

CLAIMS

1. An antibody or antigen binding portion thereof that binds to a fragment of apolipoprotein E (ApoE), wherein the fragment has

- 5 - an apparent molecular weight of 12 kDa as measured by SDS-PAGE, and
- an N-terminus corresponding to an amino acid in full-length apolipoprotein E which is selected from the group consisting of amino acids L198, A199 and G200; and wherein the antibody or antigen binding portion thereof binds to an epitope comprising the N-terminus of the fragment.

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2. The antibody or antigen binding portion thereof according to claim 1, wherein the antibody or antigen binding portion thereof binds selectively to the ApoE fragment and does not bind to full-length apolipoprotein E.

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3. The antibody or antigen binding portion thereof according to claim 1 or claim 2, wherein said fragment of apolipoprotein E is selected from

- i) a fragment consisting of the amino acid sequence of any one of SEQ ID NOs:1-3; and
- ii) a fragment having at least 80% identity to any one of SEQ ID NOs: 1-3.

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4. The antibody or antigen binding portion thereof according to any one of claims 1-3, wherein the antibody or antigen binding portion thereof binds to an epitope comprising amino acid residues selected from the following:

- (i) amino acid residues 200-205 in full-length ApoE (GQPLQE);
- 25 (ii) amino acid residues 199-204 in full-length ApoE (AGQPLQ);
- (iii) amino acid residues 199-205 in full-length ApoE (AGQPLQE);
- (iv) amino acid residues 198-203 in full-length ApoE (LAGQPL);
- (v) amino acid residues 198-204 in full-length ApoE (LAGQPLQ); and
- (vi) amino acid residues 198-205 in full-length ApoE (LAGQPLQE).

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5. The antibody or antigen binding portion thereof according to any one of claims 1-4, wherein said fragment of apolipoprotein E consists of the amino acid sequence of SEQ ID NO:1, optionally wherein the epitope comprises amino acid residues 200-205 in full-length apolipoprotein E.

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6. A method of producing an antibody or an antigen binding portion thereof, comprising a step of immunizing a host mammal with a peptide immunogen comprising an N-terminal amino acid sequence selected from the group consisting of LAGQPL (SED ID NO:4), AGQPLQ (SEQ ID NO:5), GQPLQE (SEQ ID NO:6),
 5 LAGQPLQ (SEQ ID NO:7), AGQPLQE (SEQ ID NO:8) and LAGQPLQE (SEQ ID NO:9).

7. The method according to claim 6, wherein said N-terminal amino acid sequence is GQPLQE (SEQ ID NO:6).

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8. An antibody or antigen binding portion thereof, obtainable by a method according to claim 6 or claim 7; and wherein the antibody or antigen binding portion thereof binds to an epitope selected from the group consisting of: LAGQPL (SED ID NO:4), AGQPLQ (SEQ ID NO:5), GQPLQE (SEQ ID NO:6), LAGQPLQ (SEQ ID
 15 NO:7), AGQPLQE (SEQ ID NO:8) and LAGQPLQE (SEQ ID NO:9).

9. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

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CDR-H1 comprising or consisting of SEQ ID NO: 10 (SYAMS);

CDR-H2 comprising or consisting of SEQ ID NO: 11

(EISGSGSRDHYTDSVTG);

CDR-H3 comprising or consisting of SEQ ID NO: 12 (QLTGTDYYGTDY);

CDR-L1 comprising or consisting of SEQ ID NO: 24

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(RSSQSIVYSNGNTYLE);

CDR-L2 comprising or consisting of SEQ ID NO: 25 (KVSNRFS); and

CDR-L3 comprising or consisting of SEQ ID NO: 26 (FQGSHLPYT).

10. The antibody or antigen binding portion thereof according to any one of
 30 claims 1-5, 8 or 9, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 34 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of

SEQ ID NO: 35 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

11. The antibody or antigen binding portion thereof according to any one of
5 claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

CDR-H1 comprising or consisting of SEQ ID NO: 10 (SYAMS);
CDR-H2 comprising or consisting of SEQ ID NO: 13
(EISSGGGSTNYLDTVGTG);
10 CDR-H3 comprising or consisting of SEQ ID NO: 14 (QLVGTDYYGTDY);
CDR-L1 comprising or consisting of SEQ ID NO: 27
(RSSQNIVYSNGNTYLE);
CDR-L2 comprising or consisting of SEQ ID NO: 25 (KVSNRFS); and
CDR-L3 comprising or consisting of SEQ ID NO: 28 (FQGSHVPYT).

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12. The antibody or antigen binding portion thereof according to any one of
claims 1-5, 8 or 11, wherein the antibody or antigen binding portion thereof
comprises a variable heavy chain domain (VH) and a variable light chain domain
(VL); wherein the VH domain comprises or consists of the amino acid sequence of
20 SEQ ID NO: 36 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or
99% identity thereto, and the VL domain comprises or consists of the amino acid
sequence of SEQ ID NO: 37 or an amino acid sequence having at least 80%, 90%,
95%, 98%, or 99% identity thereto.

25 13. The antibody or antigen binding portion thereof according to any one of
claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

CDR-H1 comprising or consisting of SEQ ID NO: 15 (SFAMS);
CDR-H2 comprising or consisting of SEQ ID NO: 16
30 (EISRGGGYAFYSDTVGTG);
CDR-H3 comprising or consisting of SEQ ID NO: 17 (QLTGTDYYAMDY);
CDR-L1 comprising or consisting of SEQ ID NO: 29
(RSSQSIVYTNGNTYLE);
CDR-L2 comprising or consisting of SEQ ID NO: 25 (KVSNRFS); and

CDR-L3 comprising or consisting of SEQ ID NO: 30 (FQGSQVPYT).

14. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 13, wherein the antibody or antigen binding portion thereof
5 comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 38 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid
10 sequence of SEQ ID NO: 39 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

15. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:
15 CDR-H1 comprising or consisting of SEQ ID NO: 18 (RYAMS);
CDR-H2 comprising or consisting of SEQ ID NO: 19
(EINSGGSYSFYSDTVTG);
CDR-H3 comprising or consisting of SEQ ID NO: 12 (QLTGTDYYGTDY);
CDR-L1 comprising or consisting of SEQ ID NO: 31
20 (RSSQSLLYSNGNTYLE);
CDR-L2 comprising or consisting of SEQ ID NO: 25 (KVSNRFS); and
CDR-L3 comprising or consisting of SEQ ID NO: 28 (FQGSHVPYT).

16. The antibody or antigen binding portion thereof according to any one of
25 claims 1-5, 8 or 15, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 40 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid
30 sequence of SEQ ID NO: 41 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

17. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

- CDR-H1 comprising or consisting of SEQ ID NO: 18 (RYAMS);
- 5 CDR-H2 comprising or consisting of SEQ ID NO: 19 (EINSGGSYSFYSDTVTG);
- CDR-H3 comprising or consisting of SEQ ID NO: 20 (QLSGTDYYGTDY);
- CDR-L1 comprising or consisting of SEQ ID NO: 31 (RSSQSLLYSNGNTYLE);
- 10 CDR-L2 comprising or consisting of SEQ ID NO: 25 (KVSNRFS); and
- CDR-L3 comprising or consisting of SEQ ID NO: 28 (FQGSHVPYT).

18. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 17, wherein the antibody or antigen binding portion thereof
- 15 comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 42 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of SEQ ID NO: 41 or an amino acid sequence having at least 80%, 90%,
- 20 95%, 98%, or 99% identity thereto.

19. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

- 25 CDR-H1 comprising or consisting of SEQ ID NO: 21 (NYAMH);
- CDR-H2 comprising or consisting of SEQ ID NO: 22 (WINTYTGEPFADFCKG);
- CDR-H3 comprising or consisting of SEQ ID NO: 23 (EGYYDRSHYFDY);
- CDR-L1 comprising or consisting of SEQ ID NO: 32 (RSSLSLVHGDGNTYLE);
- 30 CDR-L2 comprising or consisting of SEQ ID NO: 25 (KVSNRFS); and
- CDR-L3 comprising or consisting of SEQ ID NO: 33 (LQGSHIPFT).

20. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 19, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 43 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of SEQ ID NO: 44 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

21. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

CDR-H1 comprising or consisting of SEQ ID NO: 59;
CDR-H2 comprising or consisting of SEQ ID NO: 60;
CDR-H3 comprising or consisting of SEQ ID NO: 61;
CDR-L1 comprising or consisting of SEQ ID NO: 71;
CDR-L2 comprising or consisting of SEQ ID NO: 72; and
CDR-L3 comprising or consisting of SEQ ID NO: 73.

22. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 21, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 82 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of SEQ ID NO: 83 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

23. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

CDR-H1 comprising or consisting of SEQ ID NO: 62;
CDR-H2 comprising or consisting of SEQ ID NO: 63;
CDR-H3 comprising or consisting of SEQ ID NO: 64;

CDR-L1 comprising or consisting of SEQ ID NO: 74;
CDR-L2 comprising or consisting of SEQ ID NO: 72; and
CDR-L3 comprising or consisting of SEQ ID NO: 75.

5 24. The antibody or antigen binding portion thereof according to any one of
claims 1-5, 8 or 23, wherein the antibody or antigen binding portion thereof
comprises a variable heavy chain domain (VH) and a variable light chain domain
(VL); wherein the VH domain comprises or consists of the amino acid sequence of
SEQ ID NO: 84 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or
10 99% identity thereto, and the VL domain comprises or consists of the amino acid
sequence of SEQ ID NO: 85 or an amino acid sequence having at least 80%, 90%,
95%, 98%, or 99% identity thereto.

 25. The antibody or antigen binding portion thereof according to any one of
15 claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises
the CDR sequences:

 CDR-H1 comprising or consisting of SEQ ID NO: 65;
 CDR-H2 comprising or consisting of SEQ ID NO: 66;
 CDR-H3 comprising or consisting of SEQ ID NO: 67;
20 CDR-L1 comprising or consisting of SEQ ID NO: 76;
 CDR-L2 comprising or consisting of SEQ ID NO: 77; and
 CDR-L3 comprising or consisting of SEQ ID NO: 78.

 26. The antibody or antigen binding portion thereof according to any one of
25 claims 1-5, 8 or 25, wherein the antibody or antigen binding portion thereof
comprises a variable heavy chain domain (VH) and a variable light chain domain
(VL); wherein the VH domain comprises or consists of the amino acid sequence of
SEQ ID NO: 86 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or
99% identity thereto, and the VL domain comprises or consists of the amino acid
30 sequence of SEQ ID NO: 87 or an amino acid sequence having at least 80%, 90%,
95%, 98%, or 99% identity thereto.

27. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

- CDR-H1 comprising or consisting of SEQ ID NO: 62;
- 5 CDR-H2 comprising or consisting of SEQ ID NO: 68;
- CDR-H3 comprising or consisting of SEQ ID NO: 69;
- CDR-L1 comprising or consisting of SEQ ID NO: 79;
- CDR-L2 comprising or consisting of SEQ ID NO: 72; and
- CDR-L3 comprising or consisting of SEQ ID NO: 78.

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28. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 27, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of
15 SEQ ID NO: 88 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of SEQ ID NO: 89 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

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29. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

- CDR-H1 comprising or consisting of SEQ ID NO: 62;
- CDR-H2 comprising or consisting of SEQ ID NO: 70;
- 25 CDR-H3 comprising or consisting of SEQ ID NO: 67;
- CDR-L1 comprising or consisting of SEQ ID NO: 80;
- CDR-L2 comprising or consisting of SEQ ID NO: 77; and
- CDR-L3 comprising or consisting of SEQ ID NO: 81.

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30. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 29, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of
SEQ ID NO: 90 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or

99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of SEQ ID NO: 91 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

5 31. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

 CDR-H1 comprising or consisting of SEQ ID NO: 62;
 CDR-H2 comprising or consisting of SEQ ID NO: 92;
10 CDR-H3 comprising or consisting of SEQ ID NO: 93;
 CDR-L1 comprising or consisting of SEQ ID NO: 100;
 CDR-L2 comprising or consisting of SEQ ID NO: 101; and
 CDR-L3 comprising or consisting of SEQ ID NO: 102.

15 32. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 31, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 109 or an amino acid sequence having at least 80%, 90%, 95%, 98%,
20 or 99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of SEQ ID NO: 110 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

 33. The antibody or antigen binding portion thereof according to any one of
25 claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

 CDR-H1 comprising or consisting of SEQ ID NO: 62;
 CDR-H2 comprising or consisting of SEQ ID NO: 92;
 CDR-H3 comprising or consisting of SEQ ID NO: 93;
30 CDR-L1 comprising or consisting of SEQ ID NO: 103;
 CDR-L2 comprising or consisting of SEQ ID NO: 104; and
 CDR-L3 comprising or consisting of SEQ ID NO: 102.

34. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 33, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 111 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of SEQ ID NO: 112 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

35. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

CDR-H1 comprising or consisting of SEQ ID NO: 94;
CDR-H2 comprising or consisting of SEQ ID NO: 95;
CDR-H3 comprising or consisting of SEQ ID NO: 96;
CDR-L1 comprising or consisting of SEQ ID NO: 105;
CDR-L2 comprising or consisting of SEQ ID NO: 106; and
CDR-L3 comprising or consisting of SEQ ID NO: 107.

36. The antibody or antigen binding portion thereof according to any one of claims 1-5, 8 or 35, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain domain (VH) and a variable light chain domain (VL); wherein the VH domain comprises or consists of the amino acid sequence of SEQ ID NO: 113 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto, and the VL domain comprises or consists of the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence having at least 80%, 90%, 95%, 98%, or 99% identity thereto.

37. The antibody or antigen binding portion thereof according to any one of claims 1-5 or 8, wherein the antibody or antigen binding portion thereof comprises the CDR sequences:

CDR-H1 comprising or consisting of SEQ ID NO: 97;
CDR-H2 comprising or consisting of SEQ ID NO: 98;
CDR-H3 comprising or consisting of SEQ ID NO: 99;

CDR-L1 comprising or consisting of SEQ ID NO: 108;
CDR-L2 comprising or consisting of SEQ ID NO: 25; and
CDR-L3 comprising or consisting of SEQ ID NO: 28.

5 38. The antibody or antigen binding portion thereof according to any one of
claims 1-5, 8 or 37, wherein the antibody or antigen binding portion thereof
comprises a variable heavy chain domain (VH) and a variable light chain domain
(VL); wherein the VH domain comprises or consists of the amino acid sequence of
SEQ ID NO: 115 or an amino acid sequence having at least 80%, 90%, 95%, 98%,
10 or 99% identity thereto, and the VL domain comprises or consists of the amino acid
sequence of SEQ ID NO: 116 or an amino acid sequence having at least 80%, 90%,
95%, 98%, or 99% identity thereto.

 39. A pharmaceutical composition comprising an antibody or antigen binding
15 portion thereof according to any one of claims 1-5 and 8-38 and at least one
pharmaceutically acceptable excipient or carrier.

 40. An antibody or antigen binding portion thereof according to any one of
claims 1-5 and 8-38, or pharmaceutical composition according to claim 39, for use in
20 therapy.

 41. A method of detecting or diagnosing a neurological disorder or a disorder
characterized by a loss of cognitive memory capacity in a subject, the method
comprising contacting a sample obtained from the subject with an antibody or
25 antigen binding portion thereof according to any one of claims 1-5 and 8-38.