

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**
- 5 2. The antibody, or antigen-binding fragment thereof, according to claim 1, wherein the antigen-binding fragment is selected from the group consisting of: an Fv fragment (e.g. single chain Fv or a disulphide-bonded Fv); a Fab-like fragment (e.g. Fab fragment, Fab' fragment or a F(ab)2 fragment); and a domain antibody (e.g. a single VH variable
10 domain or VL variable domain).
3. The antibody according to any preceding claims, wherein the antibody consists of an intact antibody.
- 15 4. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody is selected from the group consisting of: an antibody of subtype IgG1, IgG2, IgG3 or IgG4.
- 20 5. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein said antibody or antigen-binding fragment thereof binds to the E Region of Sortilin as defined by **SEQ ID NO:146**.
- 25 6. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein said antibody or antigen-binding fragment thereof binds to at least 1 or more consecutive amino acids, such as 1,2,3, 4, 5, 6 or 7 consecutive amino acids, within the E Region of Sortilin as defined in **SEQ ID NO:146**.
- 30 7. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody or antigen-binding fragment exhibits one or more of the following properties:
 - a. a binding affinity (KD) for Sortilin between 0.5-10 nM, such as 1-5 nM or 1-2 nM or even higher such as between 0.5 pM and 500 pM

- b. capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;
 - c. capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;
 - 5 d. a capability to increase the amount and/or concentration of PGRN in the brain, and/or
 - e. capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice.
- 10 8. The antibody, or antigen-binding fragment thereof, according to any preceding claims 1-9, wherein the capability of said antibody or antigen-binding fragment thereof to reduce and/or inhibit clearance of PGRN comprises reducing and/or inhibiting clearance of PGRN with an IC₅₀ at or below 22 nM, such as between 22 nM and 1 nM, or between 10 nM and
- 15 1 nM, or between 5 nM and 1 nM.
9. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody or antigen-binding fragment thereof is a human, humanized, recombinant or chimeric antibody.
- 20 10. An antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody or antigen-binding fragment thereof is selected from the group consisting of antibodies (1)-(18):
- 25 Antibody (1) is characterized by:
- a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:1**;
 - b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:2**;
 - c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:3**;
 - d. a light chain variable domain CDR 1 comprising **SEQ ID NO:4**;
 - 30 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) is characterized by:

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

Antibody (3) is characterized by:

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

Antibody (4) is characterized by:

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

Antibody (5) is characterized by:

- a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:25**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:26**;
- c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:27**;
- d. a light chain variable domain CDR 1 comprising **SEQ ID NO:28**;

- e. a light chain variable domain CDR 2 comprising **SEQ ID NO:29**;
and
- f. a light chain variable domain CDR 3 comprising **SEQ ID NO:30**.

5 Antibody (6) is characterized by:

- a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:31**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:32**;
- c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:33**;
- d. a light chain variable domain CDR 1 comprising **SEQ ID NO:34**;
- 10 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) is characterized by:

- a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:37**;
- 15 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**.

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Antibody (8) is characterized by:

- 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**;
- 25 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 (9) is characterized by:

- 30 a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:49**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:50**;
- c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:51**;

- d. a light chain variable domain CDR 1 comprising **SEQ ID NO:52**;
- e. a light chain variable domain CDR 2 comprising **SEQ ID NO:53**; and
- f. a light chain variable domain CDR 3 comprising **SEQ ID NO:54**.

5 Antibody (10) is characterized by:

- a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:55**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:56**;
- c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:57**;
- d. a light chain variable domain CDR 1 comprising **SEQ ID NO:58**;
- 10 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) is characterized by:

- a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:61**;
- 15 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**.

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Antibody (12) is characterized by:

- 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**;
- 25 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) is characterized by:

- 30 a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:73**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:74**;
- c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:75**;

- d. a light chain variable domain CDR 1 comprising **SEQ ID NO:76**;
- e. a light chain variable domain CDR 2 comprising **SEQ ID NO:77**; and
- f. a light chain variable domain CDR 3 comprising **SEQ ID NO:78**.

5 Antibody (14) is characterized by:

- 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**;
- 10 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) is characterized by:

- a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:85**;
- 15 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**.

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Antibody (16) is characterized by:

- a. a heavy chain variable domain CDR1 comprising **SEQ ID NO:91**;
- b. a heavy chain variable domain CDR 2 comprising **SEQ ID NO:92**;
- c. a heavy chain variable domain CDR 3 comprising **SEQ ID NO:93**;
- 25 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**.

Antibody (17) is characterized by:

- 30 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 Antibody (18) is characterized by:

- 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**;
- 10 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**.

11. An antibody, or antigen-binding fragment thereof, according to claim 10,
wherein said antibody or antigen-binding fragment is further
15 caracterized:

Antibody (1) is further carактерized by a heavy chain variable domain
comprising **SEQ ID NO:109** and/or a light chain variable domain
comprising **SEQ ID NO:110**.

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Antibody (2) is further carактерized by a heavy chain variable domain
comprising **SEQ ID NO:111** and/or a light chain variable domain
comprising **SEQ ID NO:112**.

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Antibody (3) is further carактерized by a heavy chain variable domain
comprising **SEQ ID NO:113** and/or a light chain variable domain
comprising **SEQ ID NO:114**.

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Antibody (4) is further carактерized by a heavy chain variable domain
comprising **SEQ ID NO:115** and/or a light chain variable domain
comprising **SEQ ID NO:116**.

Antibody (5) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:117** and/or a light chain variable domain comprising **SEQ ID NO:118**.

5 Antibody (6) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:119** and/or a light chain variable domain comprising **SEQ ID NO:120**.

10 Antibody (7) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:121** and/or a light chain variable domain comprising **SEQ ID NO:122**.

15 Antibody (8) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:123** and/or a light chain variable domain comprising **SEQ ID NO:124**.

Antibody (9) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:125** and/or a light chain variable domain comprising **SEQ ID NO:126**.

20 Antibody (10) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:127** and/or a light chain variable domain comprising **SEQ ID NO:128**.

25 Antibody (11) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:129** and/or a light chain variable domain comprising **SEQ ID NO:130**.

30 Antibody (12) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:131** and/or a light chain variable domain comprising **SEQ ID NO:132**.

Antibody (13) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:133** and/or a light chain variable domain comprising **SEQ ID NO:134**.

Antibody (14) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:135** and/or a light chain variable domain comprising **SEQ ID NO:136**.

Antibody (15) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:137** and/or a light chain variable domain comprising **SEQ ID NO:138**.

Antibody (16) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:139** and/or a light chain variable domain comprising **SEQ ID NO:140**.

Antibody (17) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:141** and/or a light chain variable domain comprising **SEQ ID NO:142**.

Antibody (18) is further characterized by a heavy chain variable domain comprising **SEQ ID NO:143** and/or a light chain variable domain comprising **SEQ ID NO:144**.

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

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

- (iii) a capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;
 - (iv) a capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice; and/or
 - 5 (v) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) or Alzheimer's Disease (AD).

- 10 13. A preparation comprising the monoclonal antibody or antigen-binding fragment thereof according to any one of the previous claims, wherein said monoclonal antibody possesses a structural change in its amino acid sequence, relative to the structure of a naturally-occurring anti-Sortilin antibody, wherein said structural change causes said monoclonal antibody to exhibit an altered functionality relative to the functionality
 - 15 exhibited by said naturally-occurring anti-Sortilin antibody, wherein said functionality being selected from the group consisting of:
 - (i) a binding affinity (KD) for Sortilin;
 - (ii) a capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;
 - 20 (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
 - 25 in the brain, or
 - (vi) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and/or Alzheimer's Disease (AD).

- 30 14. A pharmaceutical composition comprising an antibody, or an antigen-binding fragment thereof, as defined in any of claims 1 to 11, or the

preparation of any one of claims 12-13, and a pharmaceutically-acceptable carrier.

15. Use of an antibody, or antigen-binding fragment thereof, as defined in any of claims 1 to 11, or the preparation of any one of claims 12-13, or the pharmaceutical composition of claim 14, for the manufacture of a medicament.

16. Use of the antibody, or antigen-binding fragment thereof, as defined in any of claims 1 to 11, or the preparation of any one of claims 12-13, or the pharmaceutical composition of claim 14 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.

17. The use of an antibody, or antigen-binding fragment thereof according to claim 15, or claim 16, wherein the disease is: FTD; ALS; or proteinopathies, such as AD.

18. The use of an antibody, or antigen-binding fragment thereof, according to claim 15, or claim 16, wherein the treatment is chronic, and is preferably for at least 2 weeks, such as at least for 1 month, or at least for 6 months, or at least for 1 year.

19. A kit comprising the antibody, or antigen-binding fragment thereof, as defined in any of claims 1-11, or the preparation of any one of claims 12-13, or the pharmaceutical composition of claim 14.

20. An antibody, or antigen-binding fragment thereof, as defined in any of claims 1-11 which has been produced or manufactured in a cell line such as a human cell line, a mammal non-human cell line, an insect, yeast or bacterial cell line.

21. The antibody, or antigen binding fragment thereof, according to claim 20 produced in a CHO cell line, HEK cell line, BHK-21 cell line, murine cell line

(such as a myeloma cell line), fibrosarcoma cell line, PER.C6 cell line, HKB-11 cell line, CAP cell line and HuH-7 human cell line.