neurotensin-site, and yet are capable of inhibiting Sortilin-PGRN interaction and of thereby increasing extracellular PGRN.

**[0009]** The inventors have defined six Sortilin binding regions and surprisingly identified that the most efficacious antibodies bind a region ("region D"). 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 these patients carry a mutation in the gene encoding PGRN leading to haploinsufficiency. Sortilin antibodies are therefore likely to have similar therapeutic benefits for patients suffering from other TDP-43 proteinopathies and diseases in which PGRN levels may influence TDP43-function and pathology, including ALS and AD.

## Summary of invention

**[0010]** The inventors of the present invention have generated monoclonal antibodies which are able to inhibit the binding of PGRN to Sortilin, and which surprisingly bind to a novel Sortilin region denominated the "D-region" as defined in **SEQ ID NO:170**. Several antibodies identified by the inventors have properties similar to the D-region antibodies and experimental evidence indicates that they also bind within the D-region, and those antibodies are herein referred to as D+ antibodies. Accordingly, in one aspect, there is provided an antibody, or an antigen-binding fragment thereof, capable of binding specifically to Sortilin and inhibiting or reducing the binding of PGRN to Sortilin. In another aspect, there is provided a pharmaceutical composition comprising an antibody, or an antigen-binding fragment thereof as described herein, or the preparation as described herein, and a pharmaceutically-acceptable carrier. Accordingly, in one embodiment, the invention relates to such antibodies, to compositions and/or kits comprising such antibodies, and to methods and uses thereof.

**[0011]** The disclosure 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 D-region of Sortilin. These diseases include *i.a.* FTD, ALS and TDP43 proteinopathies such as AD.

## Brief Description of the Drawings

CLAIMS

1. An antibody, or an antigen-binding fragment thereof, capable of binding specifically to Sortilin and inhibiting or reducing the binding of PGRN to Sortilin.

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

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

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

5. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein said antibody or antigen-binding fragment thereof binds to the D Region of Sortilin as defined by **SEQ ID NO:170**.

6. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein said antibody or antigen-binding fragment thereof binds to the D Region of Sortilin as defined by any one of **SEQ ID NO:185, 186 or 187**.

7. The antibody, or antigen-binding fragment thereof, according to claim 5 or 6, wherein said antibody or antigen-binding fragment thereof additionally binds to the A region of Sortilin as defined by **SEQ ID NO:180**.

8. The antibody, or antigen-binding fragment thereof, according to claim 5 or 6, wherein said antibody or antigen-binding fragment thereof additionally binds to the A region of Sortilin as defined by any one of **SEQ ID No 181, 182, 183 or 184**.

9. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein said antibody or antigen-binding fragment thereof binds to at least 3 consecutive amino acids, such as 4, 5, 6 or 7 consecutive amino acids, within the D Region of Sortilin as defined in **SEQ ID NO:170**.

10. 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.

11. An antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:1**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:2**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:3**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:4**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:5**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:6**.

12. An antibody, or antigen-binding fragment thereof, according to claim 11, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:8 and** said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:7**.

13. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:9**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:10**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:11**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:12**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:13**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:14**.

14. The antibody, or antigen-binding fragment thereof, according to claim 13, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:16** said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:15**.

15. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:17**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:18**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:19**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:20**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:21**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:22**.

16. The antibody, or antigen-binding fragment thereof, according to claim 15, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:24** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:23**.

17. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:25**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:26**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:27**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:28**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:29**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:30**.

18. The antibody, or antigen-binding fragment thereof, according to claim 17, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:32** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:31**.

19. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:33**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:34**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:35**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:36**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:37**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:38**.

20. The antibody, or antigen-binding fragment thereof, according to claim 19, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:40** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:39**.

21. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:41**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:42**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:43**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:44**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:45**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:46**.

22. The antibody, or antigen-binding fragment thereof, according to claim 21, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:48** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:47**.

23. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:49**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:50**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:51**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:52**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:53**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:54**.

24. The antibody, or antigen-binding fragment thereof, according to claim 23, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:56** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:55**.

25. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:57**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:58**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:59**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:60**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:61**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:62**.

26. The antibody, or antigen-binding fragment thereof, according to claim 25, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:64** said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:63**.

27. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:65**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:66**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:67**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:68**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:69**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:70**.

28. The antibody or antigen-binding fragment thereof according to claim 27, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:72** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:71**.

29. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:73**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:74**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:75**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:76**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:77**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:78**.

30. The antibody or antigen-binding fragment thereof according to claim 29, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:80** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:79**.

31. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:81**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:82**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:83**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:84**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:85**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:86**.

32. The antibody or antigen-binding fragment thereof according to claim 31, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:88** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:87**.

33. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:89**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:90**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:91**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:92**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:93**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:94**.

34. The antibody or antigen-binding fragment thereof according to claim 33, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:96** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:95**.

35. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:97**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:98**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:99**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:100**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:101**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:102**.

36. The antibody or antigen-binding fragment thereof according to claim 35, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:104** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:103**.

37. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:105**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:106**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:107**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:108**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:109**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:110**.

38. The antibody or antigen-binding fragment thereof according to claim 37, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:112**and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:111**.

39. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:113**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:114**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:115**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:116**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:117**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:118**.

40. The antibody or antigen-binding fragment thereof according to claim 39, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:120** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:119**.

41. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:121**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:122**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:123**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:124**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:125**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:126**.

42. The antibody or antigen-binding fragment thereof according to claim 41, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:128** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:127**.

43. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 1103, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:129**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:130**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:131**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:132**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:133**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:134**.

44. The antibody or antigen-binding fragment thereof according to claim 43, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:136** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:135**.

45. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:137**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:138**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:139**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:140**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:141**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:142**.

46. The antibody or antigen-binding fragment thereof according to claim 45, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:144** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:143**.

47. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:

a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:145**;
b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:146**;
c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:147**;
d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:148**;
e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:149**; and
f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:150**.

48. The antibody or antigen-binding fragment thereof according to claim 47, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:152** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:151**.

49. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:

a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:153**;
b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:154**;
c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:155**;
d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:156**;
e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:157**; and
f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:158**.

50. The antibody or antigen-binding fragment thereof according to claim 49, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:160** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:159**.

51. The antibody, or antigen-binding fragment thereof, according to any of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:
    a. a light chain variable domain L-CDR1 comprising **SEQ ID NO:161**;
    b. a light chain variable domain L-CDR 2 comprising **SEQ ID NO:162**;
    c. a light chain variable domain L-CDR 3 comprising **SEQ ID NO:163**;
    d. a heavy chain variable domain H-CDR 1 comprising **SEQ ID NO:164**;
    e. a heavy chain variable domain H-CDR 2 comprising **SEQ ID NO:165**; and
    f. a heavy chain variable domain H-CDR 3 comprising **SEQ ID NO:166**.

52. The antibody or antigen-binding fragment thereof according to claim 51, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising **SEQ ID NO:168** and said antibody or antigen-binding fragment thereof comprises a light chain variable domain comprising **SEQ ID NO:167**.

53. A pharmaceutical composition comprising an antibody, or an antigen-binding fragment thereof, as defined in any of claims 1 to 52, and a pharmaceutically-acceptable carrier.