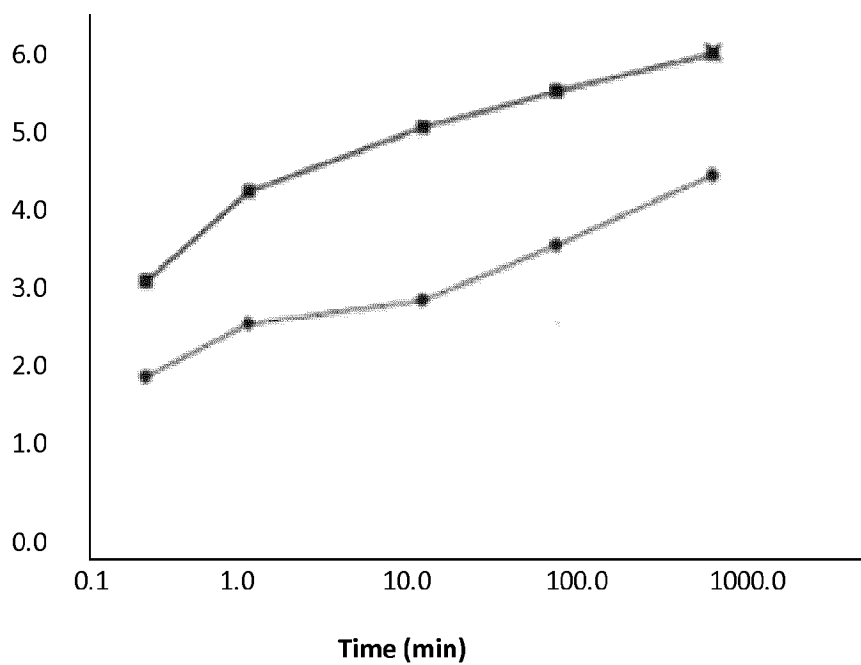
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Figure 8 D

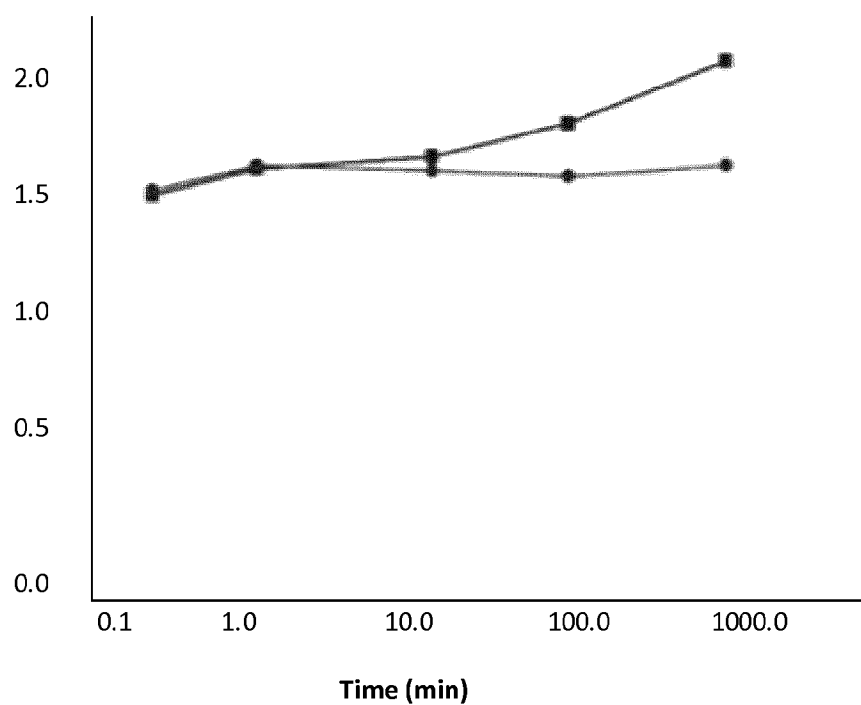
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Figure 8 E

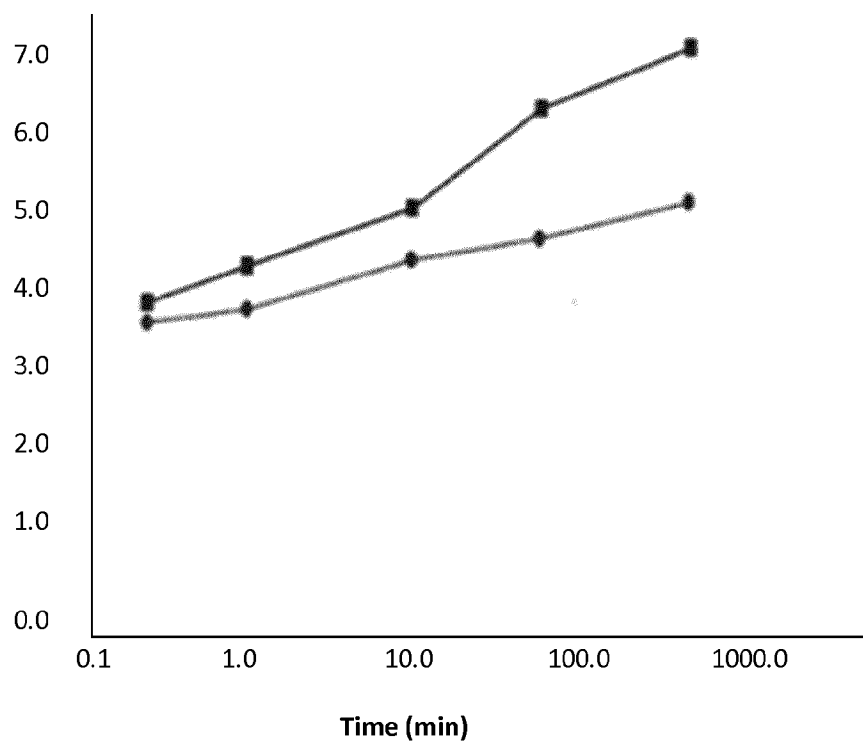
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Relative deuterium
uptake (D)

■	Sortilin
●	Sortilin + mAb30

Figure 8 F

715-728 YRKIPGDKKCQGGVN

Relative deuterium
uptake (D)

■	Sortilin
●	Sortilin + mAb30

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5 SEQUENCE LISTING

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 Gly

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55   Gly

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 35 40 45
 20 Ser Thr Ile Ser Gly Arg Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 25 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 30 Ala Asn Leu Tyr Ser Asn Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly
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 35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
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Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
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Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
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Glu Val Gln Val Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 30

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 35

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 40

Ser Ala Ile Ser Gly Arg Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 45

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 50

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 55

Ala Ile Ile Pro Ser Leu Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly
 100 105 110
 55

Thr Leu Val Thr Val Ser Ser
 115

<210> 112
 <211> 107
 <212> PRT
 5 <213> Artificial

 <220>
 <223> 6003-56 LC

 10 <400> 112

 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

 15 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Phe
 20 25 30

 20 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

 25 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
 30
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
 85 90 95

 35 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

 40 <210> 113
 <211> 119
 <212> PRT
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 45 <220>
 <223> 6003-1286 HC

 <400> 113

 50 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

1079-WO-PCT

<210> 115
 <211> 119
 <212> PRT
 5 <213> Artificial

 <220>
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 10 <400> 115

 Glu Val Gln Val Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

 20 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

 25 Ser Thr Ile Ser Gly Arg Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

 30 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

 35 Leu Gln Met Asp Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

 40 Ala Ile Ile Pro Ser Leu Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly
 100 105 110

 40 Thr Leu Val Thr Val Ser Ser
 115

 45 <210> 116
 <211> 107
 <212> PRT
 <213> Artificial

 <220>
 50 <223> 6003-30 LC

 <400> 116

 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

5 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

10 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

15 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80

20 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
 85 90 95

25 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

30 <210> 117
 <211> 116
 <212> PRT
 <213> Artificial
 <220>
 <223> 6003-1277 HC
 <400> 117

35 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

40 Ser Val Lys Val Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr His Tyr
 20 25 30

45 Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

50 Gly Trp Ile Asn Thr Tyr Asn Gly Asn Thr Lys Tyr Ala Gln Lys Leu
 50 55 60

55 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

60 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

65 Ala Ser Leu Gly Arg Asn Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110

Thr Val Ser Ser
 115

5
 <210> 118
 <211> 108
 <212> PRT
 <213> Artificial

10
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15
 <400> 118

1
 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

20
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

25
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

30
 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

35
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80

40
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ala
 85 90 95

45
 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

50
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 <211> 117
 <212> PRT
 <213> Artificial

55
 <220>
 <223> 6003-381 HC

<400> 119

1
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 20 25 30

5 Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Ala Ile Ser Tyr Asn Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 10 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 15 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Ser Tyr Cys
 85 90 95
 20 Ala Lys Gly Leu Asn Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
 100 105 110
 Val Thr Val Ser Ser
 115
 25 <210> 120
 <211> 108
 <212> PRT
 30 <213> Artificial
 <220>
 <223> 6003-381 LC
 35 <400> 120
 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 40 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Gly Tyr
 20 25 30
 45 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 50 Tyr Asn Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
 55 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
 85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

5
 <210> 121
 <211> 119
 <212> PRT
 <213> Artificial

10
 <220>
 <223> 6003-83 HC

15
 <400> 121

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

20 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

25 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

30 Ser Thr Ile Ser Gly Arg Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

35 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

40 Ala Ile Val Ala Thr Met Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly
 100 105 110

45 Thr Leu Val Thr Val Ser Ser
 115

50
 <210> 122
 <211> 107
 <212> PRT
 <213> Artificial

 <220>
 <223> 6003-83 LC

55
 <400> 122

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

5
10
15
20
25
30
35
40
45
50
55

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 123
<211> 117
<212> PRT
<213> Artificial

<220>
<223> 6003-799 HC

<400> 123

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Leu Thr Gly Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

5 Val Thr Val Ser Ser
115

10 <210> 124
<211> 108
<212> PRT
<213> Artificial

15 <220>
<223> 6003-799 LC
<400> 124

20 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

25 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

30 Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr His Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

35 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

40 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Arg
85 90 95

45 Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

50 <210> 125
<211> 124
<212> PRT
<213> Artificial
<220>
<223> 6003-910 HC

55 <400> 125

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 10 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Val Asp Ser Val
 50 55 60
 15 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 20 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 25 Ala Lys Asp Ile Arg Gly Ile Gly Phe Gly Tyr Tyr Tyr Gly Met Asp
 100 105 110
 Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120
 30 <210> 126
 <211> 107
 <212> PRT
 <213> Artificial
 35 <220>
 <223> 6003-910 LC
 40 <400> 126
 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 45 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30
 50 Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 55 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
 85 90 95

5

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 100 105

10

<210> 127
 <211> 117
 <212> PRT
 <213> Artificial

15

<220>
 <223> 6003-423 HC
 <400> 127

20

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

25

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Arg Ser Tyr
 20 25 30

30

Val Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

35

Ser Thr Ile Ser Gly Gly Gly Gly Asn Thr Asn Tyr Thr Asp Ser Val
 50 55 60

40

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

45

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

50

Ala Lys Asn Trp Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

55

<210> 128
 <211> 108
 <212> PRT
 <213> Artificial
 <220>
 <223> 6003-423 LC

<400> 128
 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 5
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30
 10
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 15
 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 20
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
 25
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Leu Ile
 85 90 95
 Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105
 30
 <210> 129
 <211> 117
 <212> PRT
 <213> Artificial
 35
 <220>
 <223> 6003-822 HC
 40
 <400> 129
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Glu
 1 5 10 15
 45
 Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
 20 25 30
 50
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 55
 Ser Ser Ile Ser Gly Arg Leu Gly Thr Thr Tyr Tyr Ala Ala Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Ser Cys
 85 90 95

5

Ala Lys Ala Pro Ser Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
 100 105 110

10

Val Thr Val Ser Ser
 115

15

<210> 130
 <211> 108
 <212> PRT
 <213> Artificial

20

<220>
 <223> 6003-822 LC

 <400> 130

25

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

30

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

35

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

40

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

45

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80

50

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
 85 90 95

55

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 131
 <211> 124
 <212> PRT
 <213> Artificial

 <220>
 <223> 6003-886 HC

<400> 131
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 5
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Lys Tyr
 20 25 30
 10
 Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 15
 Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
 50 55 60
 20
 Gln Asp Arg Val Thr Met Thr Thr Asp Thr Phe Thr Ser Thr Ala Tyr
 65 70 75 80
 25
 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
 85 90 95
 30
 Ala Arg Asp Gly Pro Leu Thr Gly Asp Phe Thr Phe Tyr Gly Met Asp
 100 105 110
 35
 Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120
 40
 <210> 132
 <211> 108
 <212> PRT
 <213> Artificial
 45
 <220>
 <223> 6003-886 LC
 <400> 132
 50
 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 55
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30
 60
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 65
 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
 5
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
 85 90 95
 10 Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105
 15 <210> 133
 <211> 121
 <212> PRT
 <213> Artificial
 20 <220>
 <223> 6003-72 HC
 <400> 133
 25 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 30 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 35 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 40 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 45 Leu Gln Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Thr Arg Gly Arg Gly Ile Gly Tyr Tyr Asn Gly Met Asp Val Trp Gly
 100 105 110
 50 Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120
 55 <210> 134
 <211> 109
 <212> PRT
 <213> Artificial

<220>
 <223> 6003-72 LC
 5 <400> 134
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 10 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 15 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 20 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 25 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
 85 90 95
 30 Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105
 35 <210> 135
 <211> 120
 <212> PRT
 <213> Artificial
 40 <220>
 <223> 6003-900 HC
 <400> 135
 45 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15
 50 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 55 Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 5
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 10
 Ala Arg Arg Gly Ser Gly Ser Tyr Asp Ala Phe Asp Ile Trp Gly Gln
 100 105 110
 15
 Gly Thr Met Val Thr Val Ser Ser
 115 120
 20
 <210> 136
 <211> 107
 <212> PRT
 <213> Artificial
 25
 <220>
 <223> 6003-900 LC
 <400> 136
 30
 Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
 1 5 10 15
 35
 Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Tyr Ser
 20 25 30
 40
 Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
 35 40 45
 45
 Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 50
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
 65 70 75 80
 55
 Glu Asp Ala Ala Ala Tyr Tyr Cys His Gln Ser Ser Ser Leu Pro Leu
 85 90 95
 60
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105
 65
 <210> 137
 <211> 122
 <212> PRT
 <213> Artificial

<220>
 <223> 6003-936 HC

5 <400> 137
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 10 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ile Phe Thr Ser Phe
 20 25 30
 15 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 20 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 25 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 30 Ala Arg His Ser Arg Gly Ser Phe Trp Tyr Gly Ala Phe Gln His Trp
 100 105 110
 35 Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

40 <210> 138
 <211> 107
 <212> PRT
 <213> Artificial

45 <220>
 <223> 6003-936 LC
 <400> 138
 Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
 1 5 10 15
 55 Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
 20 25 30
 Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
 35 40 45

Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 5
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
 65 70 75 80
 10 Glu Asp Ala Ala Ala Tyr Tyr Cys His Gln Ser Ser Ser Leu Pro His
 85 90 95
 15 Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105
 <210> 139
 <211> 124
 20 <212> PRT
 <213> Artificial
 <220>
 <223> 6003-408 HC
 25 <400> 139
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15
 30 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 35 Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 40 Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60
 45 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 50 Ala Arg Arg Arg Ile Ala Ala Ala Gly Thr Gly Tyr Gly Ala Phe Asp
 100 105 110
 55 Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
 115 120

<210> 140
 <211> 108
 <212> PRT
 <213> Artificial
 5
 <220>
 <223> 6003-408 LC
 <400> 140
 10
 Ala Arg Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 15 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Thr Ser Ala
 20 25 30
 20 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 25 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 30 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Gly Tyr Pro Met
 85 90 95
 35 Phe Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Ile
 100 105
 40
 <210> 141
 <211> 122
 <212> PRT
 <213> Artificial
 <220>
 45 <223> 6003-471 HC
 <400> 141
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
 20 25 30
 55 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Arg Ile Ile Pro Ile Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 5
 Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 10 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 15 Ala Arg Asp Arg Arg Gly Phe Ser Gly Tyr Glu Val Phe Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120
 20
 <210> 142
 <211> 107
 <212> PRT
 25 <213> Artificial
 <220>
 <223> 6003-471 LC
 30 <400> 142
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 35 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30
 40 Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
 35 40 45
 45 Tyr Ala Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 50 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Ile
 85 90 95
 55 Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 100 105

<210> 143
 <211> 119
 <212> PRT
 <213> Artificial
 5
 <220>
 <223> 6003-972 HC
 <400> 143
 10
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
 20 25 30
 20 Ala Met His Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Val Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 25 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 30 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 35 Ala Arg Asp Pro Ser Gly Gly Trp Tyr Phe Asp Leu Trp Gly Arg Gly
 100 105 110
 40 Thr Leu Val Thr Val Ser Ser
 115
 45
 <210> 144
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 55 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 5
 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 10 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
 15 Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Arg Ser His Trp Pro Arg
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 20 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
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 40 Ser Gln Asp Arg Leu Asp Ala Pro Pro Pro Pro Ala Ala Pro Leu Pro
 35 40 45
 45 Arg Trp Ser Gly Pro Ile Gly Val Ser Trp Gly Leu Arg Ala Ala Ala
 50 55 60
 Ala Gly Gly Ala Phe Pro Arg Gly Gly Arg Trp Arg Arg Ser Ala Pro
 65 70 75 80
 50 Gly Glu Asp Glu Glu Cys Gly Arg Val Arg Asp Phe Val Ala Lys Leu
 85 90 95
 55 Ala Asn Asn Thr His Gln His Val Phe Asp Asp Leu Arg Gly Ser Val
 100 105 110

Ser Leu Ser Trp Val Gly Asp Ser Thr Gly Val Ile Leu Val Leu Thr
 115 120 125

5 Thr Phe His Val Pro Leu Val Ile Met Thr Phe Gly Gln Ser Lys Leu
 130 135 140

10 Tyr Arg Ser Glu Asp Tyr Gly Lys Asn Phe Lys Asp Ile Thr Asp Leu
 145 150 155 160

15 Ile Asn Asn Thr Phe Ile Arg Thr Glu Phe Gly Met Ala Ile Gly Pro
 165 170 175

Glu Asn Ser Gly Lys Val Val Leu Thr Ala Glu Val Ser Gly Gly Ser
 180 185 190

20 Arg Gly Gly Arg Ile Phe Arg Ser Ser Asp Phe Ala Lys Asn Phe Val
 195 200 205

25 Gln Thr Asp Leu Pro Phe His Pro Leu Thr Gln Met Met Tyr Ser Pro
 210 215 220

30 Gln Asn Ser Asp Tyr Leu Leu Ala Leu Ser Thr Glu Asn Gly Leu Trp
 225 230 235 240

35 Val Ser Lys Asn Phe Gly Gly Lys Trp Glu Glu Ile His Lys Ala Val
 245 250 255

Cys Leu Ala Lys Trp Gly Ser Asp Asn Thr Ile Phe Phe Thr Thr Tyr
 260 265 270

40 Ala Asn Gly Ser Cys Lys Ala Asp Leu Gly Ala Leu Glu Leu Trp Arg
 275 280 285

45 Thr Ser Asp Leu Gly Lys Ser Phe Lys Thr Ile Gly Val Lys Ile Tyr
 290 295 300

50 Ser Phe Gly Leu Gly Gly Arg Phe Leu Phe Ala Ser Val Met Ala Asp
 305 310 315 320

55 Lys Asp Thr Thr Arg Arg Ile His Val Ser Thr Asp Gln Gly Asp Thr
 325 330 335

Trp Ser Met Ala Gln Leu Pro Ser Val Gly Gln Glu Gln Phe Tyr Ser
 340 345 350

Ile Leu Ala Ala Asn Asp Asp Met Val Phe Met His Val Asp Glu Pro
 355 360 365
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 Gly Asp Thr Gly Phe Gly Thr Ile Phe Thr Ser Asp Asp Arg Gly Ile
 370 375 380
 10
 Val Tyr Ser Lys Ser Leu Asp Arg His Leu Tyr Thr Thr Thr Gly Gly
 385 390 395 400
 15
 Glu Thr Asp Phe Thr Asn Val Thr Ser Leu Arg Gly Val Tyr Ile Thr
 405 410 415
 20
 Ser Val Leu Ser Glu Asp Asn Ser Ile Gln Thr Met Ile Thr Phe Asp
 420 425 430
 Gln Gly Gly Arg Trp Thr His Leu Arg Lys Pro Glu Asn Ser Glu Cys
 435 440 445
 25
 Asp Ala Thr Ala Lys Asn Lys Asn Glu Cys Ser Leu His Ile His Ala
 450 455 460
 30
 Ser Tyr Ser Ile Ser Gln Lys Leu Asn Val Pro Met Ala Pro Leu Ser
 465 470 475 480
 35
 Glu Pro Asn Ala Val Gly Ile Val Ile Ala His Gly Ser Val Gly Asp
 485 490 495
 40
 Ala Ile Ser Val Met Val Pro Asp Val Tyr Ile Ser Asp Asp Gly Gly
 500 505 510
 Tyr Ser Trp Thr Lys Met Leu Glu Gly Pro His Tyr Tyr Thr Ile Leu
 515 520 525
 45
 Asp Ser Gly Gly Ile Ile Val Ala Ile Glu His Ser Ser Arg Pro Ile
 530 535 540
 50
 Asn Val Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys Trp Gln Thr Tyr
 545 550 555 560
 55
 Thr Phe Thr Arg Asp Pro Ile Tyr Phe Thr Gly Leu Ala Ser Glu Pro
 565 570 575
 Gly Ala Arg Ser Met Asn Ile Ser Ile Trp Gly Phe Thr Glu Ser Phe
 580 585 590

- 134 -

820 825 830

5 <210> 146
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 <212> PRT
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10 <220>
 <223> E- Region
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15 Cys Glu Glu Lys Asp Tyr Thr Ile Trp Leu Ala His Ser Thr Asp Pro
 1 5 10 15

20 Glu Asp Tyr Glu Asp Gly Cys Ile Leu Gly Tyr Lys Glu Gln Phe Leu
 20 25 30

25 Arg Leu Arg Lys Ser Ser Val Cys Gln Asn Gly Arg Asp Tyr Val Val
 35 40 45

30 Thr Lys Gln Pro Ser Ile Cys Leu Cys Ser Leu Glu Asp Phe Leu Cys
 50 55 60

35 Asp Phe Gly Tyr Tyr Arg Pro Glu Asn Asp Ser Lys Cys Val Glu Gln
 65 70 75 80

40 Pro Glu Leu Lys Gly His Asp Leu Glu Phe Cys Leu Tyr Gly Arg Glu
 85 90 95

45 Glu His Leu Thr Thr Asn Gly Tyr Arg Lys Ile Pro Gly Asp Lys Cys
 100 105 110

50 Gln Gly Gly Val Asn Pro Val Arg Glu Val Lys Asp Leu Lys Lys Lys
 115 120 125

55 Cys Thr Ser Asn Phe Leu Ser Pro Glu Lys Gln Asn Ser Lys Ser Asn
 130 135 140

55 <210> 147
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<223> Sortilin "hSORTECDBAP"

<400> 147

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10 Ala Lys Leu Ala Asn Asn Thr His Gln His Val Phe Asp Asp Leu Arg
   20              25              30

15 Gly Ser Val Ser Leu Ser Trp Val Gly Asp Ser Thr Gly Val Ile Leu
   35              40              45

20 Val Leu Thr Thr Phe His Val Pro Leu Val Ile Met Thr Phe Gly Gln
   50              55              60

25 Ser Lys Leu Tyr Arg Ser Glu Asp Tyr Gly Lys Asn Phe Lys Asp Ile
   65              70              75              80

30 Thr Asp Leu Ile Asn Asn Thr Phe Ile Arg Thr Glu Phe Gly Met Ala
   85              90              95

35 Ile Gly Pro Glu Asn Ser Gly Lys Val Val Leu Thr Ala Glu Val Ser
   100             105             110

35 Gly Gly Ser Arg Gly Gly Arg Ile Phe Arg Ser Ser Asp Phe Ala Lys
   115             120             125

40 Asn Phe Val Gln Thr Asp Leu Pro Phe His Pro Leu Thr Gln Met Met
   130             135             140

45 Tyr Ser Pro Gln Asn Ser Asp Tyr Leu Leu Ala Leu Ser Thr Glu Asn
   145             150             155             160

50 Gly Leu Trp Val Ser Lys Asn Phe Gly Gly Lys Trp Glu Glu Ile His
   165             170             175

55 Lys Ala Val Cys Leu Ala Lys Trp Gly Ser Asp Asn Thr Ile Phe Phe
   180             185             190

   Thr Thr Tyr Ala Asn Gly Ser Cys Lys Ala Asp Leu Gly Ala Leu Glu
   195             200             205

   Leu Trp Arg Thr Ser Asp Leu Gly Lys Ser Phe Lys Thr Ile Gly Val
   210             215             220

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Lys Ile Tyr Ser Phe Gly Leu Gly Gly Arg Phe Leu Phe Ala Ser Val
 225 230 235 240
 5 Met Ala Asp Lys Asp Thr Thr Arg Arg Ile His Val Ser Thr Asp Gln
 245 250 255
 10 Gly Asp Thr Trp Ser Met Ala Gln Leu Pro Ser Val Gly Gln Glu Gln
 260 265 270
 15 Phe Tyr Ser Ile Leu Ala Ala Asn Asp Asp Met Val Phe Met His Val
 275 280 285
 20 Asp Glu Pro Gly Asp Thr Gly Phe Gly Thr Ile Phe Thr Ser Asp Asp
 290 295 300
 Arg Gly Ile Val Tyr Ser Lys Ser Leu Asp Arg His Leu Tyr Thr Thr
 305 310 315 320
 25 Thr Gly Gly Glu Thr Asp Phe Thr Asn Val Thr Ser Leu Arg Gly Val
 325 330 335
 30 Tyr Ile Thr Ser Val Leu Ser Glu Asp Asn Ser Ile Gln Thr Met Ile
 340 345 350
 35 Thr Phe Asp Gln Gly Gly Arg Trp Thr His Leu Arg Lys Pro Glu Asn
 355 360 365
 40 Ser Glu Cys Asp Ala Thr Ala Lys Asn Lys Asn Glu Cys Ser Leu His
 370 375 380
 Ile His Ala Ser Tyr Ser Ile Ser Gln Lys Leu Asn Val Pro Met Ala
 385 390 395 400
 45 Pro Leu Ser Glu Pro Asn Ala Val Gly Ile Val Ile Ala His Gly Ser
 405 410 415
 50 Val Gly Asp Ala Ile Ser Val Met Val Pro Asp Val Tyr Ile Ser Asp
 420 425 430
 55 Asp Gly Gly Tyr Ser Trp Thr Lys Met Leu Glu Gly Pro His Tyr Tyr
 435 440 445
 Thr Ile Leu Asp Ser Gly Gly Ile Ile Val Ala Ile Glu His Ser Ser
 450 455 460

5 Arg Pro Ile Asn Val Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys Trp
 465 470 475 480

 Gln Thr Tyr Thr Phe Thr Arg Asp Pro Ile Tyr Phe Thr Gly Leu Ala
 485 490 495

 10 Ser Glu Pro Gly Ala Arg Ser Met Asn Ile Ser Ile Trp Gly Phe Thr
 500 505 510

 15 Glu Ser Phe Leu Thr Ser Gln Trp Val Ser Tyr Thr Ile Asp Phe Lys
 515 520 525

 20 Asp Ile Leu Glu Arg Asn Cys Glu Glu Lys Asp Tyr Thr Ile Trp Leu
 530 535 540

 Ala His Ser Thr Asp Pro Glu Asp Tyr Glu Asp Gly Cys Ile Leu Gly
 545 550 555 560

 25 Tyr Lys Glu Gln Phe Leu Arg Leu Arg Lys Ser Ser Val Cys Gln Asn
 565 570 575

 30 Gly Arg Asp Tyr Val Val Thr Lys Gln Pro Ser Ile Cys Leu Cys Ser
 580 585 590

 35 Leu Glu Asp Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Pro Glu Asn Asp
 595 600 605

 40 Ser Lys Cys Val Glu Gln Pro Glu Leu Lys Gly His Asp Leu Glu Phe
 610 615 620

 Cys Leu Tyr Gly Arg Glu Glu His Leu Thr Thr Asn Gly Tyr Arg Lys
 625 630 635 640

 45 Ile Pro Gly Asp Lys Cys Gln Gly Gly Val Asn Pro Val Arg Glu Val
 645 650 655

 50 Lys Asp Leu Lys Lys Lys Cys Thr Ser Asn Phe Leu Ser Pro Glu Lys
 660 665 670

 55 Gln Asn Ser Lys Ser Asn Gly Ser Ala Gly Gly Ser Gly Gly Leu Asn
 675 680 685

 Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu

690 695 700

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 <212> PRT
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 <223> Sortilin SORTECDBAP_hBACK
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20 Ala Lys Leu Ala Asn Asn Thr His Gln His Ile Phe Asn Asp Leu Ser
 20 25 30

Gly Ser Val Ser Leu Ser Trp Val Gly Asp Ser Thr Gly Val Ile Leu
 35 40 45

25 Val Leu Thr Thr Phe Gln Val Pro Ile Phe Met Ile Thr Ile Gly Gln
 50 55 60

30 Ser Lys Leu Tyr Arg Ser Glu Asp Tyr Gly Lys Asn Phe Lys Asp Ile
 65 70 75 80

35 Thr Asp Leu Ile Asn Asn Thr Phe Ile Arg Ser Asp Phe Gly Ile Ala
 85 90 95

Ile Gly Pro Glu Asn Ser Gly Lys Val Val Leu Thr Ala Asp Val Ser
 100 105 110

40 Gly Ser His Gly Ser Arg Ile Phe Arg Ser Ser Asp Phe Ala Lys Asn
 115 120 125

45 Phe Val Gln Gln Glu Leu Pro Phe Val Pro Leu Met Gln Ile Met Tyr
 130 135 140

50 Ser Pro Gln Asn Ser Asp Tyr Leu Leu Ala Leu Ser Asn Lys Asn Glu
 145 150 155 160

55 Leu Trp Val Ser Lys Asn Phe Gly Gly Lys Trp Glu Lys Leu Tyr Asp
 165 170 175

Thr Val Cys Leu Ala Lys Trp Gly Ser Asp Asn Thr Ile Phe Phe Thr
 180 185 190

5	Ala	Asn	His	Asn	Gly	Ser	Cys	Ser	Asn	Asp	Arg	Gly	Met	Leu	Glu	Leu
			195					200					205			
	Trp	Arg	Thr	Ser	Asp	Leu	Gly	Lys	Ser	Phe	Lys	Thr	Ile	Gly	Ser	Lys
		210					215					220				
10	Ile	Tyr	Ser	Phe	Gly	Leu	Gly	Gly	Arg	Phe	Leu	Phe	Ala	Ser	Val	Met
	225					230					235					240
15	Thr	Gly	Lys	Gly	Thr	Leu	Arg	Ala	Ile	His	Val	Ser	Thr	Asp	Gln	Gly
					245					250					255	
20	Asp	Thr	Trp	Ser	Met	Ala	Gln	Leu	Pro	Pro	Val	Gly	His	Glu	Gln	Phe
				260					265					270		
	Tyr	Ser	Ile	Leu	Ala	Ala	Asn	Asp	Asp	Met	Val	Phe	Met	His	Val	Asp
25			275					280					285			
	Glu	Pro	Gly	Asp	Ser	Gly	Phe	Gly	Thr	Ile	Phe	Thr	Ser	Asp	Asp	Arg
		290					295					300				
30	Gly	Ile	Val	Tyr	Ser	Lys	Ser	Leu	Glu	Arg	His	Leu	Tyr	Thr	Thr	Thr
	305					310					315					320
35	Gly	Gly	Glu	Thr	Asp	Phe	Thr	Asn	Val	Thr	Ser	Leu	Arg	Gly	Val	Tyr
					325					330					335	
40	Ile	Thr	Ser	Ile	Leu	Ala	Glu	Asp	Lys	Ser	Val	Gln	Ser	Met	Ile	Thr
				340					345					350		
	Phe	Asp	Gln	Gly	Gly	Arg	Trp	Thr	His	Leu	Arg	Lys	Pro	Glu	Asn	Ser
45			355					360					365			
	Lys	Cys	Asp	Ala	Thr	Ala	Arg	Asp	Pro	Glu	Lys	Cys	Ser	Leu	His	Ile
		370					375					380				
50	His	Ala	Ala	Tyr	Ser	Ile	Ala	Thr	Gly	Leu	Asn	Val	Pro	Met	Leu	Pro
	385					390					395					400
55	Leu	Ser	Glu	Pro	Asn	Ala	Val	Gly	Ile	Val	Ile	Ala	His	Gly	Ser	Val
					405					410					415	
	Gly	Asp	Ala	Ile	Ser	Val	Met	Arg	Pro	Asp	Val	Tyr	Ile	Ser	Asp	Asp

	420	425	430
5	Gly Gly Tyr Ser Trp Thr Lys Ala Leu Glu Gly Pro His His Tyr Thr 435 440 445		
10	Ile Leu Asp Ser Gly Gly Ile Ile Val Ala Val Glu Gln Asn Ala His 450 455 460		
15	Gln Gly Val Asn Gln Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys Trp 465 470 475 480		
20	Gln Thr Tyr Asn Phe Thr Lys Asp Pro Ile Phe Phe Thr Gly Leu Ala 485 490 495		
25	Ser Glu Pro Gly Ala Arg Ser Met Asn Ile Ser Ile Trp Gly Tyr Arg 500 505 510		
30	Ser Ser Leu Phe His Gln Tyr Trp Ile Ser Tyr Thr Ile Asp Phe Lys 515 520 525		
35	Ala His Ser Thr Asp Pro Glu Asp Tyr Glu Asp Gly Cys Ile Leu Gly 545 550 555 560		
40	Tyr Lys Glu Gln Phe Leu Arg Leu Arg Lys Ser Ser Val Cys Gln Asn 565 570 575		
45	Gly Arg Asp Tyr Val Val Thr Lys Gln Pro Ser Ile Cys Leu Cys Ser 580 585 590		
50	Leu Glu Asp Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Pro Glu Asn Asp 595 600 605		
55	Ser Lys Cys Val Glu Gln Pro Glu Leu Lys Gly His Asp Leu Glu Phe 610 615 620		
	Cys Leu Tyr Gly Arg Glu Glu His Leu Thr Thr Asn Gly Tyr Arg Lys 625 630 635 640		
	Ile Pro Gly Asp Lys Cys Gln Gly Gly Val Asn Pro Val Arg Glu Val 645 650 655		

Lys Asp Leu Lys Lys Lys Cys Thr Ser Asn Phe Leu Ser Pro Glu Lys
 660 665 670

5 Gln Asn Ser Lys Ser Asn Gly Ser Ala Gly Gly Ser Gly Gly Leu Asn
 675 680 685

10 Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
 690 695 700

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25 Arg Ser Thr Glu Gln Gly Glu Ser Cys Ser Gly Leu Leu Gly Ala Asp
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30 Ala Lys Leu Ala Gly Asn Thr His Gln His Ile Phe Asn Asp Leu Ser
 20 25 30

35 Gly Ser Val Ser Leu Ala Trp Val Gly Asp Gly Thr Gly Val Ile Leu
 35 40 45

40 Ala Leu Thr Thr Phe Gln Val Pro Ile Phe Met Ile Thr Ile Gly Gln
 50 55 60

45 Ser Lys Leu Tyr Arg Ser Glu Asp Tyr Gly Lys Ser Phe Glu Asp Val
 65 70 75 80

50 Thr Asn Leu Ile Asn Asn Thr Phe Ile Arg Ser Asp Phe Gly Ile Ala
 85 90 95

55 Ile Gly Pro Glu Asn Ser Gly Lys Val Ile Leu Thr Ala Asp Val Ser
 100 105 110

60 Gly Ser His Gly Ser Arg Ile Phe Val Ser Ser Asp Phe Gly Lys Ser
 115 120 125

65 Phe Thr His Gln Glu Leu Pro Phe Val Pro Leu Met Gln Ile Thr Tyr
 130 135 140

70 Asn Pro Glu Asn Ser Asn Val Leu Leu Ala Leu Ser Asn Lys Asn Glu

	145				150					155				160		
5	Leu	Trp	Leu	Ser	Glu	Asp	Phe	Gly	Thr	Asn	Trp	Lys	Lys	Leu	Tyr	Asp
					165					170				175		
10	Thr	Val	Cys	Leu	Ala	Lys	Trp	Gly	Arg	Lys	Gly	Thr	Ile	Phe	Phe	Thr
				180					185					190		
15	Ala	Asn	His	Asn	Gly	Ser	Cys	Ser	Asn	Asp	Arg	Gly	Met	Leu	Glu	Leu
			195					200					205			
20	Glu	Arg	Thr	Thr	Asp	Tyr	Gly	Lys	Ser	Phe	Lys	Thr	Val	Ala	Ser	Lys
		210					215					220				
25	Ile	Tyr	Ser	Phe	Gly	Leu	Gly	Gly	Lys	Phe	Leu	Phe	Ala	Ser	Val	Met
	225					230					235					240
30	Thr	Gly	Lys	Gly	Thr	Leu	Arg	Ala	Ile	His	Val	Ser	Val	Asp	Asp	Gly
					245					250					255	
35	Asp	Thr	Trp	Asn	Met	Ala	Gln	Leu	Pro	Pro	Val	Gly	His	Glu	Gln	Phe
				260					265					270		
40	Tyr	Ser	Ile	Leu	Ala	Ala	Asn	Asp	Glu	Met	Val	Phe	Met	His	Val	Asp
			275					280					285			
45	Glu	Pro	Gly	Asp	Ser	Gly	Phe	Gly	Thr	Ile	Tyr	Val	Ser	Asp	Asp	Arg
		290					295					300				
50	Gly	Thr	Val	Tyr	Ser	Lys	Ser	Leu	Glu	Arg	His	Leu	Tyr	Thr	Thr	Thr
	305					310					315					320
55	Gly	Gly	Glu	Thr	Asp	Phe	Ile	Asn	Val	Thr	Ser	Leu	Arg	Gly	Val	Phe
					325					330					335	
60	Thr	Thr	Ser	Ile	Leu	Ala	Glu	Asp	Lys	Ser	Val	Gln	Ser	Val	Ile	Ser
				340					345					350		
65	Phe	Asp	Gln	Gly	Gly	Glu	Trp	Val	Pro	Leu	Arg	Lys	Pro	Ala	Asp	Ser
			355					360					365			
70	Lys	Cys	Asp	Ala	Thr	Ala	Arg	Asp	Pro	Glu	Lys	Cys	Ser	Leu	His	Ile
		370					375					380				

His Ala Ala Tyr Ser Ile Ala Thr Gly Leu Asn Val Pro Met Leu Pro
 385 390 395 400

5 Leu Ser Glu Pro Asn Ala Val Gly Leu Val Leu Ala His Gly Ser Val
 405 410 415

10 Gly Asp Ala Ile Ser Val Met Arg Pro Asp Val Tyr Val Ser Asp Asp
 420 425 430

15 Gly Gly Tyr Thr Trp Ile Lys Ala Leu Glu Gly Pro His His Tyr Ala
 435 440 445

Ile Leu Asp Ser Gly Gly Leu Leu Val Ala Val Glu Gln Asn Ala His
 450 455 460

20 Gln Gly Val Asn Gln Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys Trp
 465 470 475 480

25 Gly Val Tyr Asn Phe Thr Lys Asp Pro Ile Phe Phe Thr Gly Leu Ala
 485 490 495

30 Ser Glu Pro Gly Ala Arg Ser Met Asn Val Ser Leu Trp Gly Tyr Arg
 500 505 510

35 Ser Ser Leu Phe His Gln Tyr Trp Ile Ser Phe Thr Ile Asp Phe Arg
 515 520 525

Asp Leu Ile Thr Arg Asn Cys Thr Asp Lys Asp Tyr Val Gln Trp Leu
 530 535 540

40 Ala His Ser Asp Asp Ile Ser Asp Pro Asn Asp Gly Cys Met Leu Gly
 545 550 555 560

45 Tyr Lys Glu Lys Phe Leu Arg Leu Lys Lys Asp Ser Val Cys Leu Asn
 565 570 575

50 Gly Arg Asp Tyr Glu Val Asn Thr Gln Pro Thr Pro Cys Leu Cys Thr
 580 585 590

55 Leu Asp Asp Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Lys Glu Asn Ser
 595 600 605

Ser Glu Cys Val Glu Gln Pro Asp Leu Lys Gly Lys Val Leu Glu Phe
 610 615 620

Cys Leu His Gly Thr Glu Glu Glu Leu Leu Thr Asn Gly Tyr Arg Lys
 625 630 635 640

5

Ile Pro Gly Asp Lys Cys Glu Gly Gly Gln Ile Pro Glu Arg Lys Glu
 645 650 655

10

Ile Asn Leu Arg Arg Arg Cys Val Ser Asp Leu Leu Gly Pro Glu Phe
 660 665 670

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Leu Val Lys Lys Ser Ser Gly Ser Ala Gly Gly Ser Gly Gly Leu Asn
 675 680 685

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Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
 690 695 700

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Gly Ser Val Ser Leu Ser Trp Val Gly Asp Ser Thr Gly Val Ile Leu
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Val Leu Thr Thr Phe His Val Pro Leu Val Ile Met Thr Phe Gly Gln
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50

Ser Lys Leu Tyr Arg Ser Glu Asp Tyr Gly Lys Asn Phe Lys Asp Ile
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55

Thr Asp Leu Ile Asn Asn Thr Phe Ile Arg Thr Glu Phe Gly Met Ala
 85 90 95

Ile Gly Pro Glu Asn Ser Gly Lys Val Val Leu Thr Ala Glu Val Ser
 100 105 110

Gly Gly Ser Arg Gly Gly Arg Ile Phe Arg Ser Ser Asp Phe Ala Lys
 115 120 125

5 Asn Phe Val Gln Thr Asp Leu Pro Phe His Pro Leu Thr Gln Met Met
 130 135 140

10 Tyr Ser Pro Gln Asn Ser Asp Tyr Leu Leu Ala Leu Ser Thr Glu Asn
 145 150 155 160

15 Gly Leu Trp Val Ser Lys Asn Phe Gly Gly Lys Trp Glu Glu Ile His
 165 170 175

Lys Ala Val Cys Leu Ala Lys Trp Gly Ser Asp Asn Thr Ile Phe Phe
 180 185 190

20 Thr Thr Tyr Ala Asn Gly Ser Cys Lys Ala Asp Leu Gly Ala Leu Glu
 195 200 205

25 Leu Trp Arg Thr Ser Asp Leu Gly Lys Ser Phe Lys Thr Ile Gly Val
 210 215 220

30 Lys Ile Tyr Ser Phe Gly Leu Gly Gly Arg Phe Leu Phe Ala Ser Val
 225 230 235 240

35 Met Ala Asp Lys Asp Thr Thr Arg Arg Ile His Val Ser Thr Asp Gln
 245 250 255

Gly Asp Thr Trp Ser Met Ala Gln Leu Pro Pro Val Gly His Glu Gln
 260 265 270

40 Phe Tyr Ser Ile Leu Ala Ala Asn Asp Glu Met Val Phe Met His Val
 275 280 285

45 Asp Glu Pro Gly Asp Ser Gly Phe Gly Thr Ile Tyr Val Ser Asp Asp
 290 295 300

50 Arg Gly Thr Val Tyr Ser Lys Ser Leu Glu Arg His Leu Tyr Thr Thr
 305 310 315 320

55 Thr Gly Gly Glu Thr Asp Phe Ile Asn Val Thr Ser Leu Arg Gly Val
 325 330 335

Phe Thr Thr Ser Ile Leu Ala Glu Asp Lys Ser Val Gln Ser Val Ile
 340 345 350

Ser Phe Asp Gln Gly Gly Glu Trp Val Pro Leu Arg Lys Pro Ala Asp
 355 360 365
 5
 Ser Lys Cys Asp Ala Thr Ala Arg Asp Pro Glu Lys Cys Ser Leu His
 370 375 380
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 Ile His Ala Ala Tyr Ser Ile Ala Thr Gly Leu Asn Val Pro Met Leu
 385 390 395 400
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 Pro Leu Ser Glu Pro Asn Ala Val Gly Leu Val Leu Ala His Gly Ser
 405 410 415
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 Val Gly Asp Ala Ile Ser Val Met Arg Pro Asp Val Tyr Val Ser Asp
 420 425 430
 Asp Gly Gly Tyr Thr Trp Ile Lys Ala Leu Glu Gly Pro His His Tyr
 435 440 445
 25
 Ala Ile Leu Asp Ser Gly Gly Leu Leu Val Ala Val Glu Gln Asn Ala
 450 455 460
 30
 His Gln Gly Val Asn Gln Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys
 465 470 475 480
 35
 Trp Gly Val Tyr Asn Phe Thr Lys Asp Pro Ile Phe Phe Thr Gly Leu
 485 490 495
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 Ala Ser Glu Pro Gly Ala Arg Ser Met Asn Val Ser Leu Trp Gly Tyr
 500 505 510
 Arg Ser Ser Leu Phe His Gln Tyr Trp Ile Ser Phe Thr Ile Asp Phe
 515 520 525
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 Arg Asp Leu Ile Thr Arg Asn Cys Thr Asp Lys Asp Tyr Val Gln Trp
 530 535 540
 50
 Leu Ala His Ser Asp Asp Ile Ser Asp Pro Asn Asp Gly Cys Met Leu
 545 550 555 560
 55
 Gly Tyr Lys Glu Lys Phe Leu Arg Leu Lys Lys Asp Ser Val Cys Leu
 565 570 575
 Asn Gly Arg Asp Tyr Glu Val Asn Thr Gln Pro Thr Pro Cys Leu Cys
 580 585 590

5 Thr Leu Asp Asp Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Lys Glu Asn
 595 600 605
 Ser Ser Glu Cys Val Glu Gln Pro Asp Leu Lys Gly Lys Val Leu Glu
 610 615 620
 10 Phe Cys Leu His Gly Thr Glu Glu Glu Leu Leu Thr Asn Gly Tyr Arg
 625 630 635 640
 15 Lys Ile Pro Gly Asp Lys Cys Glu Gly Gly Gln Ile Pro Glu Arg Lys
 645 650 655
 20 Glu Ile Asn Leu Arg Arg Arg Cys Val Ser Asp Leu Leu Gly Pro Glu
 660 665 670
 Phe Leu Val Lys Lys Ser Ser Gly Ser Ala Gly Gly Ser Gly Gly Leu
 675 680 685
 25 Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
 690 695 700
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 45 Ala Lys Leu Ala Asn Asn Thr His Gln His Val Phe Asp Asp Leu Arg
 20 25 30
 50 Gly Ser Val Ser Leu Ala Trp Val Gly Asp Gly Thr Gly Val Ile Leu
 35 40 45
 Ala Leu Thr Thr Phe Gln Val Pro Ile Phe Met Ile Thr Ile Gly Gln
 50 55 60
 55 Ser Lys Leu Tyr Arg Ser Glu Asp Tyr Gly Lys Asn Phe Lys Asp Ile
 65 70 75 80

Thr Asp Leu Ile Asn Asn Thr Phe Ile Arg Ser Asp Phe Gly Ile Ala
 85 90 95
 5
 Ile Gly Pro Glu Asn Ser Gly Lys Val Ile Leu Thr Ala Asp Val Ser
 100 105 110
 10
 Gly Ser His Gly Ser Arg Ile Phe Arg Ser Ser Asp Phe Ala Lys Asn
 115 120 125
 15
 Phe Val Gln Thr Asp Leu Pro Phe Val Pro Leu Met Gln Ile Thr Tyr
 130 135 140
 20
 Asn Pro Glu Asn Ser Asn Val Leu Leu Ala Leu Ser Asn Lys Asn Glu
 145 150 155 160
 Leu Trp Val Ser Lys Asn Phe Gly Gly Lys Trp Glu Glu Ile His Asp
 165 170 175
 25
 Thr Val Cys Leu Ala Lys Trp Gly Arg Lys Gly Thr Ile Phe Phe Thr
 180 185 190
 30
 Ala Asn His Asn Gly Ser Cys Ser Asn Asp Arg Gly Met Leu Glu Leu
 195 200 205
 35
 Trp Arg Thr Ser Asp Leu Gly Lys Ser Phe Lys Thr Ile Gly Val Lys
 210 215 220
 40
 Ile Tyr Ser Phe Gly Leu Gly Gly Lys Phe Leu Phe Ala Ser Val Met
 225 230 235 240
 Thr Gly Lys Gly Thr Leu Arg Arg Ile His Val Ser Thr Asp Gln Gly
 245 250 255
 45
 Asp Thr Trp Ser Met Ala Gln Leu Pro Ser Val Gly His Glu Gln Phe
 260 265 270
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 Tyr Ser Ile Leu Ala Ala Asn Asp Glu Met Val Phe Met His Val Asp
 275 280 285
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 Glu Pro Gly Asp Ser Gly Phe Gly Thr Ile Phe Thr Ser Asp Asp Arg
 290 295 300
 Gly Ile Val Tyr Ser Lys Ser Leu Asp Arg His Leu Tyr Thr Thr Thr
 305 310 315 320

Gly Gly Glu Thr Asp Phe Ile Asn Val Thr Ser Leu Arg Gly Val Phe
 325 330 335
 5
 Thr Thr Ser Ile Leu Ala Glu Asp Lys Ser Ile Gln Thr Met Ile Thr
 340 345 350
 10
 Phe Asp Gln Gly Gly Arg Trp Thr His Leu Arg Lys Pro Glu Asn Ser
 355 360 365
 15
 Glu Cys Asp Ala Thr Ala Lys Asn Lys Asn Glu Cys Ser Leu His Ile
 370 375 380
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 His Ala Ala Tyr Ser Ile Ala Thr Gly Leu Asn Val Pro Met Leu Pro
 385 390 395 400
 Leu Ser Glu Pro Asn Ala Val Gly Leu Val Leu Ala His Gly Ser Val
 405 410 415
 25
 Gly Asp Ala Ile Ser Val Met Arg Pro Asp Val Tyr Ile Ser Asp Asp
 420 425 430
 30
 Gly Gly Tyr Ser Trp Thr Lys Met Leu Glu Gly Pro His His Tyr Ala
 435 440 445
 35
 Ile Leu Asp Ser Gly Gly Leu Leu Val Ala Val Glu Gln Asn Ala His
 450 455 460
 40
 Gln Gly Val Asn Val Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys Trp
 465 470 475 480
 Gln Thr Tyr Thr Phe Thr Arg Asp Pro Ile Phe Phe Thr Gly Leu Ala
 485 490 495
 45
 Ser Glu Pro Gly Ala Arg Ser Met Asn Val Ser Leu Trp Gly Tyr Arg
 500 505 510
 50
 Ser Ser Leu Phe His Gln Gln Trp Val Ser Tyr Thr Ile Asp Phe Lys
 515 520 525
 55
 Asp Ile Leu Glu Arg Asn Cys Glu Glu Lys Asp Tyr Thr Ile Trp Leu
 530 535 540
 Ala His Ser Thr Asp Pro Glu Asp Tyr Glu Asp Gly Cys Ile Leu Gly

545 550 555 560
 Tyr Lys Glu Gln Phe Leu Arg Leu Arg Lys Ser Ser Val Cys Gln Asn
 5 565 570 575
 Gly Arg Asp Tyr Val Val Thr Lys Gln Pro Ser Ile Cys Leu Cys Ser
 10 580 585 590
 Leu Glu Asp Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Pro Glu Asn Asp
 15 595 600 605
 Ser Lys Cys Val Glu Gln Pro Glu Leu Lys Gly His Asp Leu Glu Phe
 20 610 615 620
 Cys Leu Tyr Gly Arg Glu Glu His Leu Thr Thr Asn Gly Tyr Arg Lys
 25 625 630 635 640
 Ile Pro Gly Asp Lys Cys Gln Gly Gly Val Asn Pro Val Arg Glu Val
 30 645 650 655
 Lys Asp Leu Lys Lys Lys Cys Thr Ser Asn Phe Leu Ser Pro Glu Lys
 35 660 665 670
 Gln Asn Ser Lys Ser Asn Gly Ser Ala Gly Gly Ser Gly Gly Leu Asn
 40 675 680 685
 Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
 45 690 695 700
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 Ala Lys Leu Ala Gly Asn Thr His Gln His Ile Phe Asn Asp Leu Ser
 55 20 25 30
 Gly Ser Val Ser Leu Ala Trp Val Gly Asp Gly Thr Gly Val Ile Leu
 35 40 45

5	Ala 50	Leu	Thr	Thr	Phe	Gln	Val 55	Pro	Ile	Phe	Met	Ile 60	Thr	Ile	Gly	Gln
10	Ser 65	Lys	Leu	Tyr	Arg	Ser 70	Glu	Asp	Tyr	Gly	Lys 75	Ser	Phe	Glu	Asp	Val 80
15	Thr	Asn	Leu	Ile	Asn 85	Asn	Thr	Phe	Ile	Arg 90	Ser	Asp	Phe	Gly	Ile 95	Ala
20	Ile	Gly	Pro	Glu 100	Asn	Ser	Gly	Lys	Val 105	Ile	Leu	Thr	Ala	Asp	Val	Ser
25	Gly	Ser	His 115	Gly	Ser	Arg	Ile	Phe 120	Val	Ser	Ser	Asp	Phe 125	Gly	Lys	Ser
30	Phe 130	Thr	His	Gln	Glu	Leu	Pro 135	Phe	Val	Pro	Leu	Met 140	Gln	Ile	Thr	Tyr
35	Asn 145	Pro	Glu	Asn	Ser	Asn 150	Val	Leu	Leu	Ala	Leu 155	Ser	Asn	Lys	Asn	Glu 160
40	Leu	Trp	Leu	Ser	Glu 165	Asp	Phe	Gly	Thr	Asn 170	Trp	Lys	Lys	Leu	Tyr 175	Asp
45	Thr	Val	Cys	Leu 180	Ala	Lys	Trp	Gly	Arg 185	Lys	Gly	Thr	Ile 190	Phe	Phe	Thr
50	Ala	Asn	His 195	Asn	Gly	Ser	Cys	Ser 200	Asn	Asp	Arg	Gly	Met 205	Leu	Glu	Leu
55	Glu	Arg 210	Thr	Thr	Asp	Tyr	Gly 215	Lys	Ser	Phe	Lys	Thr 220	Val	Ala	Ser	Lys
60	Ile 225	Tyr	Ser	Phe	Gly	Leu 230	Gly	Gly	Lys	Phe	Leu 235	Phe	Ala	Ser	Val	Met 240
65	Thr	Gly	Lys	Gly	Thr 245	Leu	Arg	Ala	Ile	His 250	Val	Ser	Val	Asp	Asp	Gly
70	Asp	Thr	Trp	Asn 260	Met	Ala	Gln	Leu	Pro 265	Ser	Val	Gly	Gln	Glu	Gln	Phe
75	Tyr	Ser	Ile	Leu	Ala	Ala	Asn	Asp	Asp	Met	Val	Phe	Met	His	Val	Asp

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Ser Phe Leu Thr Ser Gln Trp Val Ser Tyr Thr Ile Asp Phe Lys Asp
 515 520 525

5 Ile Leu Glu Arg Asn Cys Glu Glu Lys Asp Tyr Thr Ile Trp Leu Ala
 530 535 540

10 His Ser Thr Asp Pro Glu Asp Tyr Glu Asp Gly Cys Ile Leu Gly Tyr
 545 550 555 560

15 Lys Glu Gln Phe Leu Arg Leu Arg Lys Ser Ser Val Cys Gln Asn Gly
 565 570 575

Arg Asp Tyr Val Val Thr Lys Gln Pro Ser Ile Cys Leu Cys Ser Leu
 580 585 590

20 Glu Asp Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Pro Glu Asn Asp Ser
 595 600 605

25 Lys Cys Val Glu Gln Pro Glu Leu Lys Gly His Asp Leu Glu Phe Cys
 610 615 620

30 Leu Tyr Gly Arg Glu Glu His Leu Thr Thr Asn Gly Tyr Arg Lys Ile
 625 630 635 640

35 Pro Gly Asp Lys Cys Gln Gly Gly Val Asn Pro Val Arg Glu Val Lys
 645 650 655

40 Asp Leu Lys Lys Lys Cys Thr Ser Asn Phe Leu Ser Pro Glu Lys Gln
 660 665 670

Asn Ser Lys Ser Asn Gly Ser Ala Gly Gly Ser Gly Gly Leu Asn Asp
 675 680 685

45 Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
 690 695

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55 <220>
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			20						25					30		
10	Gly	Ser	Val	Ser	Leu	Ser	Trp	Val	Gly	Asp	Ser	Thr	Gly	Val	Ile	Leu
			35					40					45			
15	Val	Leu	Thr	Thr	Phe	His	Val	Pro	Leu	Val	Ile	Met	Thr	Phe	Gly	Gln
	50						55					60				
20	Ser	Lys	Leu	Tyr	Arg	Ser	Glu	Asp	Tyr	Gly	Lys	Asn	Phe	Lys	Asp	Ile
	65					70					75				80	
25	Thr	Asp	Leu	Ile	Asn	Asn	Thr	Phe	Ile	Arg	Thr	Glu	Phe	Gly	Met	Ala
					85					90					95	
30	Ile	Gly	Pro	Glu	Asn	Ser	Gly	Lys	Val	Val	Leu	Thr	Ala	Glu	Val	Ser
				100					105					110		
35	Gly	Gly	Ser	Arg	Gly	Gly	Arg	Ile	Phe	Arg	Ser	Ser	Asp	Phe	Ala	Lys
			115					120					125			
40	Asn	Phe	Val	Gln	Thr	Asp	Leu	Pro	Phe	His	Pro	Leu	Thr	Gln	Met	Met
	130						135					140				
45	Tyr	Ser	Pro	Gln	Asn	Ser	Asp	Tyr	Leu	Leu	Ala	Leu	Ser	Thr	Glu	Asn
	145				150						155				160	
50	Gly	Leu	Trp	Val	Ser	Lys	Asn	Phe	Gly	Gly	Lys	Trp	Glu	Glu	Ile	His
					165					170					175	
55	Lys	Thr	Val	Cys	Leu	Ala	Lys	Trp	Gly	Arg	Lys	Gly	Thr	Ile	Phe	Phe
			180						185					190		
60	Thr	Ala	Asn	His	Asn	Gly	Ser	Cys	Ser	Asn	Asp	Arg	Gly	Met	Leu	Glu
		195						200					205			
65	Leu	Glu	Arg	Thr	Thr	Asp	Tyr	Gly	Lys	Ser	Phe	Lys	Thr	Val	Ala	Ser
	210						215					220				
70	Lys	Ile	Tyr	Ser	Phe	Gly	Leu	Gly	Gly	Lys	Phe	Leu	Phe	Ala	Ser	Val
	225					230					235					240

Met Thr Gly Lys Gly Thr Leu Arg Ala Ile His Val Ser Val Asp Asp
245 250 255

5 Gly Asp Thr Trp Asn Met Ala Gln Leu Pro Pro Val Gly His Glu Gln
260 265 270

10 Phe Tyr Ser Ile Leu Ala Ala Asn Asp Glu Met Val Phe Met His Val
275 280 285

15 Asp Glu Pro Gly Asp Ser Gly Phe Gly Thr Ile Tyr Val Ser Asp Asp
290 295 300

Arg Gly Thr Val Tyr Ser Lys Ser Leu Glu Arg His Leu Tyr Thr Thr
305 310 315 320

20 Thr Gly Gly Glu Thr Asp Phe Ile Asn Val Thr Ser Leu Arg Gly Val
325 330 335

25 Phe Thr Thr Ser Ile Leu Ala Glu Asp Lys Ser Val Gln Ser Val Ile
340 345 350

30 Ser Phe Asp Gln Gly Gly Glu Trp Val Pro Leu Arg Lys Pro Ala Asp
355 360 365

35 Ser Lys Cys Asp Ala Thr Ala Arg Asp Pro Glu Lys Cys Ser Leu His
370 375 380

Ile His Ala Ala Tyr Ser Ile Ala Thr Gly Leu Asn Val Pro Met Leu
385 390 395 400

40 Pro Leu Ser Glu Pro Asn Ala Val Gly Leu Val Leu Ala His Gly Ser
405 410 415

45 Val Gly Asp Ala Ile Ser Val Met Arg Pro Asp Val Tyr Val Ser Asp
420 425 430

50 Asp Gly Gly Tyr Thr Trp Ile Lys Ala Leu Glu Gly Pro His Tyr Tyr
435 440 445

55 Thr Ile Leu Asp Ser Gly Gly Ile Ile Val Ala Ile Glu His Ser Ser
450 455 460

Arg Pro Ile Asn Val Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys Trp
465 470 475 480

Gln Thr Tyr Thr Phe Thr Arg Asp Pro Ile Tyr Phe Thr Gly Leu Ala
 485 490 495
 5
 Ser Glu Pro Gly Ala Arg Ser Met Asn Ile Ser Ile Trp Gly Phe Thr
 500 505 510
 10
 Glu Ser Phe Leu Thr Ser Gln Trp Val Ser Tyr Thr Ile Asp Phe Lys
 515 520 525
 15
 Asp Ile Leu Glu Arg Asn Cys Glu Glu Lys Asp Tyr Thr Ile Trp Leu
 530 535 540
 20
 Ala His Ser Thr Asp Pro Glu Asp Tyr Glu Asp Gly Cys Ile Leu Gly
 545 550 555 560
 Tyr Lys Glu Gln Phe Leu Arg Leu Arg Lys Ser Ser Val Cys Gln Asn
 565 570 575
 25
 Gly Arg Asp Tyr Val Val Thr Lys Gln Pro Ser Ile Cys Leu Cys Ser
 580 585 590
 30
 Leu Glu Asp Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Pro Glu Asn Asp
 595 600 605
 35
 Ser Lys Cys Val Glu Gln Pro Glu Leu Lys Gly His Asp Leu Glu Phe
 610 615 620
 40
 Cys Leu Tyr Gly Arg Glu Glu His Leu Thr Thr Asn Gly Tyr Arg Lys
 625 630 635 640
 Ile Pro Gly Asp Lys Cys Gln Gly Gly Val Asn Pro Val Arg Glu Val
 645 650 655
 45
 Lys Asp Leu Lys Lys Lys Cys Thr Ser Asn Phe Leu Ser Pro Glu Lys
 660 665 670
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 Gln Asn Ser Lys Ser Asn Gly Ser Ala Gly Gly Ser Gly Gly Leu Asn
 675 680 685
 55
 Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
 690 695 700

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<211> 700

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<212> PRT
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Ala Lys Leu Ala Gly Asn Thr His Gln His Ile Phe Asn Asp Leu Ser
15   20             25             30

Gly Ser Val Ser Leu Ala Trp Val Gly Asp Gly Thr Gly Val Ile Leu
   35             40             45

20 Ala Leu Thr Thr Phe Gln Val Pro Ile Phe Met Ile Thr Ile Gly Gln
   50             55             60

25 Ser Lys Leu Tyr Arg Ser Glu Asp Tyr Gly Lys Ser Phe Glu Asp Val
   65             70             75             80

30 Thr Asn Leu Ile Asn Asn Thr Phe Ile Arg Ser Asp Phe Gly Ile Ala
   85             90             95

Ile Gly Pro Glu Asn Ser Gly Lys Val Ile Leu Thr Ala Asp Val Ser
35   100            105            110

Gly Ser His Gly Ser Arg Ile Phe Val Ser Ser Asp Phe Gly Lys Ser
   115            120            125

40 Phe Thr His Gln Glu Leu Pro Phe Val Pro Leu Met Gln Ile Thr Tyr
   130            135            140

45 Asn Pro Glu Asn Ser Asn Val Leu Leu Ala Leu Ser Asn Lys Asn Glu
   145            150            155            160

50 Leu Trp Leu Ser Glu Asp Phe Gly Thr Asn Trp Lys Lys Leu Tyr Asp
   165            170            175

Ala Val Cys Leu Ala Lys Trp Gly Ser Asp Asn Thr Ile Phe Phe Thr
55   180            185            190

Thr Tyr Ala Asn Gly Ser Cys Lys Ala Asp Leu Gly Ala Leu Glu Leu
   195            200            205

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Trp Arg Thr Ser Asp Leu Gly Lys Ser Phe Lys Thr Ile Gly Val Lys
 210 215 220
 5
 Ile Tyr Ser Phe Gly Leu Gly Gly Arg Phe Leu Phe Ala Ser Val Met
 225 230 235 240
 10 Ala Asp Lys Asp Thr Thr Arg Arg Ile His Val Ser Thr Asp Gln Gly
 245 250 255
 15 Asp Thr Trp Ser Met Ala Gln Leu Pro Ser Val Gly Gln Glu Gln Phe
 260 265 270
 20 Tyr Ser Ile Leu Ala Ala Asn Asp Asp Met Val Phe Met His Val Asp
 275 280 285
 Glu Pro Gly Asp Thr Gly Phe Gly Thr Ile Phe Thr Ser Asp Asp Arg
 290 295 300
 25 Gly Ile Val Tyr Ser Lys Ser Leu Asp Arg His Leu Tyr Thr Thr Thr
 305 310 315 320
 30 Gly Gly Glu Thr Asp Phe Thr Asn Val Thr Ser Leu Arg Gly Val Tyr
 325 330 335
 35 Ile Thr Ser Val Leu Ser Glu Asp Asn Ser Ile Gln Thr Met Ile Thr
 340 345 350
 40 Phe Asp Gln Gly Gly Arg Trp Thr His Leu Arg Lys Pro Glu Asn Ser
 355 360 365
 Glu Cys Asp Ala Thr Ala Lys Asn Lys Asn Glu Cys Ser Leu His Ile
 370 375 380
 45 His Ala Ser Tyr Ser Ile Ser Gln Lys Leu Asn Val Pro Met Ala Pro
 385 390 395 400
 50 Leu Ser Glu Pro Asn Ala Val Gly Ile Val Ile Ala His Gly Ser Val
 405 410 415
 55 Gly Asp Ala Ile Ser Val Met Val Pro Asp Val Tyr Ile Ser Asp Asp
 420 425 430
 Gly Gly Tyr Ser Trp Thr Lys Met Leu Glu Gly Pro His His Tyr Ala
 435 440 445

5	Ile 450	Leu	Asp	Ser	Gly	Gly 455	Leu	Leu	Val	Ala	Val	Glu 460	Gln	Asn	Ala	His
10	Gln 465	Gly	Val	Asn	Gln	Ile 470	Lys	Phe	Ser	Thr	Asp 475	Glu	Gly	Gln	Cys	Trp 480
15	Gly	Val	Tyr	Asn	Phe 485	Thr	Lys	Asp	Pro	Ile 490	Phe	Phe	Thr	Gly	Leu 495	Ala
20	Ser	Glu	Pro	Gly 500	Ala	Arg	Ser	Met	Asn 505	Val	Ser	Leu	Trp	Gly 510	Tyr	Arg
25	Ser	Ser	Leu 515	Phe	His	Gln	Tyr	Trp 520	Ile	Ser	Phe	Thr	Ile 525	Asp	Phe	Arg
30	Asp	Leu 530	Ile	Thr	Arg	Asn	Cys 535	Glu	Glu	Lys	Asp	Tyr 540	Thr	Ile	Trp	Leu
35	Ala 545	His	Ser	Thr	Asp	Pro 550	Glu	Asp	Tyr	Glu	Asp 555	Gly	Cys	Ile	Leu	Gly 560
40	Tyr	Lys	Glu	Gln	Phe 565	Leu	Arg	Leu	Arg	Lys 570	Ser	Ser	Val	Cys	Gln 575	Asn
45	Gly	Arg	Asp	Tyr 580	Val	Val	Thr	Lys	Gln 585	Pro	Ser	Ile	Cys	Leu 590	Cys	Ser
50	Leu	Glu	Asp 595	Phe	Leu	Cys	Asp	Phe 600	Gly	Tyr	Tyr	Arg	Pro 605	Glu	Asn	Asp
55	Ser	Lys 610	Cys	Val	Glu	Gln	Pro 615	Glu	Leu	Lys	Gly	His 620	Asp	Leu	Glu	Phe
60	Cys 625	Leu	Tyr	Gly	Arg	Glu 630	Glu	His	Leu	Thr	Thr 635	Asn	Gly	Tyr	Arg	Lys 640
65	Ile	Pro	Gly	Asp	Lys 645	Cys	Gln	Gly	Gly	Val 650	Asn	Pro	Val	Arg	Glu 655	Val
70	Lys	Asp	Leu	Lys 660	Lys	Lys	Cys	Thr	Ser 665	Asn	Phe	Leu	Ser	Pro 670	Glu	Lys
75	Gln	Asn	Ser	Lys	Ser	Asn	Gly	Ser	Ala	Gly	Gly	Ser	Gly	Gly	Leu	Asn

675 680 685
 5 Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
 690 695 700

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 Gly Leu Gly Leu Leu Leu Leu Leu Gln Leu Leu Pro Pro Ser Thr Leu
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 25 Ser Gln Asp Arg Leu Asp Ala Pro Pro Pro Pro Ala Ala Pro Leu Pro
 35 40 45
 30 Arg Trp Ser Gly Pro Ile Gly Val Ser Trp Gly Leu Arg Ala Ala Ala
 50 55 60

 35 Ala Gly Gly Ala Phe Pro Arg Gly Gly Arg Trp Arg Arg Ser Ala Pro
 65 70 75 80

 Gly Glu Asp Glu Glu Cys Gly Arg Val Arg Asp Phe Val Ala Lys Leu
 85 90 95
 40 Ala Asn Asn Thr His Gln His Val Phe Asp Asp Leu Arg Gly Ser Val
 100 105 110
 45 Ser Leu Ser Trp Val Gly Asp Ser Thr Gly Val Ile Leu Val Leu Thr
 115 120 125
 50 Thr Phe His Val Pro Leu Val Ile Met Thr Phe Gly Gln Ser Lys Leu
 130 135 140

 55 Tyr Arg Ser Glu Asp Tyr Gly Lys Asn Phe Lys Asp Ile Thr Asp Leu
 145 150 155 160

 Ile Asn Asn Thr Phe Ile Arg Thr Glu Phe Gly Met Ala Ile Gly Pro
 165 170 175

5	Glu	Asn	Ser	Gly	Lys	Val	Val	Leu	Thr	Ala	Glu	Val	Ser	Gly	Gly	Ser
				180					185					190		
	Arg	Gly	Gly	Arg	Ile	Phe	Arg	Ser	Ser	Asp	Phe	Ala	Lys	Asn	Phe	Val
			195					200					205			
10	Gln	Thr	Asp	Leu	Pro	Phe	His	Pro	Leu	Thr	Gln	Met	Met	Tyr	Ser	Pro
		210					215					220				
15	Gln	Asn	Ser	Asp	Tyr	Leu	Leu	Ala	Leu	Ser	Thr	Glu	Asn	Gly	Leu	Trp
	225					230					235					240
20	Val	Ser	Lys	Asn	Phe	Gly	Gly	Lys	Trp	Glu	Glu	Ile	His	Lys	Ala	Val
					245					250					255	
	Cys	Leu	Ala	Lys	Trp	Gly	Ser	Asp	Asn	Thr	Ile	Phe	Phe	Thr	Thr	Tyr
				260					265					270		
25	Ala	Asn	Gly	Ser	Cys	Lys	Ala	Asp	Leu	Gly	Ala	Leu	Glu	Leu	Trp	Arg
			275					280					285			
30	Thr	Ser	Asp	Leu	Gly	Lys	Ser	Phe	Lys	Thr	Ile	Gly	Val	Lys	Ile	Tyr
		290					295					300				
35	Ser	Phe	Gly	Leu	Gly	Gly	Arg	Phe	Leu	Phe	Ala	Ser	Val	Met	Ala	Asp
	305					310					315					320
40	Lys	Asp	Thr	Thr	Arg	Arg	Ile	His	Val	Ser	Thr	Asp	Gln	Gly	Asp	Thr
					325					330					335	
	Trp	Ser	Met	Ala	Gln	Leu	Pro	Ser	Val	Gly	Gln	Glu	Gln	Phe	Tyr	Ser
				340					345					350		
45	Ile	Leu	Ala	Ala	Asn	Asp	Asp	Met	Val	Phe	Met	His	Val	Asp	Glu	Pro
			355					360					365			
50	Gly	Asp	Thr	Gly	Phe	Gly	Thr	Ile	Phe	Thr	Ser	Asp	Asp	Arg	Gly	Ile
		370					375					380				
55	Val	Tyr	Ser	Lys	Ser	Leu	Asp	Arg	His	Leu	Tyr	Thr	Thr	Thr	Gly	Gly
	385					390					395					400
	Glu	Thr	Asp	Phe	Thr	Asn	Val	Thr	Ser	Leu	Arg	Gly	Val	Tyr	Ile	Thr

				405					410					415			
5	Ser	Val	Leu	Ser	Glu	Asp	Asn	Ser	Ile	Gln	Thr	Met	Ile	Thr	Phe	Asp	
				420					425					430			
10	Gln	Gly	Gly	Arg	Trp	Thr	His	Leu	Arg	Lys	Pro	Glu	Asn	Ser	Glu	Cys	
			435					440					445				
15	Asp	Ala	Thr	Ala	Lys	Asn	Lys	Asn	Glu	Cys	Ser	Leu	His	Ile	His	Ala	
		450					455					460					
20	Ser	Tyr	Ser	Ile	Ser	Gln	Lys	Leu	Asn	Val	Pro	Met	Ala	Pro	Leu	Ser	
	465					470					475				480		
25	Glu	Pro	Asn	Ala	Val	Gly	Ile	Val	Ile	Ala	His	Gly	Ser	Val	Gly	Asp	
					485					490					495		
30	Ala	Ile	Ser	Val	Met	Val	Pro	Asp	Val	Tyr	Ile	Ser	Asp	Asp	Gly	Gly	
				500					505					510			
35	Tyr	Ser	Trp	Thr	Lys	Met	Leu	Glu	Gly	Pro	His	Tyr	Tyr	Thr	Ile	Leu	
			515					520					525				
40	Asp	Ser	Gly	Gly	Ile	Ile	Val	Ala	Ile	Glu	His	Ser	Ser	Arg	Pro	Ile	
		530					535					540					
45	Asn	Val	Ile	Lys	Phe	Ser	Thr	Asp	Glu	Gly	Gln	Cys	Trp	Gln	Thr	Tyr	
	545					550					555					560	
50	Thr	Phe	Thr	Arg	Asp	Pro	Ile	Tyr	Phe	Thr	Gly	Leu	Ala	Ser	Glu	Pro	
				565					570						575		
55	Gly	Ala	Arg	Ser	Met	Asn	Ile	Ser	Ile	Trp	Gly	Phe	Thr	Glu	Ser	Phe	
				580					585					590			
60	Leu	Thr	Ser	Gln	Trp	Val	Ser	Tyr	Thr	Ile	Asp	Phe	Lys	Asp	Ile	Leu	
			595					600					605				
65	Glu	Arg	Asn	Cys	Glu	Glu	Lys	Asp	Tyr	Thr	Ile	Trp	Leu	Ala	His	Ser	
		610					615					620					
70	Thr	Asp	Pro	Glu	Asp	Tyr	Glu	Asp	Gly	Cys	Ile	Leu	Gly	Tyr	Lys	Glu	
	625					630					635					640	

Gln Phe Leu Arg Leu Arg Lys Ser Ser Val Cys Gln Asn Gly Arg Asp
 645 650 655

5 Tyr Val Val Thr Lys Gln Pro Ser Ile Cys Leu Cys Ser Leu Glu Asp
 660 665 670

10 Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Pro Glu Asn Asp Ser Lys Cys
 675 680 685

15 Val Glu Gln Pro Glu Leu Lys Gly His Asp Leu Glu Phe Cys Leu Tyr
 690 695 700

Gly Arg Glu Glu His Leu Thr Thr Asn Gly Tyr Arg Lys Ile Pro Gly
 705 710 715 720

20 Asp Lys Cys Gln Gly Gly Val Asn Pro Val Arg Glu Val Lys Asp Leu
 725 730 735

25 Lys Lys Lys Cys Thr Ser Asn Phe Leu Ser Pro Glu Lys Gln Asn Ser
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30 Lys Ser Asn His His His His His His His His
 755 760

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40 <400> 156

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45 Ala Lys Leu Ala Asn Asn Thr His Gln His Val Phe Asp Asp Leu Arg
 20 25 30

50 Gly Ser Val Ser Leu Ser Trp Val Gly Asp Ser Thr Gly Val Ile Leu
 35 40 45

55 Val Leu Thr Thr Phe His Val Pro Leu Val Ile Met Thr Phe Gly Gln
 50 55 60

Ser Lys Leu Tyr Arg Ser Glu Asp Tyr Gly Lys Asn Phe Lys Asp Ile
 65 70 75 80

Thr Asp Leu Ile Asn Asn Thr Phe Ile Arg Thr Glu Phe Gly Met Ala
 85 90 95
 5
 Ile Gly Pro Glu Asn Ser Gly Lys Val Val Leu Thr Ala Glu Val Ser
 100 105 110
 10
 Gly Gly Ser Arg Gly Gly Arg Ile Phe Arg Ser Ser Asp Phe Ala Lys
 115 120 125
 15
 Asn Phe Val Gln Thr Asp Leu Pro Phe His Pro Leu Thr Gln Met Met
 130 135 140
 20
 Tyr Ser Pro Gln Asn Ser Asp Tyr Leu Leu Ala Leu Ser Thr Glu Asn
 145 150 155 160
 Gly Leu Trp Val Ser Lys Asn Phe Gly Gly Lys Trp Glu Glu Ile His
 165 170 175
 25
 Lys Ala Val Cys Leu Ala Lys Trp Gly Ser Asp Asn Thr Ile Phe Phe
 180 185 190
 30
 Thr Thr Tyr Ala Asn Gly Ser Cys Lys Ala Asp Leu Gly Ala Leu Glu
 195 200 205
 35
 Leu Trp Arg Thr Ser Asp Leu Gly Lys Ser Phe Lys Thr Ile Gly Val
 210 215 220
 40
 Lys Ile Tyr Ser Phe Gly Leu Gly Gly Arg Phe Leu Phe Ala Ser Val
 225 230 235 240
 Met Ala Asp Lys Asp Thr Thr Arg Arg Ile His Val Ser Thr Asp Gln
 245 250 255
 45
 Gly Asp Thr Trp Ser Met Ala Gln Leu Pro Ser Val Gly Gln Glu Gln
 260 265 270
 50
 Phe Tyr Ser Ile Leu Ala Ala Asn Asp Asp Met Val Phe Met His Val
 275 280 285
 55
 Asp Glu Pro Gly Asp Thr Gly Phe Gly Thr Ile Phe Thr Ser Asp Asp
 290 295 300
 Arg Gly Ile Val Tyr Ser Lys Ser Leu Asp Arg His Leu Tyr Thr Thr

	305		310		315		320
5	Thr Gly Gly Glu Thr Asp Phe Thr Asn Val Thr Ser Leu Arg Gly Val	325		330		335	
10	Tyr Ile Thr Ser Val Leu Ser Glu Asp Asn Ser Ile Gln Thr Met Ile	340		345		350	
15	Thr Phe Asp Gln Gly Gly Arg Trp Thr His Leu Arg Lys Pro Glu Asn	355		360		365	
20	Ser Glu Cys Asp Ala Thr Ala Lys Asn Lys Asn Glu Cys Ser Leu His	370		375		380	
25	Ile His Ala Ser Tyr Ser Ile Ser Gln Lys Leu Asn Val Pro Met Ala	385		390		395	400
30	Pro Leu Ser Glu Pro Asn Ala Val Gly Ile Val Ile Ala His Gly Ser	405		410		415	
35	Val Gly Asp Ala Ile Ser Val Met Val Pro Asp Val Tyr Ile Ser Asp	420		425		430	
40	Asp Gly Gly Tyr Ser Trp Thr Lys Met Leu Glu Gly Pro His Tyr Tyr	435		440		445	
45	Thr Ile Leu Asp Ser Gly Gly Ile Ile Val Ala Ile Glu His Ser Ser	450		455		460	
50	Arg Pro Ile Asn Val Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys Trp	465		470		475	480
55	Gln Thr Tyr Thr Phe Thr Arg Asp Pro Ile Tyr Phe Thr Gly Leu Ala	485		490		495	
	Ser Glu Pro Gly Ala Arg Ser Met Asn Ile Ser Ile Trp Gly Phe Thr	500		505		510	
	Glu Ser Phe Leu Thr Ser Gln Trp Val Ser Tyr Thr Ile Asp Phe Lys	515		520		525	
	Asp Ile Leu Glu Arg Asn Cys Glu Glu Lys Asp Tyr Thr Ile Trp Leu	530		535		540	

	Ala	His	Ser	Thr	Asp	Pro	Glu	Asp	Tyr	Glu	Asp	Gly	Cys	Ile	Leu	Gly	
	545					550					555					560	
5	Tyr	Lys	Glu	Gln	Phe	Leu	Arg	Leu	Arg	Lys	Ser	Ser	Val	Cys	Gln	Asn	
					565					570					575		
10	Gly	Arg	Asp	Tyr	Val	Val	Thr	Lys	Gln	Pro	Ser	Ile	Cys	Leu	Cys	Ser	
				580					585					590			
15	Leu	Glu	Asp	Phe	Leu	Cys	Asp	Phe	Gly	Tyr	Tyr	Arg	Pro	Glu	Asn	Asp	
			595					600					605				
20	Ser	Lys	Cys	Val	Glu	Gln	Pro	Glu	Leu	Lys	Gly	His	Asp	Leu	Glu	Phe	
		610					615					620					
25	Cys	Leu	Tyr	Gly	Arg	Glu	Glu	His	Leu	Thr	Thr	Asn	Gly	Tyr	Arg	Lys	
	625					630					635					640	
30	Ile	Pro	Gly	Asp	Lys	Cys	Gln	Gly	Gly	Val	Asn	Pro	Val	Arg	Glu	Val	
					645					650					655		
35	Lys	Asp	Leu	Lys	Lys	Lys	Cys	Thr	Ser	Asn	Phe	Leu	Ser	Pro	Glu	Lys	
				660					665					670			
40	Gln	Asn	Ser	Lys	Ser	Asn	Ser	Gly	Ser	Ala	Met	Ile	Glu	Gly	Arg	Gly	
			675					680					685				
	Val	Gly	His	His	His	His	His	His									
		690					695										