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(71) Applicant *(for all designated States except US)*: **IMMUNAS PHARMA, INC.** [JP/JP]; Kanagawa Science Park R&D D11F, 3-2-1, Sakado, Takatsu-ku, Kawasaki-shi, Kanagawa, 2130012 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **YOKOSEKI, Tatsuki** [JP/JP]; c/o IMMUNAS PHARMA, INC., Kanagawa Science Park R&D D11F, 3-2-1, Sakado, Takatsu-ku, Kawasaki-shi, Kanagawa, 2130012 (JP). **OKAMOTO, Yasuhide** [JP/JP]; c/o IMMUNAS PHARMA, INC., Kanagawa Science Park R&D D11F, 3-2-1, Sakado, Takatsu-ku, Kawasaki-shi, Kanagawa, 2130012 (JP). **UMEDA, Makoto** [JP/JP]; c/o IMMUNAS PHARMA, INC., Kanagawa Science Park R&D D11F, 3-2-1, Sakado, Takatsu-ku, Kawasaki-shi, Kanagawa, 2130012 (JP). **ITO, Toshiyuki** [JP/JP]; c/o IMMUNAS PHARMA, INC., Kanagawa Science Park R&D D11F, 3-2-1, Sakado, Takatsu-ku, Kawasaki-shi, Kanagawa, 2130012 (JP). **IMAI, Yukiho** [JP/JP]; c/o IMMUNAS PHARMA, INC., Kanagawa Science Park R&D D11F, 3-2-1, Sakado, Takatsu-ku, Kawasaki-shi, Kanagawa, 2130012 (JP). **FUJII, Shinobu** [JP/JP]; c/o IMMUNAS PHARMA, INC., Kanagawa Science Park R&D D11F, 3-2-1, Sakado, Takatsu-ku, Kawasaki-shi, Kanagawa, 2130012 (JP). **TAKAMATSU, Naofumi** [JP/JP]; c/o IMMUNAS PHARMA, INC., Kanagawa Science Park R&D D11F, 3-2-1, Sakado, Takatsu-ku, Kawasaki-shi, Kanagawa, 2130012 (JP).

(74) Agents: **SHIMIZU, Hatsushi** et al.; Kantetsu Tsukuba Bldg. 6F, 1-1-1, Oroshi-machi, Tsuchiura-shi, Ibaraki, 3000847 (JP).

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(54) **Title**: ANTIBODIES THAT SPECIFICALLY BIND TO A BETA OLIGOMERS AND USE THEREOF

(57) **Abstract**: The present inventors successfully produced monoclonal antibodies that are specific to only soluble A beta oligomers, but do not recognize soluble A beta monomers, which are physiological molecules. It was demonstrated that the antibodies are useful as diagnostic/therapeutic monoclonal antibodies for Alzheimer's disease.

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Description

Title of Invention: ANTIBODIES THAT SPECIFICALLY BIND TO A BETA OLIGOMERS AND USE THEREOF

Technical Field

[0001] The present application claims the benefit of U.S. Provisional Application No. 61/212,986, filed on April 17, 2009, and U.S. Provisional Application No. 61/282,549, filed on February 26, 2010, the entire contents of which are incorporated by reference herein.

[0002] The present invention relates to antibodies that specifically bind to Abeta oligomers and uses thereof.

Background Art

[0003] The number of Alzheimer's disease (AD) patients is more than about 26 million worldwide in 2006, and it is predicted to continue increasing in an aging society (Non-Patent Document 1). However, there is no curative therapeutic agent that arrests or reverses the progression of Alzheimer's disease, although therapeutic agents that retard the progression of the disease are commercially available.

[0004] Various evidence has shown that deterioration of memory arises from synaptic dysfunction triggered by soluble amyloid beta (A beta) oligomers (see Non-Patent Documents 2 and 3). Excessive accumulation and deposition of A beta oligomers may be the trigger for a series of pathological cascades that lead to Alzheimer's disease. Therefore, therapeutic intervention targeting A beta oligomers may be effective for blocking these cascades (see Non-Patent Documents 4 and 5).

[0005] Recently, antibody pharmaceuticals that target A beta are being developed. However, previously-reported anti-A beta oligomer antibodies do not specifically bind to A beta oligomers, but bind to all of the three forms, i.e., A beta monomers, oligomers, and fibrils. Thus, even if they are administered in vivo, it is thought that the amount of antibodies that bind to A beta oligomers would be relatively low, and the dosage may need to be increased to obtain effect. Moreover, since A beta monomers are present in the brain of healthy individuals, side effects may be cause by the binding of the antibodies to A beta monomers.

[0006] Furthermore, the amount of A beta oligomer could be an index of Alzheimer's disease; however, it was difficult to measure A beta oligomers alone using conventional anti-A beta antibodies.

[0007] Prior art information related to the present invention is shown below.

Citation List

Non Patent Literature

[0008] [NPL 1]Brookmeyer R et al., Alzheimers Dement. Jul; 3(3):186-91, 2007
[NPL 2]Klein WL, Trends Neurosci. 24: 219-224, 2001
[NPL 3]Selkoe DJ, Science 298: 789-791, 2002
[NPL 4]Haass C et al.: Nat Rev Mol Cell Biol. 8: 101-12, 2007
[NPL 5]Lee EB, et al.: J. Biol. Chem. 281: 4292-4299, 2006

Summary of Invention

Technical Problem

[0009] The present invention was achieved in view of the above circumstances. An objective of the present invention is to provide antibodies that bind specifically to A beta oligomers, and uses thereof. More specifically, the present invention provides antibodies that bind specifically to A beta oligomers, methods for detecting A beta oligomers using the antibodies, methods for diagnosing Alzheimer's disease using the antibodies, pharmaceutical compositions and agents comprising the antibodies, agents and kits for detecting A beta oligomers, and agents and kits for diagnosing Alzheimer's disease.

Solution to Problem

[0010] The present inventors successfully produced multiple monoclonal antibodies that are specific to only soluble amyloid beta (A beta) oligomers and do not recognize soluble A beta monomers which are physiological molecules, using an isolated A beta tetramer as an antigen.

[0011] Thus, the present inventors disclose that the multiple antibodies are promising candidates for therapeutic antibodies for treating/preventing Alzheimer's disease, or for diagnostic antibodies for diagnosing Alzheimer's disease.

[0012] More specifically, the present invention provides the following:

[1]An antibody that recognizes an isolated A beta tetramer as an antigen, wherein the antibody does not bind to an A beta monomer.

[2]The antibody of [1], which is any one of (1) to (99) below:

(1) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 530;

(2) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 532;

(3) an antibody that comprises the H chain of (1) and the L chain of (2);

(4) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 534;

(5) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 536;

(6) an antibody that comprises the H chain of (4) and the L chain of (5);

(7) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 538;
(8) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 540;
(9) an antibody that comprises the H chain of (7) and the L chain of (8);
(10) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 542;
(11) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 544;
(12) an antibody that comprises the H chain of (10) and the L chain of (11);
(13) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 546;
(14) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 548;
(15) an antibody that comprises the H chain of (13) and the L chain of (14);
(16) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 550;
(17) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 552;
(18) an antibody that comprises the H chain of (16) and the L chain of (17);
(19) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 554;
(20) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 556;
(21) an antibody that comprises the H chain of (19) and the L chain of (20);
(22) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 558;
(23) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 560;
(24) an antibody that comprises the H chain of (22) and the L chain of (23);
(25) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 562;
(26) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 564;
(27) an antibody that comprises the H chain of (25) and the L chain of (26);
(28) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 566;
(29) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which

are identified in VL comprising the amino acid sequence of SEQ ID NO: 568;
(30) an antibody that comprises the H chain of (28) and the L chain of (29);
(31) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 570;
(32) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 572;
(33) an antibody that comprises the H chain of (31) and the L chain of (32);
(34) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 574;
(35) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 576;
(36) an antibody that comprises the H chain of (34) and the L chain of (35);
(37) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 578;
(38) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 580;
(39) an antibody that comprises the H chain of (37) and the L chain of (38);
(40) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 582;
(41) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 584;
(42) an antibody that comprises the H chain of (40) and the L chain of (41);
(43) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 586;
(44) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 588;
(45) an antibody that comprises the H chain of (43) and the L chain of (44);
(46) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 590;
(47) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 592;
(48) an antibody that comprises the H chain of (46) and the L chain of (47);
(49) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 594;
(50) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 596;
(51) an antibody that comprises the H chain of (49) and the L chain of (50);
(52) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which

are identified in VH comprising the amino acid sequence of SEQ ID NO: 598;
(53) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 600;
(54) an antibody that comprises the H chain of (52) and the L chain of (53);
(55) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 602;
(56) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 604;
(57) an antibody that comprises the H chain of (55) and the L chain of (56);
(58) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 606;
(59) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 608;
(60) an antibody that comprises the H chain of (58) and the L chain of (59);
(61) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 610;
(62) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 612;
(63) an antibody that comprises the H chain of (61) and the L chain of (62);
(64) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 614;
(65) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 616;
(66) an antibody that comprises the H chain of (64) and the L chain of (65);
(67) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 618;
(68) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 620;
(69) an antibody that comprises the H chain of (67) and the L chain of (68);
(70) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 622;
(71) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 624;
(72) an antibody that comprises the H chain of (70) and the L chain of (71);
(73) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 626;
(74) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 628;

(75) an antibody that comprises the H chain of (73) and the L chain of (74);
(76) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 630;
(77) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 632;
(78) an antibody that comprises the H chain of (76) and the L chain of (77);
(79) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 634;
(80) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 636;
(81) an antibody that comprises the H chain of (79) and the L chain of (80);
(82) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 638;
(83) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 640;
(84) an antibody that comprises the H chain of (82) and the L chain of (83);
(85) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 642;
(86) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 644;
(87) an antibody that comprises the H chain of (85) and the L chain of (86);
(88) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 646;
(89) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 648;
(90) an antibody that comprises the H chain of (88) and the L chain of (89);
(91) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 650;
(92) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 652;
(93) an antibody that comprises the H chain of (91) and the L chain of (92);
(94) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 654;
(95) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 656;
(96) an antibody that comprises the H chain of (94) and the L chain of (95);
(97) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 658;

(98) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 660; and
(99) an antibody that comprises the H chain of (97) and the L chain of (98).
[3]The antibody of [1], which is any one of (1) to (200) below:
(1) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 6 as CDR1, the amino acid sequence of SEQ ID NO: 8 as CDR2, and the amino acid sequence of SEQ ID NO: 10 as CDR3;
(2) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 12 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2, and the amino acid sequence of SEQ ID NO: 16 as CDR3;
(3) an antibody that comprises the H chain of (1) and the L chain of (2);
(4) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 530 as VH;
(5) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 532 as VL;
(6) an antibody that comprises the H chain of (4) and the L chain of (5);
(7) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 22 as CDR1, the amino acid sequence of SEQ ID NO: 24 as CDR2, and the amino acid sequence of SEQ ID NO: 26 as CDR3;
(8) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 28 as CDR1, the amino acid sequence of SEQ ID NO: 30 as CDR2, and the amino acid sequence of SEQ ID NO: 32 as CDR3;
(9) an antibody that comprises the H chain of (7) and the L chain of (8);
(10) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 534 as VH;
(11) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 536 as VL;
(12) an antibody that comprises the H chain of (10) and the L chain of (11);
(13) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 38 as CDR1, the amino acid sequence of SEQ ID NO: 40 as CDR2, and the amino acid sequence of SEQ ID NO: 42 as CDR3;
(14) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 44 as CDR1, the amino acid sequence of SEQ ID NO: 46 as CDR2, and the amino acid sequence of SEQ ID NO: 48 as CDR3;
(15) an antibody that comprises the H chain of (13) and the L chain of (14);
(16) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 538 as VH;
(17) an antibody that comprises an L chain having the amino acid sequence of SEQ ID

NO: 540 as VL;

(18) an antibody that comprises the H chain of (16) and the L chain of (17);

(19) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 54 as CDR1, the amino acid sequence of SEQ ID NO: 56 as CDR2, and the amino acid sequence of SEQ ID NO: 58 as CDR3;

(20) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 60 as CDR1, the amino acid sequence of SEQ ID NO: 62 as CDR2, and the amino acid sequence of SEQ ID NO: 64 as CDR3;

(21) an antibody that comprises the H chain of (19) and the L chain of (20);

(22) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 542 as VH;

(23) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 544 as VL;

(24) an antibody that comprises the H chain of (22) and the L chain of (23);

(25) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 70 as CDR1, the amino acid sequence of SEQ ID NO: 72 as CDR2, and the amino acid sequence of SEQ ID NO: 74 as CDR3;

(26) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 76 as CDR1, the amino acid sequence of SEQ ID NO: 78 as CDR2, and the amino acid sequence of SEQ ID NO: 80 as CDR3;

(27) an antibody that comprises the H chain of (25) and the L chain of (26);

(28) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 546 as VH;

(29) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 548 as VL;

(30) an antibody that comprises the H chain of (28) and the L chain of (29);

(31) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 86 as CDR1, the amino acid sequence of SEQ ID NO: 88 as CDR2, and the amino acid sequence of SEQ ID NO: 90 as CDR3;

(32) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 92 as CDR1, the amino acid sequence of SEQ ID NO: 94 as CDR2, and the amino acid sequence of SEQ ID NO: 96 as CDR3;

(33) an antibody that comprises the H chain of (31) and the L chain of (32);

(34) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 550 as VH;

(35) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 552 as VL;

(36) an antibody that comprises the H chain of (34) and the L chain of (35);

(37) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 102 as CDR1, the amino acid sequence of SEQ ID NO: 104 as CDR2, and the amino acid sequence of SEQ ID NO: 106 as CDR3;
(38) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 108 as CDR1, the amino acid sequence of SEQ ID NO: 110 as CDR2, and the amino acid sequence of SEQ ID NO: 112 as CDR3;
(39) an antibody that comprises the H chain of (37) and the L chain of (38);
(40) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 554 as VH;
(41) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 556 as VL;
(42) an antibody that comprises the H chain of (40) and the L chain of (41);
(43) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 118 as CDR1, the amino acid sequence of SEQ ID NO: 120 as CDR2, and the amino acid sequence of SEQ ID NO: 122 as CDR3;
(44) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 124 as CDR1, the amino acid sequence of SEQ ID NO: 126 as CDR2, and the amino acid sequence of SEQ ID NO: 128 as CDR3;
(45) an antibody that comprises the H chain of (43) and the L chain of (44);
(46) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 558 as VH;
(47) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 560 as VL;
(48) an antibody that comprises the H chain of (46) and the L chain of (47);
(49) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 134 as CDR1, the amino acid sequence of SEQ ID NO: 136 as CDR2, and the amino acid sequence of SEQ ID NO: 138 as CDR3;
(50) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 140 as CDR1, the amino acid sequence of SEQ ID NO: 142 as CDR2, and the amino acid sequence of SEQ ID NO: 144 as CDR3;
(51) an antibody that comprises the H chain of (49) and the L chain of (50);
(52) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 562 as VH;
(53) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 564 as VL;
(54) an antibody that comprises the H chain of (52) and the L chain of (53);
(55) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 150 as CDR1, the amino acid sequence of SEQ ID NO: 152 as CDR2, and the

amino acid sequence of SEQ ID NO: 154 as CDR3;

(56) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 156 as CDR1, the amino acid sequence of SEQ ID NO: 158 as CDR2, and the amino acid sequence of SEQ ID NO: 160 as CDR3;

(57) an antibody that comprises the H chain of (55) and the L chain of (56);

(58) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 566 as VH;

(59) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 568 as VL;

(60) an antibody that comprises the H chain of (58) and the L chain of (59);

(61) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 166 as CDR1, the amino acid sequence of SEQ ID NO: 168 as CDR2, and the amino acid sequence of SEQ ID NO: 170 as CDR3;

(62) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 172 as CDR1, the amino acid sequence of SEQ ID NO: 174 as CDR2, and the amino acid sequence of SEQ ID NO: 176 as CDR3;

(63) an antibody that comprises the H chain of (61) and the L chain of (62);

(64) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 570 as VH;

(65) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 572 as VL;

(66) an antibody that comprises the H chain of (64) and the L chain of (65);

(67) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 182 as CDR1, the amino acid sequence of SEQ ID NO: 184 as CDR2, and the amino acid sequence of SEQ ID NO: 186 as CDR3;

(68) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 188 as CDR1, the amino acid sequence of SEQ ID NO: 190 as CDR2, and the amino acid sequence of SEQ ID NO: 192 as CDR3;

(69) an antibody that comprises the H chain of (67) and the L chain of (68);

(70) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 574 as VH;

(71) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 576 as VL;

(72) an antibody that comprises the H chain of (70) and the L chain of (71);

(73) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 198 as CDR1, the amino acid sequence of SEQ ID NO: 200 as CDR2, and the amino acid sequence of SEQ ID NO: 202 as CDR3;

(74) an antibody that comprises an L chain having the amino acid sequence of SEQ ID

NO: 204 as CDR1, the amino acid sequence of SEQ ID NO: 206 as CDR2, and the amino acid sequence of SEQ ID NO: 208 as CDR3;

(75) an antibody that comprises the H chain of (73) and the L chain of (74);

(76) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 578 as VH;

(77) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 580 as VL;

(78) an antibody that comprises the H chain of (75) and the L chain of (76);

(79) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 214 as CDR1, the amino acid sequence of SEQ ID NO: 216 as CDR2, and the amino acid sequence of SEQ ID NO: 218 as CDR3;

(80) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 220 as CDR1, the amino acid sequence of SEQ ID NO: 222 as CDR2, and the amino acid sequence of SEQ ID NO: 224 as CDR3;

(81) an antibody that comprises the H chain of (79) and the L chain of (80);

(82) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 582 as VH;

(83) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 584 as VL;

(84) an antibody that comprises the H chain of (82) and the L chain of (83);

(85) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 230 as CDR1, the amino acid sequence of SEQ ID NO: 232 as CDR2, and the amino acid sequence of SEQ ID NO: 234 as CDR3;

(86) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 236 as CDR1, the amino acid sequence of SEQ ID NO: 238 as CDR2, and the amino acid sequence of SEQ ID NO: 240 as CDR3;

(87) an antibody that comprises the H chain of (85) and the L chain of (86);

(88) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 586 as VH;

(89) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 588 as VL;

(90) an antibody that comprises the H chain of (88) and the L chain of (89);

(91) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 246 as CDR1, the amino acid sequence of SEQ ID NO: 248 as CDR2, and the amino acid sequence of SEQ ID NO: 250 as CDR3;

(92) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 252 as CDR1, the amino acid sequence of SEQ ID NO: 254 as CDR2, and the amino acid sequence of SEQ ID NO: 256 as CDR3;

(93) an antibody that comprises the H chain of (91) and the L chain of (92);
(94) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 590 as VH;
(95) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 592 as VL;
(96) an antibody that comprises the H chain of (94) and the L chain of (95);
(97) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 262 as CDR1, the amino acid sequence of SEQ ID NO: 264 as CDR2, and the amino acid sequence of SEQ ID NO: 266 as CDR3;
(98) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 268 as CDR1, the amino acid sequence of SEQ ID NO: 270 as CDR2, and the amino acid sequence of SEQ ID NO: 272 as CDR3;
(99) an antibody that comprises the H chain of (97) and the L chain of (98);
(100) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 594 as VH;
(101) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 596 as VL;
(102) an antibody that comprises the H chain of (100) and the L chain of (101);
(103) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 278 as CDR1, the amino acid sequence of SEQ ID NO: 280 as CDR2, and the amino acid sequence of SEQ ID NO: 282 as CDR3;
(104) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 284 as CDR1, the amino acid sequence of SEQ ID NO: 286 as CDR2, and the amino acid sequence of SEQ ID NO: 288 as CDR3;
(105) an antibody that comprises the H chain of (103) and the L chain of (104);
(106) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 598 as VH;
(107) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 600 as VL;
(108) an antibody that comprises the H chain of (106) and the L chain of (107);
(109) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 294 as CDR1, the amino acid sequence of SEQ ID NO: 296 as CDR2, and the amino acid sequence of SEQ ID NO: 298 as CDR3;
(110) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 300 as CDR1, the amino acid sequence of SEQ ID NO: 302 as CDR2, and the amino acid sequence of SEQ ID NO: 304 as CDR3;
(111) an antibody that comprises the H chain of (109) and the L chain of (110);
(112) an antibody that comprises an H chain having the amino acid sequence of SEQ

ID NO: 602 as VH;
(113) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 604 as VL;
(114) an antibody that comprises the H chain of (112) and the L chain of (113);
(115) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 310 as CDR1, the amino acid sequence of SEQ ID NO: 312 as CDR2, and the amino acid sequence of SEQ ID NO: 314 as CDR3;
(116) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 316 as CDR1, the amino acid sequence of SEQ ID NO: 318 as CDR2, and the amino acid sequence of SEQ ID NO: 320 as CDR3;
(117) an antibody that comprises the H chain of (115) and the L chain of (116);
(118) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 606 as VH;
(119) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 608 as VL;
(120) an antibody that comprises the H chain of (118) and the L chain of (119);
(121) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 326 as CDR1, the amino acid sequence of SEQ ID NO: 328 as CDR2, and the amino acid sequence of SEQ ID NO: 330 as CDR3;
(122) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 332 as CDR1, the amino acid sequence of SEQ ID NO: 334 as CDR2, and the amino acid sequence of SEQ ID NO: 336 as CDR3;
(123) an antibody that comprises the H chain of (121) and the L chain of (122);
(124) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 610 as VH;
(125) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 612 as VL;
(126) an antibody that comprises the H chain of (124) and the L chain of (125);
(127) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 342 as CDR1, the amino acid sequence of SEQ ID NO: 344 as CDR2, and the amino acid sequence of SEQ ID NO: 346 as CDR3;
(128) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 348 as CDR1, the amino acid sequence of SEQ ID NO: 350 as CDR2, and the amino acid sequence of SEQ ID NO: 352 as CDR3;
(129) an antibody that comprises the H chain of (127) and the L chain of (128);
(130) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 614 as VH;
(131) an antibody that comprises an L chain having the amino acid sequence of SEQ

ID NO: 616 as VL;

(132) an antibody that comprises the H chain of (130) and the L chain of (131);

(133) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 358 as CDR1, the amino acid sequence of SEQ ID NO: 360 as CDR2, and the amino acid sequence of SEQ ID NO: 362 as CDR3;

(134) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 364 as CDR1, the amino acid sequence of SEQ ID NO: 366 as CDR2, and the amino acid sequence of SEQ ID NO: 368 as CDR3;

(135) an antibody that comprises the H chain of (133) and the L chain of (134);

(136) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 618 as VH;

(137) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 620 as VL;

(138) an antibody that comprises the H chain of (136) and the L chain of (137);

(139) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 374 as CDR1, the amino acid sequence of SEQ ID NO: 376 as CDR2, and the amino acid sequence of SEQ ID NO: 378 as CDR3;

(140) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 380 as CDR1, the amino acid sequence of SEQ ID NO: 382 as CDR2, and the amino acid sequence of SEQ ID NO: 384 as CDR3;

(141) an antibody that comprises the H chain of (139) and the L chain of (140);

(142) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 622 as VH;

(143) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 624 as VL;

(144) an antibody that comprises the H chain of (142) and the L chain of (143);

(145) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 390 as CDR1, the amino acid sequence of SEQ ID NO: 392 as CDR2, and the amino acid sequence of SEQ ID NO: 394 as CDR3;

(146) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 396 as CDR1, the amino acid sequence of SEQ ID NO: 398 as CDR2, and the amino acid sequence of SEQ ID NO: 400 as CDR3;

(147) an antibody that comprises the H chain of (145) and the L chain of (146);

(148) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 626 as VH;

(149) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 628 as VL;

(150) an antibody that comprises the H chain of (148) and the L chain of (149);

(151) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 406 as CDR1, the amino acid sequence of SEQ ID NO: 408 as CDR2, and the amino acid sequence of SEQ ID NO: 410 as CDR3;
(152) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 412 as CDR1, the amino acid sequence of SEQ ID NO: 414 as CDR2, and the amino acid sequence of SEQ ID NO: 416 as CDR3;
(153) an antibody that comprises the H chain of (151) and the L chain of (152);
(154) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 630 as VH;
(155) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 632 as VL;
(156) an antibody that comprises the H chain of (154) and the L chain of (155);
(157) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 422 as CDR1, the amino acid sequence of SEQ ID NO: 424 as CDR2, and the amino acid sequence of SEQ ID NO: 426 as CDR3;
(158) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 428 as CDR1, the amino acid sequence of SEQ ID NO: 430 as CDR2, and the amino acid sequence of SEQ ID NO: 432 as CDR3;
(159) an antibody that comprises the H chain of (157) and the L chain of (158);
(160) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 634 as VH;
(161) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 636 as VL;
(162) an antibody that comprises the H chain of (160) and the L chain of (161);
(163) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 438 as CDR1, the amino acid sequence of SEQ ID NO: 440 as CDR2, and the amino acid sequence of SEQ ID NO: 442 as CDR3;
(164) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 444 as CDR1, the amino acid sequence of SEQ ID NO: 446 as CDR2, and the amino acid sequence of SEQ ID NO: 448 as CDR3;
(165) an antibody that comprises the H chain of (163) and the L chain of (164);
(166) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 638 as VH;
(167) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 640 as VL;
(168) an antibody that comprises the H chain of (166) and the L chain of (167);
(169) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 454 as CDR1, the amino acid sequence of SEQ ID NO: 456 as CDR2, and the

amino acid sequence of SEQ ID NO: 458 as CDR3;

(170) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 460 as CDR1, the amino acid sequence of SEQ ID NO: 462 as CDR2, and the amino acid sequence of SEQ ID NO: 464 as CDR3;

(171) an antibody that comprises the H chain of (169) and the L chain of (170);

(172) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 642 as VH;

(173) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 644 as VL;

(174) an antibody that comprises the H chain of (172) and the L chain of (173);

(175) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 470 as CDR1, the amino acid sequence of SEQ ID NO: 472 as CDR2, and the amino acid sequence of SEQ ID NO: 474 as CDR3;

(176) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 476 as CDR1, the amino acid sequence of SEQ ID NO: 478 as CDR2, and the amino acid sequence of SEQ ID NO: 480 as CDR3;

(177) an antibody that comprises the H chain of (175) and the L chain of (176);

(178) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 646 as VH;

(179) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 648 as VL;

(180) an antibody that comprises the H chain of (178) and the L chain of (179);

(181) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 486 as CDR1, the amino acid sequence of SEQ ID NO: 488 as CDR2, and the amino acid sequence of SEQ ID NO: 490 as CDR3;

(182) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 492 as CDR1, the amino acid sequence of SEQ ID NO: 494 as CDR2, and the amino acid sequence of SEQ ID NO: 496 as CDR3;

(183) an antibody that comprises the H chain of (181) and the L chain of (182);

(184) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 650 as VH;

(185) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 652 as VL;

(186) an antibody that comprises the H chain of (184) and the L chain of (185);

(187) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 502 as CDR1, the amino acid sequence of SEQ ID NO: 504 as CDR2, and the amino acid sequence of SEQ ID NO: 506 as CDR3;

(188) an antibody that comprises an L chain having the amino acid sequence of SEQ

ID NO: 508 as CDR1, the amino acid sequence of SEQ ID NO: 510 as CDR2, and the amino acid sequence of SEQ ID NO: 512 as CDR3;

(189) an antibody that comprises the H chain of (187) and the L chain of (188);

(190) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 654 as VH;

(191) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 656 as VL;

(192) an antibody that comprises the H chain of (190) and the L chain of (191);

(193) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 518 as CDR1, the amino acid sequence of SEQ ID NO: 520 as CDR2, and the amino acid sequence of SEQ ID NO: 522 as CDR3;

(194) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 524 as CDR1, the amino acid sequence of SEQ ID NO: 526 as CDR2, and the amino acid sequence of SEQ ID NO: 528 as CDR3;

(195) an antibody that comprises the H chain of (193) and the L chain of (194);

(196) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 658 as VH;

(197) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 660 as VL;

(198) an antibody that comprises the H chain of (196) and the L chain of (197);

(199) an antibody that comprises one or more amino acid substitutions, deletions, additions, and/or insertions in the antibody of any one of (1) to (198), which has equivalent activity to the antibody of any one of (1) to (198); and

(200) an antibody that binds to the epitope bound by the antibody of any one of (1) to (198).

[4]The antibody of any one of [1]to [3], wherein the antibody is a chimeric antibody or a humanized antibody.

[5]An antigen-binding fragment of the antibody of any one of [1]to [4].

[6]A pharmaceutical composition comprising the antibody of any one of [1]to [4]or the antigen-binding fragment of [5], and a pharmaceutically acceptable carrier.

[7]The composition of [6], which comprises an agent against cognitive impairment, a therapeutic agent for Alzheimer's disease, an agent for suppressing the progression of Alzheimer's disease, an agent for suppressing senile plaque formation, an agent for suppressing A beta accumulation, an anti-neurotoxic agent, an agent for inhibiting A beta amyloid fibril formation, or an agent against synaptic toxicity.

[8]A method for detecting an A beta oligomer, which comprises the step of detecting an A beta oligomer contained in a sample using the antibody of any one of [1]to [4]or the antigen-binding fragment of [5].

[9]A method of diagnosing whether or not a subject is a possible Alzheimer's disease patient, which comprises using the antibody of any one of [1]to [4]or the antigen-binding fragment of [5], to detect an A beta oligomer in a sample collected from a subject.

[10]A method of diagnosing whether or not a subject is a possible Alzheimer's disease patient, which comprises the steps of:

(a) contacting a sample collected from a subject with the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]; and

(b) measuring the amount of A beta oligomer in the sample,

wherein the subject is determined to be a possible Alzheimer's disease patient, when the amount measured in step (b) is higher than that of a healthy individual.

[11]A method of diagnosing whether or not a subject is a possible Alzheimer's disease patient, which comprises the steps of:

(a) contacting a sample collected from a subject with the antibody of any one of [1]to [4]or the antigen-binding fragment of [5], and an antibody that binds to an A beta monomer; and

(b) measuring the ratio of A beta oligomer to A beta monomer in the sample,

wherein the subject is determined to be a possible Alzheimer's disease patient, when the ratio measured in step (b) is higher than that of a healthy individual.

[12]The method of any one of [8]to [11], wherein the sample is blood or cerebrospinal fluid.

[13]A pharmaceutical agent for use in the method of any one of [8]to [12].

[14]A kit for use in the method of any one of [8]to [12].

Furthermore, the present invention provides the following:

[15]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]in the production of an agent against cognitive impairment, a therapeutic agent for Alzheimer's disease, an agent for suppressing the progression of Alzheimer's disease, an agent for suppressing senile plaque formation, an agent for suppressing A beta accumulation, an anti-neurotoxic agent, an agent for inhibiting A beta amyloid fibril formation, or an agent against synaptic toxicity.

[16]The antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for use in preventing and/or treating cognitive impairment.

[17]The antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for use in preventing and/or treating Alzheimer's disease.

[18]The antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for use in suppressing the progression of Alzheimer's disease.

[19]The antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for use in suppressing senile plaque formation.

[20]The antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for use in suppressing A beta accumulation.

[21]The antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for use in neutralizing (suppressing) neurotoxicity.

[22]The antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for use in inhibiting A beta amyloid fibril formation.

[23]The antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for use in neutralizing (suppressing) synaptic toxicity.

[24]A method for preventing and/or treating cognitive impairment, which comprises the step of administering the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]as an active ingredient.

[25]A method for preventing and/or treating Alzheimer's disease, which comprises the step of administering the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]as an active ingredient.

[26]A method for suppressing the progression of Alzheimer's disease, which comprises the step of administering the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]as an active ingredient.

[27]A method for suppressing senile plaque formation, which comprises the step of administering the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]as an active ingredient.

[28]A method for suppressing A beta accumulation, which comprises the step of administering the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]as an active ingredient.

[29]A method for neutralizing neurotoxicity, which comprises the step of administering the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]as an active ingredient.

[30]A method for inhibiting A beta amyloid fibril formation, which comprises the step of administering the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]as an active ingredient.

[31]A method for neutralizing synaptic toxicity, which comprises the step of administering the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]as an active ingredient.

[32]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for preventing and/or treating cognitive impairment.

[33]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for preventing and/or treating Alzheimer's disease.

[34]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for suppressing the progression of Alzheimer's disease.

[35]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for suppressing senile plaque formation.

[36]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for suppressing A beta accumulation.

[37]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for neutralizing neurotoxicity.

[38]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for inhibiting A beta amyloid fibril formation.

[39]Use of the antibody of any one of [1]to [4]or the antigen-binding fragment of [5]for neutralizing (suppressing) synaptic toxicity.

Advantageous Effects of Invention

[0013] The antibodies provided by the present invention are expected to contribute to the establishment of preventive/therapeutic methods selective to molecules responsible for evoking pathological conditions of Alzheimer's disease, and the establishment of early diagnostic markers for Alzheimer's disease.

Brief Description of Drawings

[0014] [fig.1]Fig. 1 presents photographs of dot-blot analysis results on each of the AL-201 to AL-233 antibodies.

[fig.2-1]Fig. 2 presents competitive ELISA results on the 19 antibodies. The vertical axis shows the absorbance at a wavelength of 450nm, and horizontal axis shows the concentration of A beta oligomer or monomer used as an inhibitor. The dotted lines of each graph show the antigen binding activity when the A beta oligomer was used as an inhibitor. The solid lines of each graph show the antigen binding activity when the A beta monomer was used as an inhibitor. The molar concentration (mol/L) of A beta oligomer was calculated by converting the molar number of A beta oligomer into that of A beta monomer.

[fig.2-2]Fig. 2 presents competitive ELISA results on the 19 antibodies. The vertical axis shows the absorbance at a wavelength of 450nm, and horizontal axis shows the concentration of A beta oligomer or monomer used as an inhibitor. The dotted lines of each graph show the antigen binding activity when the A beta oligomer was used as an inhibitor. The solid lines of each graph show the antigen binding activity when the A beta monomer was used as an inhibitor. The molar concentration (mol/L) of A beta oligomer was calculated by converting the molar number of A beta oligomer into that of A beta monomer.

[fig.3]Fig. 3 shows the results of analysis of the affinity of the three antibodies, whose selectivity was higher in the competitive ELISA, to A beta oligomers, by Biacore 3000.

[fig.4]Fig. 4 shows the results of neutralization assay against A beta-induced cytotoxicity using the three anti-A beta oligomer antibodies (AL-217, AL-224 and AL-225).

[fig.5]Fig. 5 shows the results of inhibition assay against A beta fibril formation using the three anti-A beta oligomer antibodies (AL-217, and AL224 and AL-225).

[fig.6]Fig. 6 shows the results of immunoblotting assay to assess whether the three anti-A beta oligomer antibodies (AL-217, AL-224 and AL-225) bind to APP. APP was detected in the result of Tg2576 using the control antibody 6E10 (marked by arrow head).

Description of Embodiments

[0015] The present invention will be described more specifically below.

As described above, the present inventors succeeded in obtaining antibodies that bind specifically to A beta oligomers but not to A beta monomers. That is, the present invention provides antibodies that bind to A beta oligomers but not to A beta monomers. The antibodies are preferably isolated or purified.

[0016] The terms "isolated" and "purified" used for substances (antibodies and such) of the present invention indicate that the substances do not substantially include at least one other substance that may be contained in the natural source. Therefore, "isolated antibodies" and "purified antibodies" refer to antibodies that do not substantially include cell materials such as hydrocarbons, lipids, or other contaminant proteins from the cell or tissue source from which the antibodies (proteins) are derived. When the antibodies are chemically synthesized, the terms refer to antibodies that do not substantially include chemical precursor substances or other chemical substances. In a preferred embodiment, the antibodies of the present invention are isolated or purified.

[0017] "Antibodies" refers to glycoproteins that have the same structural characteristics. Antibodies show binding specificity towards specific antigens. Herein, "antigens" refers to proteins that have the ability to bind to the corresponding antibodies, and induce antigen-antibody reactions in vivo.

[0018] Herein, the antibody heavy chain may be denoted as "H chain", the antibody light chain may be denoted as "L chain", the heavy chain variable region may be denoted as "VH", the light chain variable region may be denoted as "VL", the heavy chain constant region may be denoted as "CH", the light chain constant region may be denoted as "CL", the framework region may be denoted as "FR", and the complementarity-determining region may be denoted as "CDR".

[0019] A beta proteins, which are the major constituents of amyloids, are peptides consisting of 40 to 42 amino acids, and are known to be produced from precursor proteins called amyloid precursor proteins (APPs) by the action of proteases. Besides amyloid fibrils

collected in ultracentrifuged sediment fractions, the amyloid molecules produced from APPs include oligomeric non-fibrous assemblies in addition to soluble monomers. "A beta oligomers" of the present invention refer to non-fibrous assemblies. The degree of A beta polymerization of "A beta oligomer" of the present invention is not particularly limited, but is typically 2 to 150. The "A beta oligomers" of the present invention include, for example, A beta40 (A beta 1-40) oligomers, A beta42 (A beta 1-42) oligomers, and A beta40/A beta42 oligomers (in which A beta40 and A beta42 are polymerized). For example, "A beta oligomers" of the present invention are, typically, molecules showing a molecular weight of 45 to 160 kDa in SDS-PAGE, and 22.5 to 1,035 kDa in Blue Native PAGE. Using molecular sieves, the molecules are collected mainly in the >100 kDa retention solution. When observed under an atomic force microscope, the molecules show mixed morphologies of granular, bead-shaped, and ring-shaped molecules having a height of 1.5 to 3.1 nm.There is no limitation on the origin and form of the antibodies used in the present invention as long as they bind to A beta oligomers but not to A beta monomers.

[0020] The antibodies of the present invention are featured by the characteristics that they bind to A beta oligomers but not to A beta monomers. Preferably, these antibodies have the following characteristics.

[0021] In dot-blot analysis, they react with A beta40 oligomers and A beta42 oligomers, but not with A beta40 monomers.

[0022] In competitive ELISA assay using immobilized A beta oligomers, the 50%-inhibition concentration (IC50) of A beta monomer for the binding of the antibodies to the immobilized A beta oligomers is higher than that of A beta oligomer.

[0023] In competitive ELISA assay using immobilized A beta oligomers, IC50 of A beta monomer is 500 nmol/L or more, preferably 1000 nmol/L or more, more preferably 1500 nmol/L or more, or more preferably 2000 nmol/L or more.

[0024] In competitive ELISA assay using immobilized A beta oligomers, IC50 of A beta oligomer is 100 nmol/L or less, preferably 50 nmol/L or less, more preferably 25 nmol/L or less, or more preferably 20 nmol/L or less.

[0025] In competitive ELISA assay using immobilized A beta oligomers, the antigen selectivity shown by IC50 of A beta monomer versus A beta oligomer for the binding of the antibodies to the immobilized A beta oligomers, i.e., IC50 of A beta monomer/IC50 of A beta oligomer, is 50 or more, preferably 100 or more, more preferably 150 or more, or more preferably 200 or more.

[0026] In the affinity analysis for A beta oligomers using Biacore (Biacore 3000), the binding rate constant (ka) is 1.0E+04 $M^{-1}S^{-1}$ or more, preferably 2.0E+04 $M^{-1}S^{-1}$ or more, more preferably 5.0E+04 $M^{-1}S^{-1}$ or more, more preferably 1.0E+05 $M^{-1}S^{-1}$ or more, or more preferably 1.5E+05 $M^{-1}S^{-1}$ or more.

[0027] In the affinity analysis for A beta oligomers using Biacore (Biacore 3000), the dissociation rate constant (kd) is 0.5 S^{-1} or less, preferably 0.2 S^{-1} or less, more preferably 0.1 S^{-1} or less, more preferably 0.05 S^{-1} or less, more preferably 0.01 S^{-1} or less, or more preferably 6.0E-03 S^{-1} or less.

[0028] In the affinity analysis for A beta oligomers using Biacore (Biacore 3000), the dissociation constant (KD) is 5.0E-06 M or less, preferably 1.0E-06 M or less, more preferably 7.0E-07 M or less, more preferably 1.0E-07 M or less, or more preferably 5.0E-08 M or less.

[0029] The antibodies of the present invention may be featured by at least one of the above characteristics. Furthermore, the antibodies may be featured by two or more of the above characteristics.

[0030] "Antibodies" of the present invention include both monoclonal and polyclonal antibodies. The antibodies of the present invention also include any type of antibodies such as non-human animal antibodies, humanized antibodies, chimeric antibodies, human antibodies, the later-described minibodies, amino acid sequence-modified antibodies, modified antibodies conjugated to other molecules (for example, polymers such as polyethylene glycol), and sugar chain-modified antibodies.

[0031] Herein, the term "monoclonal antibodies" refers to antibodies that are obtained from a substantially homogeneous population of antibodies. That is, the individual antibodies constituting the population are identical with the exception of possible natural mutants that may be present in a trace amount. Monoclonal antibodies are highly specific and recognize a single antigenic site. Each of the monoclonal antibodies recognizes a single determinant of the antigen, in contrast to conventional (polyclonal) antibody preparations that typically contain different antibodies against different antigenic determinants (epitopes).

[0032] In addition to the above-mentioned specificity, monoclonal antibodies have the advantage that they can be synthesized from a hybridoma culture that is not contaminated with other immunoglobulins. Therefore, "monoclonal" indicates the characteristics of antibodies that can be obtained from a substantially homogeneous antibody population. This term does not indicate the requirement for any specific method for antibody production.

[0033] Basically, monoclonal antibodies can be produced by using known techniques. For example, they may be produced by the hybridoma method first described by Kohler and Milstein (Nature 256: 495-7, 1975), or by the recombinant DNA method (Cabilly et al., Proc. Natl. Acad. Sci. USA 81:3273-7, 1984), but the methods are not limited thereto. For example, when using the hybridoma method, an A beta oligomer (for example, the A beta tetramer described in the Examples) is used as a sensitizing antigen, and immunization is carried out according to a conventional immunization

method. The obtained immune cells are fused with known parent cells by a conventional cell fusion method, and monoclonal antibody-producing cells can be screened and isolated using a conventional screening method.

[0034] The monoclonal antibodies of the present invention can be produced, for example, as follows. First, synthetic A beta 1-42 (Peptide Institute, Inc., Osaka) is dissolved in distilled deionized water or a 10 mM phosphate buffer solution, and this is incubated at 37degrees C for 18 hours. Then, the peptides are separated by 4-12% SDS-PAGE, and visualized by CBB staining, and the portion of the A beta 1-42 tetramer alone which is not contaminated with the A beta 1-42 monomer is cut out. Next, BALB/c mice are immunized at their foot pad with 2.5 micro g of the A beta 1-42 tetramer emulsified using complete Freund's adjuvant. Subsequently, booster immunizations are carried out six times. Hybridomas are produced from the inguinal lymph node by fusion with Sp2/O-Ag14 cells using Polyethylene Glycol 1500.

[0035] In the present invention, the animals immunized with sensitizing antigens are not particularly limited, but are preferably selected considering the compatibility with parent cells used for cell fusion. Generally, rodents, lagomorphs, or primates are used. Rodents include, for example, mice, rats, and hamsters. Lagomorphs include, for example, rabbits. Primates include, for example, Catarrhini (old-world) monkeys such as Macaca fascicularis, Macaca mulatta, hamadryas, and chimpanzees.

[0036] Animals are immunized with sensitizing antigens according to known methods. For example, as a standard method, immunization is performed by intraperitoneal or subcutaneous injection of a sensitizing antigen into mammals.

[0037] An example of the parent cells fused with the aforementioned immunocytes is the Sp2/O-Ag14 cell, which will be described below in the Examples. However, various other known cell lines can be used.

[0038] Cell fusion between the aforementioned immunocyte and a myeloma cell can be carried out basically according to known methods including the method by Kohler and Milstein (Kohler G. and Milstein C., Methods Enzymol. (1981) 73, 3-46).

[0039] Hybridomas obtained in this manner are selected by culturing them in a conventional selection culture medium such as a HAT culture medium, which contains hypoxanthine, aminopterin, and thymidine. Culturing in the above-mentioned HAT culture medium is generally continued for several days to several weeks for an adequate time for killing cells other than the desired hybridomas (non-fused cells). Next, a conventional limiting dilution method is performed for screening and singly-cloning of a hybridoma that produces the desired antibody.

[0040] Thereafter, the obtained hybridoma is transplanted into the abdominal cavity of a mouse, and ascitic fluid containing the desired monoclonal antibodies is extracted. For example, the antibodies can be purified from the ascitic fluid by conventional protein

separation and/or purification methods such as a selected combination of column chromatography including, but not limited to, affinity chromatography, filtration, ultrafiltration, salt precipitation, dialysis, SDS polyacrylamide gel electrophoresis, and isoelectric focusing (Antibodies: A Laboratory manual, Harlow and David, Lane (edit.), Cold Spring Harbor Laboratory, 1988).

[0041] Protein A columns and Protein G columns can be used for affinity columns. Examples of the Protein A columns used include Hyper D, POROS, and Sepharose F.F. (Pharmacia).

[0042] Chromatography (excluding affinity chromatography) includes ion exchange chromatography, hydrophobic chromatography, gel filtration, reverse-phase chromatography, and adsorption chromatography ("Strategies for Protein Purification and Characterization: A Laboratory Course Manual", Daniel R Marshak et al., Cold Spring Harbor Laboratory Press, 1996). When chromatography is carried out, liquid-phase chromatography methods such as HPLC and FPLC can be used.

[0043] Monoclonal antibody-producing hybridomas prepared in this manner can be subcultured in a conventional culture medium, and they can be stored for a long time in liquid nitrogen.

[0044] Any mammal can be immunized using an immunogen for antibody production. However, when preparing monoclonal antibodies by producing hybridomas, the compatibility with parent cells used in cell fusion for hybridoma production is preferably considered.

[0045] Generally, rodents, lagomorphs, or primates are used for the immunization. Rodents include, for example, mice, rats, and hamsters. Lagomorphs include, for example, rabbits. Primates include, for example, Catarrhini (old-world) monkeys such as Macaca fascicularis, Macaca mulatta, hamadryas, and chimpanzees.

[0046] The use of transgenic animals that have a human antibody gene repertoire is known in the art (Ishida I, et al., Cloning and Stem Cells 4: 91-102, 2002). As with other animals, to obtain human monoclonal antibodies, the transgenic animals are immunized, then antibody-producing cells are collected from the animals and fused with myeloma cells to produce hybridomas, and anti-protein human antibodies can be prepared from these hybridomas (see International Publication Nos. WO92/03918, WO94/02602, WO94/25585, WO96/33735, and WO96/34096).

[0047] Alternatively, lymphocytes immortalized with oncogenes may be used for monoclonal antibody production. For example, human lymphocytes infected with EB virus or such is immunized in vitro with immunogens. Next, the immunized lymphocytes are fused with human-derived myeloma cells (U266, etc) capable of unlimited division, and thus hybridomas that produce the desired human antibodies are obtained (Japanese Patent Application Kokai Publication No. (JP-A) S63-17688

(unexamined, published Japanese patent application)).

[0048] Once monoclonal antibodies can be obtained by any of the aforementioned methods, the antibodies may also be prepared using genetic engineering methods (see, for example, Borrebaeck CAK and Larrick JW, Therapeutic Monoclonal Antibodies, MacMillan Publishers, UK, 1990). For example, recombinant antibodies may be prepared by cloning DNAs that encode the desired antibodies from antibody-producing cells such as hybridomas or immunized lymphocytes that produce the antibodies, then inserting the cloned DNAs into appropriate vectors, and transfecting the vectors into suitable host cells. Such recombinant antibodies are also included in the present invention.

[0049] Examples of the monoclonal antibodies of the present invention include the following: AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, and AL-233 antibody.

[0050] In an embodiment, the antibodies of the present invention include minibodies. A minibody contains an antibody fragment lacking a portion of a whole antibody, and is not particularly limited as long as it has the ability to bind to an antigen. Examples of antibody fragments include Fab, Fab', F(ab')2, and Fv. Examples of minibodies include Fab, Fab', F(ab')2, Fv, scFv (single chain Fv), diabody, and sc(Fv)2 (single chain (Fv)2).

[0051] These minibodies can be obtained, for example, by treating an antibody with an enzyme to produce an antibody fragment. Known enzymes for producing an antibody fragment include papain, pepsin, and plasmin. Alternatively, a gene construct encoding an antibody fragment can be produced, inserted into an expression vector, and expressed in a suitable host cell (see, for example, Co, M.S. et al., J. Immunol. (1994) 152, 2968-2976, Better, M. and Horwitz, A. H. Methods in Enzymology (1989) 178, 476-496, Plueckthun, A. and Skerra, A. Methods in Enzymology (1989) 178, 476-496, Lamoyi, E., Methods in Enzymology (1989) 121, 652-663, Rousseaux, J. et al., Methods in Enzymology (1989) 121, 663-669, Bird, R. E. et al., TIBTECH (1991) 9, 132-137).

[0052] Herein, "antigen-binding fragments" means the above-mentioned antibody fragments having antigen-binding ability, or minibodies including the antibody fragments having antigen-binding ability. Antibody fragments that bind to A beta oligomers but not to A

beta monomers are also included in the present invention. Hereinafter, reference to "antibody" includes reference to the above "antigen-binding fragment".

[0053] Polyclonal antibodies of the present invention can be obtained by the following methods. To obtain the polyclonal antibodies, blood is removed from a mammal sensitized with an antigen after the mammal is immunized with an A beta oligomer (e.g., A beta tetramer) as a sensitizing antigen using a conventional method and the serum level of the desired antibody is confirmed to be increased. Serum is separated from blood by a known method. When a polyclonal antibody is used, serum containing the polyclonal antibody may be utilized. Alternatively, if necessary, a fraction containing the polyclonal antibody may be isolated from serum and then used. For example, immunoglobulin G or M can be prepared by obtaining a fraction that specifically recognizes an A beta oligomer using an affinity column coupled with an A beta oligomer, and then purifying this fraction using a Protein A or Protein G column.

[0054] The present invention provides A beta oligomers bound by the antibodies of the present invention. Preferably, the antibodies include the following: AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, and AL-233 antibody. The A beta oligomers can be used as antigens for preparing antibodies, or vaccines.

[0055] In other words, in the present invention, the A beta oligomers are antigens bound by the following antibodies: AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody.

[0056] Furthermore, the antibodies of the present invention include antibodies that bind to the antigens bound by the following antibodies: AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216

antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody.

[0057] Furthermore, the present invention provides an antibody of any one of (1) to (99) below:

(1) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 530;

(2) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 532;

(3) an antibody that comprises the H chain of (1) and the L chain of (2);

(4) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 534;

(5) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 536;

(6) an antibody that comprises the H chain of (4) and the L chain of (5);

(7) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 538;

(8) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 540;

(9) an antibody that comprises the H chain of (7) and the L chain of (8);

(10) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 542;

(11) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 544;

(12) an antibody that comprises the H chain of (10) and the L chain of (11);

(13) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 546;

(14) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 548;

(15) an antibody that comprises the H chain of (13) and the L chain of (14);

(16) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 550;

(17) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 552;

(18) an antibody that comprises the H chain of (16) and the L chain of (17);

(19) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 554;

(20) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 556;
(21) an antibody that comprises the H chain of (19) and the L chain of (20);
(22) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 558;
(23) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 560;
(24) an antibody that comprises the H chain of (22) and the L chain of (23);
(25) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 562;
(26) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 564;
(27) an antibody that comprises the H chain of (25) and the L chain of (26);
(28) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 566;
(29) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 568;
(30) an antibody that comprises the H chain of (28) and the L chain of (29);
(31) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 570;
(32) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 572;
(33) an antibody that comprises the H chain of (31) and the L chain of (32);
(34) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 574;
(35) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 576;
(36) an antibody that comprises the H chain of (34) and the L chain of (35);
(37) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 578;
(38) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 580;
(39) an antibody that comprises the H chain of (37) and the L chain of (38);
(40) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 582;
(41) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 584;
(42) an antibody that comprises the H chain of (40) and the L chain of (41);

(43) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 586;
(44) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 588;
(45) an antibody that comprises the H chain of (43) and the L chain of (44);
(46) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 590;
(47) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 592;
(48) an antibody that comprises the H chain of (46) and the L chain of (47);
(49) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 594;
(50) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 596;
(51) an antibody that comprises the H chain of (49) and the L chain of (50);
(52) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 598;
(53) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 600;
(54) an antibody that comprises the H chain of (52) and the L chain of (53);
(55) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 602;
(56) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 604;
(57) an antibody that comprises the H chain of (55) and the L chain of (56);
(58) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 606;
(59) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 608;
(60) an antibody that comprises the H chain of (58) and the L chain of (59);
(61) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 610;
(62) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 612;
(63) an antibody that comprises the H chain of (61) and the L chain of (62);
(64) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 614;
(65) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which

are identified in VL comprising the amino acid sequence of SEQ ID NO: 616;
(66) an antibody that comprises the H chain of (64) and the L chain of (65);
(67) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 618;
(68) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 620;
(69) an antibody that comprises the H chain of (67) and the L chain of (68);
(70) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 622;
(71) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 624;
(72) an antibody that comprises the H chain of (70) and the L chain of (71);
(73) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 626;
(74) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 628;
(75) an antibody that comprises the H chain of (73) and the L chain of (74);
(76) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 630;
(77) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 632;
(78) an antibody that comprises the H chain of (76) and the L chain of (77);
(79) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 634;
(80) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 636;
(81) an antibody that comprises the H chain of (79) and the L chain of (80);
(82) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 638;
(83) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 640;
(84) an antibody that comprises the H chain of (82) and the L chain of (83);
(85) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 642;
(86) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 644;
(87) an antibody that comprises the H chain of (85) and the L chain of (86);
(88) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which

are identified in VH comprising the amino acid sequence of SEQ ID NO: 646;
(89) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 648;
(90) an antibody that comprises the H chain of (88) and the L chain of (89);
(91) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 650;
(92) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 652;
(93) an antibody that comprises the H chain of (91) and the L chain of (92);
(94) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 654;
(95) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 656;
(96) an antibody that comprises the H chain of (94) and the L chain of (95);
(97) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 658;
(98) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 660; and
(99) an antibody that comprises the H chain of (97) and the L chain of (98);
As mentioned above, "CDR1, CDR2, and CDR3" refers to CDR determined by a method well-known in the art (e.g., see Kabat, Elvin A., Sequences of proteins of immunological interest 5th ed., National Institutes of Health, 1991; Chothia et al, J Mol Biol 196:901-917,1987). It is a technical common knowledge in the art that the amino acid sequences of CDR1, CDR2, and CDR3 can be identified in amino acid sequences of regions including CDR1, CDR2, and CDR3, using a method well-known in the art. In the following embodiments, for each antibody, an example of the CDR amino acid sequence determined according to the definition by Kabat is shown.

[0058] In a preferred embodiment, the antibody of the present invention is any one of (1) to (200) below.

AL-201 antibody:

(1) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 6 as CDR1, the amino acid sequence of SEQ ID NO: 8 as CDR2, and the amino acid sequence of SEQ ID NO: 10 as CDR3;

(2) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 12 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2, and the amino acid sequence of SEQ ID NO: 16 as CDR3;

(3) an antibody that comprises the H chain of (1) and the L chain of (2);

(4) an antibody that comprises an H chain having the amino acid sequence of SEQ

ID NO: 530 as VH;
(5) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 532 as VL;
(6) an antibody that comprises the H chain of (4) and the L chain of (5);
AL-202 antibody:
(7) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 22 as CDR1, the amino acid sequence of SEQ ID NO: 24 as CDR2, and the amino acid sequence of SEQ ID NO: 26 as CDR3;
(8) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 28 as CDR1, the amino acid sequence of SEQ ID NO: 30 as CDR2, and the amino acid sequence of SEQ ID NO: 32 as CDR3;
(9) an antibody that comprises the H chain of (7) and the L chain of (8);
(10) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 534 as VH;
(11) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 536 as VL;
(12) an antibody that comprises the H chain of (10) and the L chain of (11);
AL-203 antibody:
(13) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 38 as CDR1, the amino acid sequence of SEQ ID NO: 40 as CDR2, and the amino acid sequence of SEQ ID NO: 42 as CDR3;
(14) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 44 as CDR1, the amino acid sequence of SEQ ID NO: 46 as CDR2, and the amino acid sequence of SEQ ID NO: 48 as CDR3;
(15) an antibody that comprises the H chain of (13) and the L chain of (14);
(16) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 538 as VH;
(17) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 540 as VL;
(18) an antibody that comprises the H chain of (16) and the L chain of (17);
AL-204 antibody:
(19) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 54 as CDR1, the amino acid sequence of SEQ ID NO: 56 as CDR2, and the amino acid sequence of SEQ ID NO: 58 as CDR3;
(20) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 60 as CDR1, the amino acid sequence of SEQ ID NO: 62 as CDR2, and the amino acid sequence of SEQ ID NO: 64 as CDR3;
(21) an antibody that comprises the H chain of (19) and the L chain of (20);

(22) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 542 as VH;
(23) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 544 as VL;
(24) an antibody that comprises the H chain of (22) and the L chain of (23);
AL-205 antibody:
(25) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 70 as CDR1, the amino acid sequence of SEQ ID NO: 72 as CDR2, and the amino acid sequence of SEQ ID NO: 74 as CDR3;
(26) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 76 as CDR1, the amino acid sequence of SEQ ID NO: 78 as CDR2, and the amino acid sequence of SEQ ID NO: 80 as CDR3;
(27) an antibody that comprises the H chain of (25) and the L chain of (26);
(28) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 546 as VH;
(29) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 548 as VL;
(30) an antibody that comprises the H chain of (28) and the L chain of (29);
AL-206 antibody:
(31) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 86 as CDR1, the amino acid sequence of SEQ ID NO: 88 as CDR2, and the amino acid sequence of SEQ ID NO: 90 as CDR3;
(32) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 92 as CDR1, the amino acid sequence of SEQ ID NO: 94 as CDR2, and the amino acid sequence of SEQ ID NO: 96 as CDR3;
(33) an antibody that comprises the H chain of (31) and the L chain of (32);
(34) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 550 as VH;
(35) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 552 as VL;
(36) an antibody that comprises the H chain of (34) and the L chain of (35);
AL-207 antibody:
(37) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 102 as CDR1, the amino acid sequence of SEQ ID NO: 104 as CDR2, and the amino acid sequence of SEQ ID NO: 106 as CDR3;
(38) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 108 as CDR1, the amino acid sequence of SEQ ID NO: 110 as CDR2, and the amino acid sequence of SEQ ID NO: 112 as CDR3;

(39) an antibody that comprises the H chain of (37) and the L chain of (38);
(40) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 554 as VH;
(41) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 556 as VL;
(42) an antibody that comprises the H chain of (40) and the L chain of (41);
AL-208 antibody:
(43) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 118 as CDR1, the amino acid sequence of SEQ ID NO: 120 as CDR2, and the amino acid sequence of SEQ ID NO: 122 as CDR3;
(44) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 124 as CDR1, the amino acid sequence of SEQ ID NO: 126 as CDR2, and the amino acid sequence of SEQ ID NO: 128 as CDR3;
(45) an antibody that comprises the H chain of (43) and the L chain of (44);
(46) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 558 as VH;
(47) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 560 as VL;
(48) an antibody that comprises the H chain of (46) and the L chain of (47);
AL-209 antibody:
(49) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 134 as CDR1, the amino acid sequence of SEQ ID NO: 136 as CDR2, and the amino acid sequence of SEQ ID NO: 138 as CDR3;
(50) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 140 as CDR1, the amino acid sequence of SEQ ID NO: 142 as CDR2, and the amino acid sequence of SEQ ID NO: 144 as CDR3;
(51) an antibody that comprises the H chain of (49) and the L chain of (50);
(52) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 562 as VH;
(53) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 564 as VL;
(54) an antibody that comprises the H chain of (52) and the L chain of (53);
AL-210 antibody:
(55) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 150 as CDR1, the amino acid sequence of SEQ ID NO: 152 as CDR2, and the amino acid sequence of SEQ ID NO: 154 as CDR3;
(56) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 156 as CDR1, the amino acid sequence of SEQ ID NO: 158 as CDR2, and the

amino acid sequence of SEQ ID NO: 160 as CDR3;

(57) an antibody that comprises the H chain of (55) and the L chain of (56);

(58) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 566 as VH;

(59) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 568 as VL;

(60) an antibody that comprises the H chain of (58) and the L chain of (59);

AL-211 antibody:

(61) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 166 as CDR1, the amino acid sequence of SEQ ID NO: 168 as CDR2, and the amino acid sequence of SEQ ID NO: 170 as CDR3;

(62) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 172 as CDR1, the amino acid sequence of SEQ ID NO: 174 as CDR2, and the amino acid sequence of SEQ ID NO: 176 as CDR3;

(63) an antibody that comprises the H chain of (61) and the L chain of (62);

(64) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 570 as VH;

(65) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 572 as VL;

(66) an antibody that comprises the H chain of (64) and the L chain of (65);

AL-212 antibody:

(67) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 182 as CDR1, the amino acid sequence of SEQ ID NO: 184 as CDR2, and the amino acid sequence of SEQ ID NO: 186 as CDR3;

(68) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 188 as CDR1, the amino acid sequence of SEQ ID NO: 190 as CDR2, and the amino acid sequence of SEQ ID NO: 192 as CDR3;

(69) an antibody that comprises the H chain of (67) and the L chain of (68);

(70) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 574 as VH;

(71) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 576 as VL;

(72) an antibody that comprises the H chain of (70) and the L chain of (71);

AL-213 antibody:

(73) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 198 as CDR1, the amino acid sequence of SEQ ID NO: 200 as CDR2, and the amino acid sequence of SEQ ID NO: 202 as CDR3;

(74) an antibody that comprises an L chain having the amino acid sequence of SEQ ID

NO: 204 as CDR1, the amino acid sequence of SEQ ID NO: 206 as CDR2, and the amino acid sequence of SEQ ID NO: 208 as CDR3;
(75) an antibody that comprises the H chain of (73) and the L chain of (74);
(76) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 578 as VH;
(77) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 580 as VL;
(78) an antibody that comprises the H chain of (75) and the L chain of (76);
AL-214 antibody:
(79) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 214 as CDR1, the amino acid sequence of SEQ ID NO: 216 as CDR2, and the amino acid sequence of SEQ ID NO: 218 as CDR3;
(80) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 220 as CDR1, the amino acid sequence of SEQ ID NO: 222 as CDR2, and the amino acid sequence of SEQ ID NO: 224 as CDR3;
(81) an antibody that comprises the H chain of (79) and the L chain of (80);
(82) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 582 as VH;
(83) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 584 as VL;
(84) an antibody that comprises the H chain of (82) and the L chain of (83);
AL-215 antibody:
(85) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 230 as CDR1, the amino acid sequence of SEQ ID NO: 232 as CDR2, and the amino acid sequence of SEQ ID NO: 234 as CDR3;
(86) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 236 as CDR1, the amino acid sequence of SEQ ID NO: 238 as CDR2, and the amino acid sequence of SEQ ID NO: 240 as CDR3;
(87) an antibody that comprises the H chain of (85) and the L chain of (86);
(88) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 586 as VH;
(89) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 588 as VL;
(90) an antibody that comprises the H chain of (88) and the L chain of (89);
AL-216 antibody:
(91) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 246 as CDR1, the amino acid sequence of SEQ ID NO: 248 as CDR2, and the amino acid sequence of SEQ ID NO: 250 as CDR3;

(92) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 252 as CDR1, the amino acid sequence of SEQ ID NO: 254 as CDR2, and the amino acid sequence of SEQ ID NO: 256 as CDR3;
(93) an antibody that comprises the H chain of (91) and the L chain of (92);
(94) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 590 as VH;
(95) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 592 as VL;
(96) an antibody that comprises the H chain of (94) and the L chain of (95);
AL-217 antibody:
(97) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 262 as CDR1, the amino acid sequence of SEQ ID NO: 264 as CDR2, and the amino acid sequence of SEQ ID NO: 266 as CDR3;
(98) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 268 as CDR1, the amino acid sequence of SEQ ID NO: 270 as CDR2, and the amino acid sequence of SEQ ID NO: 272 as CDR3;
(99) an antibody that comprises the H chain of (97) and the L chain of (98);
(100) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 594 as VH;
(101) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 596 as VL;
(102) an antibody that comprises the H chain of (100) and the L chain of (101);
AL-218 antibody:
(103) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 278 as CDR1, the amino acid sequence of SEQ ID NO: 280 as CDR2, and the amino acid sequence of SEQ ID NO: 282 as CDR3;
(104) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 284 as CDR1, the amino acid sequence of SEQ ID NO: 286 as CDR2, and the amino acid sequence of SEQ ID NO: 288 as CDR3;
(105) an antibody that comprises the H chain of (103) and the L chain of (104);
(106) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 598 as VH;
(107) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 600 as VL;
(108) an antibody that comprises the H chain of (106) and the L chain of (107);
AL-219 antibody:
(109) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 294 as CDR1, the amino acid sequence of SEQ ID NO: 296 as CDR2, and the

amino acid sequence of SEQ ID NO: 298 as CDR3;
(110) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 300 as CDR1, the amino acid sequence of SEQ ID NO: 302 as CDR2, and the amino acid sequence of SEQ ID NO: 304 as CDR3;
(111) an antibody that comprises the H chain of (109) and the L chain of (110);
(112) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 602 as VH;
(113) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 604 as VL;
(114) an antibody that comprises the H chain of (112) and the L chain of (113);
AL-220 antibody:
(115) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 310 as CDR1, the amino acid sequence of SEQ ID NO: 312 as CDR2, and the amino acid sequence of SEQ ID NO: 314 as CDR3;
(116) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 316 as CDR1, the amino acid sequence of SEQ ID NO: 318 as CDR2, and the amino acid sequence of SEQ ID NO: 320 as CDR3;
(117) an antibody that comprises the H chain of (115) and the L chain of (116);
(118) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 606 as VH;
(119) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 608 as VL;
(120) an antibody that comprises the H chain of (118) and the L chain of (119);
AL-221 antibody:
(121) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 326 as CDR1, the amino acid sequence of SEQ ID NO: 328 as CDR2, and the amino acid sequence of SEQ ID NO: 330 as CDR3;
(122) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 332 as CDR1, the amino acid sequence of SEQ ID NO: 334 as CDR2, and the amino acid sequence of SEQ ID NO: 336 as CDR3;
(123) an antibody that comprises the H chain of (121) and the L chain of (122);
(124) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 610 as VH;
(125) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 612 as VL;
(126) an antibody that comprises the H chain of (124) and the L chain of (125);
AL-222 antibody:
(127) an antibody that comprises an H chain having the amino acid sequence of SEQ

ID NO: 342 as CDR1, the amino acid sequence of SEQ ID NO: 344 as CDR2, and the amino acid sequence of SEQ ID NO: 346 as CDR3;

(128) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 348 as CDR1, the amino acid sequence of SEQ ID NO: 350 as CDR2, and the amino acid sequence of SEQ ID NO: 352 as CDR3;

(129) an antibody that comprises the H chain of (127) and the L chain of (128);

(130) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 614 as VH;

(131) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 616 as VL;

(132) an antibody that comprises the H chain of (130) and the L chain of (131);

AL-223 antibody:

(133) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 358 as CDR1, the amino acid sequence of SEQ ID NO: 360 as CDR2, and the amino acid sequence of SEQ ID NO: 362 as CDR3;

(134) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 364 as CDR1, the amino acid sequence of SEQ ID NO: 366 as CDR2, and the amino acid sequence of SEQ ID NO: 368 as CDR3;

(135) an antibody that comprises the H chain of (133) and the L chain of (134);

(136) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 618 as VH;

(137) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 620 as VL;

(138) an antibody that comprises the H chain of (136) and the L chain of (137);

AL-224 antibody:

(139) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 374 as CDR1, the amino acid sequence of SEQ ID NO: 376 as CDR2, and the amino acid sequence of SEQ ID NO: 378 as CDR3;

(140) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 380 as CDR1, the amino acid sequence of SEQ ID NO: 382 as CDR2, and the amino acid sequence of SEQ ID NO: 384 as CDR3;

(141) an antibody that comprises the H chain of (139) and the L chain of (140);

(142) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 622 as VH;

(143) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 624 as VL;

(144) an antibody that comprises the H chain of (142) and the L chain of (143);

AL-225 antibody:

(145) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 390 as CDR1, the amino acid sequence of SEQ ID NO: 392 as CDR2, and the amino acid sequence of SEQ ID NO: 394 as CDR3;
(146) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 396 as CDR1, the amino acid sequence of SEQ ID NO: 398 as CDR2, and the amino acid sequence of SEQ ID NO: 400 as CDR3;
(147) an antibody that comprises the H chain of (145) and the L chain of (146);
(148) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 626 as VH;
(149) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 628 as VL;
(150) an antibody that comprises the H chain of (148) and the L chain of (149);
AL-226 antibody:
(151) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 406 as CDR1, the amino acid sequence of SEQ ID NO: 408 as CDR2, and the amino acid sequence of SEQ ID NO: 410 as CDR3;
(152) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 412 as CDR1, the amino acid sequence of SEQ ID NO: 414 as CDR2, and the amino acid sequence of SEQ ID NO: 416 as CDR3;
(153) an antibody that comprises the H chain of (151) and the L chain of (152);
(154) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 630 as VH;
(155) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 632 as VL;
(156) an antibody that comprises the H chain of (154) and the L chain of (155);
AL-227 antibody:
(157) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 422 as CDR1, the amino acid sequence of SEQ ID NO: 424 as CDR2, and the amino acid sequence of SEQ ID NO: 426 as CDR3;
(158) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 428 as CDR1, the amino acid sequence of SEQ ID NO: 430 as CDR2, and the amino acid sequence of SEQ ID NO: 432 as CDR3;
(159) an antibody that comprises the H chain of (157) and the L chain of (158);
(160) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 634 as VH;
(161) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 636 as VL;
(162) an antibody that comprises the H chain of (160) and the L chain of (161);

AL-228 antibody:

(163) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 438 as CDR1, the amino acid sequence of SEQ ID NO: 440 as CDR2, and the amino acid sequence of SEQ ID NO: 442 as CDR3;

(164) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 444 as CDR1, the amino acid sequence of SEQ ID NO: 446 as CDR2, and the amino acid sequence of SEQ ID NO: 448 as CDR3;

(165) an antibody that comprises the H chain of (163) and the L chain of (164);

(166) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 638 as VH;

(167) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 640 as VL;

(168) an antibody that comprises the H chain of (166) and the L chain of (167);

AL-229 antibody:

(169) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 454 as CDR1, the amino acid sequence of SEQ ID NO: 456 as CDR2, and the amino acid sequence of SEQ ID NO: 458 as CDR3;

(170) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 460 as CDR1, the amino acid sequence of SEQ ID NO: 462 as CDR2, and the amino acid sequence of SEQ ID NO: 464 as CDR3;

(171) an antibody that comprises the H chain of (169) and the L chain of (170);

(172) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 642 as VH;

(173) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 644 as VL;

(174) an antibody that comprises the H chain of (172) and the L chain of (173);

AL-230 antibody:

(175) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 470 as CDR1, the amino acid sequence of SEQ ID NO: 472 as CDR2, and the amino acid sequence of SEQ ID NO: 474 as CDR3;

(176) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 476 as CDR1, the amino acid sequence of SEQ ID NO: 478 as CDR2, and the amino acid sequence of SEQ ID NO: 480 as CDR3;

(177) an antibody that comprises the H chain of (175) and the L chain of (176);

(178) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 646 as VH;

(179) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 648 as VL;

(180) an antibody that comprises the H chain of (178) and the L chain of (179);
AL-231 antibody:
(181) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 486 as CDR1, the amino acid sequence of SEQ ID NO: 488 as CDR2, and the amino acid sequence of SEQ ID NO: 490 as CDR3;
(182) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 492 as CDR1, the amino acid sequence of SEQ ID NO: 494 as CDR2, and the amino acid sequence of SEQ ID NO: 496 as CDR3;
(183) an antibody that comprises the H chain of (181) and the L chain of (182);
(184) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 650 as VH;
(185) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 652 as VL;
(186) an antibody that comprises the H chain of (184) and the L chain of (185);
AL-232 antibody:
(187) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 502 as CDR1, the amino acid sequence of SEQ ID NO: 504 as CDR2, and the amino acid sequence of SEQ ID NO: 506 as CDR3;
(188) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 508 as CDR1, the amino acid sequence of SEQ ID NO: 510 as CDR2, and the amino acid sequence of SEQ ID NO: 512 as CDR3;
(189) an antibody that comprises the H chain of (187) and the L chain of (188);
(190) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 654 as VH;
(191) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 656 as VL;
(192) an antibody that comprises the H chain of (190) and the L chain of (191);
AL-233 antibody:
(193) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 518 as CDR1, the amino acid sequence of SEQ ID NO: 520 as CDR2, and the amino acid sequence of SEQ ID NO: 522 as CDR3;
(194) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 524 as CDR1, the amino acid sequence of SEQ ID NO: 526 as CDR2, and the amino acid sequence of SEQ ID NO: 528 as CDR3;
(195) an antibody that comprises the H chain of (193) and the L chain of (194);
(196) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 658 as VH;
(197) an antibody that comprises an L chain having the amino acid sequence of SEQ

ID NO: 660 as VL;

(198) an antibody that comprises the H chain of (196) and the L chain of (197);

(199) an antibody that comprises one or more amino acid substitutions, deletions, additions, and/or insertions in the antibody of any one of (1) to (198), which has equivalent activity to the antibody of any one of (1) to (198); and

(200) an antibody that binds to the epitope bound by the antibody of any one of (1) to (198).

[0059] AL-201 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 6 (sequence of the AL-201antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 8 (sequence of the AL-201 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 10 (sequence of the AL-201 antibody H-chain CDR3) as CDR3"of (1) is a VH comprising the amino acid sequence of SEQ ID NO: 530 (sequence of the AL-201 antibody VH).

[0060] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 12 (sequence of the AL-201 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 14 (sequence of the AL-201 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 16 (sequence of the AL-201 antibody L-chain CDR3) as CDR3"of (2) is a VL comprising the amino acid sequence of SEQ ID NO: 4 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 532 (sequence of the AL-201 antibody VL).

[0061] AL-202 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 22 (sequence of the AL-202 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 24 (sequence of the AL-202 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 26 (sequence of the AL-202 antibody H-chain CDR3) as CDR3"of (7) is a VH comprising the amino acid sequence of SEQ ID NO: 534 (sequence of the AL-202 antibody VH).

[0062] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 28 (sequence of the AL-202 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 30 (sequence of the AL-202 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 32 (sequence of the AL-202 antibody L-chain CDR3) as CDR3"of (8) is a VL comprising the amino acid sequence of SEQ ID NO: 536 (sequence of the AL-202 antibody VL).

[0063] AL-203 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 38 (sequence of the AL-203 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 40 (sequence of the AL-203 antibody

H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 42 (sequence of the AL-203 antibody H-chain CDR3) as CDR3"of (13) is a VH comprising the amino acid sequence of SEQ ID NO: 538 (sequence of the AL-203 antibody VH).

[0064] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 44 (sequence of the AL-203 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 46 (sequence of the AL-203 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 48 (sequence of the AL-203 antibody L-chain CDR3) as CDR3"of (14) is a VL comprising the amino acid sequence of SEQ ID NO: 36 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 540 (sequence of the AL-203 antibody VL).

[0065] AL-204 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 54 (sequence of the AL-204 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 56 (sequence of the AL-204 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 58 (sequence of the AL-204 antibody H-chain CDR3) as CDR3"of (19) is a VH comprising the amino acid sequence of SEQ ID NO: 542 (sequence of the AL-204 antibody VH).

[0066] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 60 (sequence of the AL-204 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 62 (sequence of the AL-204 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 64 (sequence of the AL-204 antibody L-chain CDR3) as CDR3"of (20) is a VL comprising the amino acid sequence of SEQ ID NO: 52 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 544 (sequence of the AL-204 antibody VL).

[0067] AL-205 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 70 (sequence of the AL-205 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 72 (sequence of the AL-205 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 74 (sequence of the AL-205 antibody H-chain CDR3) as CDR3"of (25) is a VH comprising the amino acid sequence of SEQ ID NO: 66, more preferably, a VH comprising the amino acid sequence of SEQ ID NO: 546 (sequence of the AL-205 antibody VH).

[0068] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 76 (sequence of the AL-205 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 78 (sequence of the AL-205 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 80 (sequence of the AL-205 antibody L-chain CDR3) as CDR3"of (26) is a VL comprising the amino acid sequence of SEQ ID NO: 548 (sequence of the AL-205 antibody VL).

[0069] AL-206 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 86 (sequence of the AL-206 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 88 (sequence of the AL-206 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 90 (sequence of the AL-206 antibody H-chain CDR3) as CDR3"of (31) is a VH comprising the amino acid sequence of SEQ ID NO: 550 (sequence of the AL-206 antibody VH).

[0070] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 92 (sequence of the AL-206 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 94 (sequence of the AL-206 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 96 (sequence of the AL-206 antibody L-chain CDR3) as CDR3"of (32) is a VL comprising the amino acid sequence of SEQ ID NO: 84 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 552 (sequence of the AL-206 antibody VL).

[0071] AL-207 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 102 (sequence of the AL-207 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 104 (sequence of the AL-207 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 106 (sequence of the AL-207 antibody H-chain CDR3) as CDR3"of (37) is a VH comprising the amino acid sequence of SEQ ID NO: 554 (sequence of the AL-207 antibody VH).

[0072] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 108 (sequence of the AL-207 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 110 (sequence of the AL-207 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 112 (sequence of the AL-207 antibody L-chain CDR3) as CDR3"of (38) is a VL comprising the amino acid sequence of SEQ ID NO: 100 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 556 (sequence of the AL-207 antibody VL).

[0073] AL-208 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 118 (sequence of the AL-208 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 120 (sequence of the AL-208 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 122 (sequence of the AL-208 antibody H-chain CDR3) as CDR3"of (43) is a VH comprising the amino acid sequence of SEQ ID NO: 558 (sequence of the AL-208 antibody VH).

[0074] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 124 (sequence of the AL-208 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 126 (sequence of the AL-208 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 128 (sequence of the AL-208 antibody L-chain CDR3) as CDR3"of (44) is a VL comprising the amino acid sequence of SEQ ID NO: 116 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 560 (sequence of the AL-208 antibody VL).

[0075] AL-209 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 134 (sequence of the AL-209antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 136 (sequence of the AL-209 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 138 (sequence of the AL-209 antibody H-chain CDR3) as CDR3"of (49) is a VH comprising the amino acid sequence of SEQ ID NO: 562 (sequence of the AL-209 antibody VH).

[0076] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 140 (sequence of the AL-209 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 142 (sequence of the AL-209 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 144 (sequence of the AL-209 antibody L-chain CDR3) as CDR3"of (50) is a VL comprising the amino acid sequence of SEQ ID NO: 132 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 564 (sequence of the AL-209 antibody VL).

[0077] AL-210 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 150 (sequence of the AL-210 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 152 (sequence of the AL-210 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 154 (sequence of the AL-210 antibody H-chain CDR3) as CDR3"of (55) is a VH comprising the amino acid sequence of SEQ ID NO: 566 (sequence of the AL-210 antibody VH).

[0078] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 156 (sequence of the AL-210 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 158 (sequence of the AL-210 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 160 (sequence of the AL-210 antibody L-chain CDR3) as CDR3"of (56) is a VL comprising the amino acid sequence of SEQ ID NO: 148 , more preferably a VL

comprising the amino acid sequence of SEQ ID NO: 568 (sequence of the AL-210 antibody VL).

[0079] AL-211 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 166 (sequence of the AL-211 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 168 (sequence of the AL-211 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 170 (sequence of the AL-211 antibody H-chain CDR3) as CDR3"of (61) is a VH comprising the amino acid sequence of SEQ ID NO: 570 (sequence of the AL-211 antibody VH).

[0080] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 172 (sequence of the AL-211 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 174 (sequence of the AL-211 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 176 (sequence of the AL-211 antibody L-chain CDR3) as CDR3"of (62) is a VL comprising the amino acid sequence of SEQ ID NO: 164 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 572 (sequence of the AL-211 antibody VL).

[0081] AL-212 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 182 (sequence of the AL-212 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 184 (sequence of the AL-212 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 186 (sequence of the AL-212 antibody H-chain CDR3) as CDR3"of (67) is a VH comprising the amino acid sequence of SEQ ID NO: 574 (sequence of the AL-212 antibody VH).

[0082] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 188 (sequence of the AL-212 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 190 (sequence of the AL-212 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 192 (sequence of the AL-212 antibody L-chain CDR3) as CDR3"of (68) is a VL comprising the amino acid sequence of SEQ ID NO: 180 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 576 (sequence of the AL-212 antibody VL).

[0083] AL-213 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 198 (sequence of the AL-213 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 200 (sequence of the AL-213

antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 202 (sequence of the AL-213 antibody H-chain CDR3) as CDR3"of (73) is a VH comprising the amino acid sequence of SEQ ID NO: 578 (sequence of the AL-213 antibody VH).

[0084] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 204 (sequence of the AL-213 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 206 (sequence of the AL-213 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 208 (sequence of the AL-213 antibody L-chain CDR3) as CDR3"of (74) is a VL comprising the amino acid sequence of SEQ ID NO: 196 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 580 (sequence of the AL-213 antibody VL).

[0085] AL-214 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 214 (sequence of the AL-214 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 216 (sequence of the AL-214 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 218 (sequence of the AL-214 antibody H-chain CDR3) as CDR3"of (79) is a VH comprising the amino acid sequence of SEQ ID NO: 582 (sequence of the AL-214 antibody VH).

[0086] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 220 (sequence of the AL-214 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 222 (sequence of the AL-214 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 224 (sequence of the AL-214 antibody L-chain CDR3) as CDR3"of (80) is a VL comprising the amino acid sequence of SEQ ID NO: 212 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 584 (sequence of the AL-214 antibody VL).

[0087] AL-215 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 230 (sequence of the AL-215 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 232 (sequence of the AL-215 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 234 (sequence of the AL-215 antibody H-chain CDR3) as CDR3"of (85) is a VH comprising the amino acid sequence of SEQ ID NO: 586 (sequence of the AL-215 antibody VH).

[0088] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 236 (sequence of the AL-215 antibody L-chain CDR1) as

CDR1, the amino acid sequence of SEQ ID NO: 238 (sequence of the AL-215 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 240 (sequence of the AL-215 antibody L-chain CDR3) as CDR3"of (86) is a VL comprising the amino acid sequence of SEQ ID NO: 228 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 588 (sequence of the AL-215 antibody VL).

[0089] AL-216 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 246 (sequence of the AL-216 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 248 (sequence of the AL-216 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 250 (sequence of the AL-216 antibody H-chain CDR3) as CDR3"of (91) is a VH comprising the amino acid sequence of SEQ ID NO: 590 (sequence of the AL-216 antibody VH).

[0090] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 252 (sequence of the AL-216 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 254 (sequence of the AL-216 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 256 (sequence of the AL-216 antibody L-chain CDR3) as CDR3"of (92) is a VL comprising the amino acid sequence of SEQ ID NO: 244 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 592 (sequence of the AL-216 antibody VL).

[0091] AL-217 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 262 (sequence of the AL-217 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 264 (sequence of the AL-217 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 266 (sequence of the AL-217 antibody H-chain CDR3) as CDR3"of (97) is a VH comprising the amino acid sequence of SEQ ID NO: 594 (sequence of the AL-217 antibody VH).

[0092] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 268 (sequence of the AL-217 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 270 (sequence of the AL-217 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 272 (sequence of the AL-217 antibody L-chain CDR3) as CDR3"of (98) is a VL comprising the amino acid sequence of SEQ ID NO: 260 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 596 (sequence of the AL-217 antibody VL).

[0093] AL-218 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 278 (sequence of the AL-218 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 280 (sequence of the AL-218 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 282 (sequence of the AL-218 antibody H-chain CDR3) as CDR3"of (103) is a VH comprising the amino acid sequence of SEQ ID NO: 598 (sequence of the AL-218 antibody VH).

[0094] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 284 (sequence of the AL-218 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 286 (sequence of the AL-218 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 288 (sequence of the AL-218 antibody L-chain CDR3) as CDR3"of (104) is a VL comprising the amino acid sequence of SEQ ID NO: 276 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 600 (sequence of the AL-218 antibody VL).

[0095] AL-219 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 294 (sequence of the AL-219 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 296 (sequence of the AL-219 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 298 (sequence of the AL-219 antibody H-chain CDR3) as CDR3"of (109) is a VH comprising the amino acid sequence of SEQ ID NO: 602 (sequence of the AL-219 antibody VH).

[0096] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 300 (sequence of the AL-219 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 302 (sequence of the AL-219 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 304 (sequence of the AL-219 antibody L-chain CDR3) as CDR3"of (110) is a VL comprising the amino acid sequence of SEQ ID NO: 292 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 604 (sequence of the AL-219 antibody VL).

[0097] AL-220 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 310 (sequence of the AL-220 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 312 (sequence of the AL-220 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 314 (sequence of the AL-220 antibody H-chain CDR3) as CDR3"of (115) is a VH

comprising the amino acid sequence of SEQ ID NO: 606 (sequence of the AL-220 antibody VH).

[0098] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 316 (sequence of the AL-220 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 318 (sequence of the AL-220 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 320 (sequence of the AL-220 antibody L-chain CDR3) as CDR3"of (116) is a VL comprising the amino acid sequence of SEQ ID NO: 308 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 608 (sequence of the AL-220 antibody VL).

[0099] AL-221 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 326 (sequence of the AL-221 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 328 (sequence of the AL-221 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 330 (sequence of the AL-221 antibody H-chain CDR3) as CDR3"of (121) is a VH comprising the amino acid sequence of SEQ ID NO: 610 (sequence of the AL-221 antibody VH).

[0100] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 332 (sequence of the AL-221 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 334 (sequence of the AL-221 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 336 (sequence of the AL-221 antibody L-chain CDR3) as CDR3"of (122) is a VL comprising the amino acid sequence of SEQ ID NO: 324 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 612 (sequence of the AL-221 antibody VL).

[0101] AL-222 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 342 (sequence of the AL-222 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 344 (sequence of the AL-222 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 346 (sequence of the AL-222 antibody H-chain CDR3) as CDR3"of (127) is a VH comprising the amino acid sequence of SEQ ID NO: 614 (sequence of the AL-222 antibody VH).

[0102] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 348 (sequence of the AL-222 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 350 (sequence of the AL-222 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 352

(sequence of the AL-222 antibody L-chain CDR3) as CDR3"of (128) is a VL comprising the amino acid sequence of SEQ ID NO: 340 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 616 (sequence of the AL-222 antibody VL).

[0103] AL-223 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 358 (sequence of the AL-223 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 360 (sequence of the AL-223 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 362 (sequence of the AL-223 antibody H-chain CDR3) as CDR3"of (133) is a VH comprising the amino acid sequence of SEQ ID NO: 618 (sequence of the AL-223 antibody VH).

[0104] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 364 (sequence of the AL-223 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 366 (sequence of the AL-223 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 368 (sequence of the AL-223 antibody L-chain CDR3) as CDR3"of (134) is a VL comprising the amino acid sequence of SEQ ID NO: 356 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 620 (sequence of the AL-223 antibody VL).

[0105] AL-224 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 374 (sequence of the AL-224 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 376 (sequence of the AL-224 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 378 (sequence of the AL-224 antibody H-chain CDR3) as CDR3"of (139) is a VH comprising the amino acid sequence of SEQ ID NO: 622 (sequence of the AL-224 antibody VH).

[0106] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 380 (sequence of the AL-224 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 382 (sequence of the AL-224 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 384 (sequence of the AL-224 antibody L-chain CDR3) as CDR3"of (140) is a VL comprising the amino acid sequence of SEQ ID NO: 372 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 624 (sequence of the AL-224 antibody VL).

[0107] AL-225 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid

sequence of SEQ ID NO: 390 (sequence of the AL-225 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 392 (sequence of the AL-225 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 394 (sequence of the AL-225 antibody H-chain CDR3) as CDR3"of (145) is a VH comprising the amino acid sequence of SEQ ID NO: 626 (sequence of the AL-225 antibody VH).

[0108] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 396 (sequence of the AL-225 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 398 (sequence of the AL-225 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 400 (sequence of the AL-225 antibody L-chain CDR3) as CDR3"of (146) is a VL comprising the amino acid sequence of SEQ ID NO: 388 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 628 (sequence of the AL-225 antibody VL).

[0109] AL-226 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 406 (sequence of the AL-226 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 408 (sequence of the AL-226 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 410 (sequence of the AL-226 antibody H-chain CDR3) as CDR3"of (151) is a VH comprising the amino acid sequence of SEQ ID NO: 630 (sequence of the AL-226 antibody VH).

[0110] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 412 (sequence of the AL-226 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 414 (sequence of the AL-226 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 416 (sequence of the AL-226 antibody L-chain CDR3) as CDR3"of (152) is a VL comprising the amino acid sequence of SEQ ID NO: 404 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 632 (sequence of the AL-226 antibody VL).

[0111] AL-227 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 422 (sequence of the AL-227 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 424 (sequence of the AL-227 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 426 (sequence of the AL-227 antibody H-chain CDR3) as CDR3"of (157) is a VH comprising the amino acid sequence of SEQ ID NO: 634 (sequence of the AL-227 antibody VH).

[0112] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 428 (sequence of the AL-227 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 430 (sequence of the AL-227 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 432 (sequence of the AL-227 antibody L-chain CDR3) as CDR3"of (158) is a VL comprising the amino acid sequence of SEQ ID NO: 420 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 636 (sequence of the AL-227 antibody VL).

[0113] AL-228 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 438 (sequence of the AL-228 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 440 (sequence of the AL-228 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 442 (sequence of the AL-228 antibody H-chain CDR3) as CDR3"of (163) is a VH comprising the amino acid sequence of SEQ ID NO: 638 (sequence of the AL-228 antibody VH).

[0114] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 444 (sequence of the AL-228 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 446 (sequence of the AL-228 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 448 (sequence of the AL-228 antibody L-chain CDR3) as CDR3"of (164) is a VL comprising the amino acid sequence of SEQ ID NO: 436 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 640 (sequence of the AL-228 antibody VL).

[0115] AL-229 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 454 (sequence of the AL-229 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 456 (sequence of the AL-229 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 458 (sequence of the AL-229 antibody H-chain CDR3) as CDR3"of (169) is a VH comprising the amino acid sequence of SEQ ID NO: 642 (sequence of the AL-229 antibody VH).

[0116] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 460 (sequence of the AL-229 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 462 (sequence of the AL-229 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 464 (sequence of the AL-229 antibody L-chain CDR3) as CDR3"of (170) is a VL comprising the amino acid sequence of SEQ ID NO: 452 , more preferably a VL

comprising the amino acid sequence of SEQ ID NO: 644 (sequence of the AL-229 antibody VL).

[0117] AL-230 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 470 (sequence of the AL-230 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 472 (sequence of the AL-230 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 474 (sequence of the AL-230 antibody H-chain CDR3) as CDR3"of (175) is a VH comprising the amino acid sequence of SEQ ID NO: 646 (sequence of the AL-230 antibody VH).

[0118] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 476 (sequence of the AL-230 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 478 (sequence of the AL-230 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 480 (sequence of the AL-230 antibody L-chain CDR3) as CDR3"of (176) is a VL comprising the amino acid sequence of SEQ ID NO: 468 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 648 (sequence of the AL-230 antibody VL).

[0119] AL-231 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 486 (sequence of the AL-231 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 488 (sequence of the AL-231 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 490 (sequence of the AL-231 antibody H-chain CDR3) as CDR3"of (181) is a VH comprising the amino acid sequence of SEQ ID NO: 650 (sequence of the AL-231 antibody VH).

[0120] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 492 (sequence of the AL-231 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 494 (sequence of the AL-231 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 496 (sequence of the AL-231 antibody L-chain CDR3) as CDR3"of (182) is a VL comprising the amino acid sequence of SEQ ID NO: 484 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 652 (sequence of the AL-231 antibody VL).

[0121] AL-232 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 502 (sequence of the AL-232 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 504 (sequence of the AL-232

antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 506 (sequence of the AL-232 antibody H-chain CDR3) as CDR3"of (187) is a VH comprising the amino acid sequence of SEQ ID NO: 654 (sequence of the AL-232 antibody VH).

[0122] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 508 (sequence of the AL-232 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 510 (sequence of the AL-232 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 512 (sequence of the AL-232 antibody L-chain CDR3) as CDR3"of (188) is a VL comprising the amino acid sequence of SEQ ID NO: 500 , more preferably a VL comprising the amino acid sequence of SEQ ID NO: 656 (sequence of the AL-232 antibody VL).

[0123] AL-233 antibody:

An example of the VH in the above-mentioned "H chain having the amino acid sequence of SEQ ID NO: 518 (sequence of the AL-233 antibody H-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 520 (sequence of the AL-233 antibody H-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 524 (sequence of the AL-233 antibody H-chain CDR3) as CDR3"of (193) is a VH comprising the amino acid sequence of SEQ ID NO: 658 (sequence of the AL-233 antibody VH).

[0124] An example of the VL in the above-mentioned "L chain having the amino acid sequence of SEQ ID NO: 524 (sequence of the AL-233 antibody L-chain CDR1) as CDR1, the amino acid sequence of SEQ ID NO: 526 (sequence of the AL-233 antibody L-chain CDR2) as CDR2, and the amino acid sequence of SEQ ID NO: 528 (sequence of the AL-233 antibody L-chain CDR3) as CDR3"of (188) is a VL comprising the amino acid sequence of SEQ ID NO: 660 (sequence of the AL-233 antibody VL).

[0125] The above-mentioned H chains, L chains, VHs, and VLs can be used to prepare the antibodies of the present invention. The present invention also relates to the above-mentioned H chains, L chains, VHs, and VLs.

[0126] For the AL-201 antibody of the present invention:

the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 530 and SEQ ID NO: 529, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 532 and SEQ ID NO: 531, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 6 and SEQ ID NO: 5, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are

shown in SEQ ID NO: 8 and SEQ ID NO: 7, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 10 and SEQ ID NO: 9, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 12 and SEQ ID NO: 11, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 14 and SEQ ID NO: 13, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 16 and SEQ ID NO: 15 , respectively.

[0127] For the AL-202 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 534 and SEQ ID NO: 533, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 536 and SEQ ID NO: 535, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 22 and SEQ ID NO: 21, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 24 and SEQ ID NO: 23, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 26 and SEQ ID NO: 25, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 28 and SEQ ID NO: 27, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 30 and SEQ ID NO: 29, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 32 and SEQ ID NO: 31, respectively.

[0128] For the AL-203 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 538 and SEQ ID NO: 537, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 540 and SEQ ID NO: 539, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 38 and SEQ ID NO: 37, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 40 and SEQ ID NO: 39, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 42 and SEQ ID NO: 41, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are

shown in SEQ ID NO: 44 and SEQ ID NO: 43, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 46 and SEQ ID NO: 45, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 48 and SEQ ID NO: 47, respectively.

[0129] For the AL-204 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 542 and SEQ ID NO: 541, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 544 and SEQ ID NO: 543, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 54 and SEQ ID NO: 53, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 56 and SEQ ID NO: 55, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 58 and SEQ ID NO: 57, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 60 and SEQ ID NO: 59, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 62 and SEQ ID NO: 61, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 64 and SEQ ID NO: 63, respectively.

[0130] For the AL-205 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 546 and SEQ ID NO: 545, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 548 and SEQ ID NO: 547, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 70 and SEQ ID NO: 69, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 72 and SEQ ID NO: 71, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 74 and SEQ ID NO: 73, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 76 and SEQ ID NO: 75, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 78 and SEQ ID NO: 77, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are

shown in SEQ ID NO: 80 and SEQ ID NO: 79, respectively.

[0131] For the AL-206 antibody of the present invention:

the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 550 and SEQ ID NO: 549, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 552 and SEQ ID NO: 551, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 86 and SEQ ID NO: 85, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 88 and SEQ ID NO: 87, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 90 and SEQ ID NO: 89, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 92 and SEQ ID NO: 91, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 94 and SEQ ID NO: 93, respectively; and

the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 96 and SEQ ID NO: 95, respectively.

[0132] For the AL-207 antibody of the present invention:

the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 554 and SEQ ID NO: 553, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 556 and SEQ ID NO: 555, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 102 and SEQ ID NO: 101, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 104 and SEQ ID NO: 103, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 106 and SEQ ID NO: 105, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 108 and SEQ ID NO: 107, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 110 and SEQ ID NO: 109, respectively; and

the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 112 and SEQ ID NO: 111, respectively.

[0133] For the AL-208 antibody of the present invention:

the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 558 and SEQ ID NO: 557, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 560 and SEQ ID NO: 559, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 118 and SEQ ID NO: 117, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 120 and SEQ ID NO: 119, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 122 and SEQ ID NO: 121, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 124 and SEQ ID NO: 123, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 126 and SEQ ID NO: 125, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 128 and SEQ ID NO: 127, respectively.

[0134] For the AL-209 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 562 and SEQ ID NO: 561, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 564 and SEQ ID NO: 563, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 134 and SEQ ID NO: 133, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 136 and SEQ ID NO: 135, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 138 and SEQ ID NO: 137, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 140 and SEQ ID NO: 139, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 142 and SEQ ID NO: 141, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 144 and SEQ ID NO: 143, respectively.

[0135] For the AL-210 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 566 and SEQ ID NO: 565, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 568 and SEQ ID NO: 567, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 150 and SEQ ID NO: 149, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 152 and SEQ ID NO: 151, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 154 and SEQ ID NO: 153, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 156 and SEQ ID NO: 155, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 158 and SEQ ID NO: 157, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 160 and SEQ ID NO: 159, respectively.

[0136] For the AL-211 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 570 and SEQ ID NO: 569, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 572 and SEQ ID NO: 571, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 166 and SEQ ID NO: 165, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 168 and SEQ ID NO: 167, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 170 and SEQ ID NO: 169, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 172 and SEQ ID NO: 171, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 174 and SEQ ID NO: 173, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 176 and SEQ ID NO: 175, respectively.

[0137] For the AL-212 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 574 and SEQ ID NO: 573, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 576 and SEQ ID NO: 575, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 182 and SEQ ID NO: 181, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 184 and SEQ ID NO: 183, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 186 and SEQ ID NO: 185, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 188 and SEQ ID NO: 187, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 190 and SEQ ID NO: 189, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 192 and SEQ ID NO: 191, respectively.

[0138] For the AL-213 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 578 and SEQ ID NO: 577, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 580 and SEQ ID NO: 579, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 198 and SEQ ID NO: 197, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 200 and SEQ ID NO: 199, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 202 and SEQ ID NO: 201, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 204 and SEQ ID NO: 203, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 206 and SEQ ID NO: 205, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 208 and SEQ ID NO: 207, respectively.

[0139] For the AL-214 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 582 and SEQ ID NO: 581, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 584 and SEQ ID NO: 583, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 214 and SEQ ID NO: 213, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 216 and SEQ ID NO: 215, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 218 and SEQ ID NO: 217, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 220 and SEQ ID NO: 219, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 222 and SEQ ID NO: 221, respectively; and

the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 224 and SEQ ID NO: 223, respectively.

[0140] For the AL-215 antibody of the present invention:

the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 586 and SEQ ID NO: 585, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 588 and SEQ ID NO: 587, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 230 and SEQ ID NO: 229, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 232 and SEQ ID NO: 231, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 234 and SEQ ID NO: 233, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 236 and SEQ ID NO: 235, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 238 and SEQ ID NO: 237, respectively; and

the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 240 and SEQ ID NO: 239, respectively.

[0141] For the AL-216 antibody of the present invention:

the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 590 and SEQ ID NO: 589, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 592 and SEQ ID NO: 591, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 246 and SEQ ID NO: 245, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 248 and SEQ ID NO: 247, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 250 and SEQ ID NO: 249, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 252 and SEQ ID NO: 251, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 254 and SEQ ID NO: 253, respectively; and

the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 256 and SEQ ID NO: 255, respectively.

[0142] For the AL-217 antibody of the present invention:

the amino acid sequence and the nucleotide sequence of the H-chain variable region

(VH) are shown in SEQ ID NO: 594 and SEQ ID NO: 593, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 596 and SEQ ID NO: 595, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 262 and SEQ ID NO: 261, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 264 and SEQ ID NO: 263, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 266 and SEQ ID NO: 265, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 268 and SEQ ID NO: 267, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 270 and SEQ ID NO: 269, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 272 and SEQ ID NO: 271, respectively.

[0143] For the AL-218 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 598 and SEQ ID NO: 597, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 600 and SEQ ID NO: 599, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 278 and SEQ ID NO: 277, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 280 and SEQ ID NO: 279, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 282 and SEQ ID NO: 281, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 284 and SEQ ID NO: 283, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 286 and SEQ ID NO: 285, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 288 and SEQ ID NO: 287, respectively.

[0144] For the AL-219 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 602 and SEQ ID NO: 601, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 604 and SEQ ID NO: 603, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are

shown in SEQ ID NO: 294 and SEQ ID NO: 293, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 296 and SEQ ID NO: 295, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 298 and SEQ ID NO: 297, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 300 and SEQ ID NO: 299, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 302 and SEQ ID NO: 301, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 304 and SEQ ID NO: 303, respectively.

[0145] For the AL-220 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 606 and SEQ ID NO: 605, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 608 and SEQ ID NO: 607, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 310 and SEQ ID NO: 309, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 312 and SEQ ID NO: 311, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 314 and SEQ ID NO: 313, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 316 and SEQ ID NO: 315, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 318 and SEQ ID NO: 317, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 320 and SEQ ID NO: 319, respectively.

[0146] For the AL-221 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 610 and SEQ ID NO: 609, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 612 and SEQ ID NO: 611, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 326 and SEQ ID NO: 325, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 328 and SEQ ID NO: 327, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are

shown in SEQ ID NO: 330 and SEQ ID NO: 329, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 332 and SEQ ID NO: 331, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 334 and SEQ ID NO: 333, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 336 and SEQ ID NO: 335, respectively.

[0147] For the AL-222 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 614 and SEQ ID NO: 613, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 616 and SEQ ID NO: 615, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 342 and SEQ ID NO: 341, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 344 and SEQ ID NO: 343, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 346 and SEQ ID NO: 345, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 348 and SEQ ID NO: 347, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 350 and SEQ ID NO: 349, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 352 and SEQ ID NO: 351, respectively.

[0148] For the AL-223 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 618 and SEQ ID NO: 617, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 620 and SEQ ID NO: 619, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 358 and SEQ ID NO: 357, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 360 and SEQ ID NO: 359, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 362 and SEQ ID NO: 361, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 364 and SEQ ID NO: 363, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are

shown in SEQ ID NO: 366 and SEQ ID NO: 365, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 368 and SEQ ID NO: 367, respectively.

[0149] For the AL-224 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 622 and SEQ ID NO: 621, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 624 and SEQ ID NO: 623, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 374 and SEQ ID NO: 373, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 376 and SEQ ID NO: 375, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 378 and SEQ ID NO: 377, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 380 and SEQ ID NO: 379, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 382 and SEQ ID NO: 381, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 384 and SEQ ID NO: 383, respectively.

[0150] For the AL-225 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 626 and SEQ ID NO: 625, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 628 and SEQ ID NO: 627, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 390 and SEQ ID NO: 389, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 392 and SEQ ID NO: 391, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 394 and SEQ ID NO: 393, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 396 and SEQ ID NO: 395, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 398 and SEQ ID NO: 397, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 400 and SEQ ID NO: 399, respectively.

[0151] For the AL-226 antibody of the present invention:

the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 630 and SEQ ID NO: 629, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 632 and SEQ ID NO: 631, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 406 and SEQ ID NO: 405, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 408 and SEQ ID NO: 407, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 410 and SEQ ID NO: 409, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 412 and SEQ ID NO: 411, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 414 and SEQ ID NO: 413, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 416 and SEQ ID NO: 415, respectively.

[0152] For the AL-227 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 634 and SEQ ID NO: 633, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 636 and SEQ ID NO: 635, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 422 and SEQ ID NO: 421, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 424 and SEQ ID NO: 423, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 426 and SEQ ID NO: 425, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 428 and SEQ ID NO: 427, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 430 and SEQ ID NO: 429, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 432 and SEQ ID NO: 431, respectively.

[0153] For the AL-228 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 638 and SEQ ID NO: 637, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 640 and SEQ ID NO: 639, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 438 and SEQ ID NO: 437, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 440 and SEQ ID NO: 439, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 442 and SEQ ID NO: 441, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 444 and SEQ ID NO: 443, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 446 and SEQ ID NO: 445, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 448 and SEQ ID NO: 447, respectively.

[0154] For the AL-229 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 642 and SEQ ID NO: 641, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 644 and SEQ ID NO: 643, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 454 and SEQ ID NO: 453, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 456 and SEQ ID NO: 455, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 458 and SEQ ID NO: 457, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 460 and SEQ ID NO: 459, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 462 and SEQ ID NO: 461, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 464 and SEQ ID NO: 463, respectively.

[0155] For the AL-230 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 646 and SEQ ID NO: 645, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 648 and SEQ ID NO: 647, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 470 and SEQ ID NO: 469, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 472 and SEQ ID NO: 471, respectively;

the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 474 and SEQ ID NO: 473, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 476 and SEQ ID NO: 475, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 478 and SEQ ID NO: 477, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 480 and SEQ ID NO: 479, respectively.

[0156] For the AL-231 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 650 and SEQ ID NO: 649, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 652 and SEQ ID NO: 651, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 486 and SEQ ID NO: 485, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 488 and SEQ ID NO: 487, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 490 and SEQ ID NO: 489, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 492 and SEQ ID NO: 491, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 494 and SEQ ID NO: 493, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 496 and SEQ ID NO: 495, respectively.

[0157] For the AL-232 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 654 and SEQ ID NO: 653, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 656 and SEQ ID NO: 655, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 502 and SEQ ID NO: 501, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 504 and SEQ ID NO: 503, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 506 and SEQ ID NO: 505, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 508 and SEQ ID NO: 507, respectively;

the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 510 and SEQ ID NO: 509, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 512 and SEQ ID NO: 511, respectively.

[0158] For the AL-233 antibody of the present invention:
the amino acid sequence and the nucleotide sequence of the H-chain variable region (VH) are shown in SEQ ID NO: 658 and SEQ ID NO: 657, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain variable region (VL) are shown in SEQ ID NO: 660 and SEQ ID NO: 659, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR1 are shown in SEQ ID NO: 518 and SEQ ID NO: 517, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR2 are shown in SEQ ID NO: 520 and SEQ ID NO: 519, respectively;
the amino acid sequence and the nucleotide sequence of the H-chain CDR3 are shown in SEQ ID NO: 522 and SEQ ID NO: 521, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR1 are shown in SEQ ID NO: 524 and SEQ ID NO: 523, respectively;
the amino acid sequence and the nucleotide sequence of the L-chain CDR2 are shown in SEQ ID NO: 526 and SEQ ID NO: 525, respectively; and
the amino acid sequence and the nucleotide sequence of the L-chain CDR3 are shown in SEQ ID NO: 528 and SEQ ID NO: 527, respectively.

[0159] The above-mentioned antibodies of (1) to (200) include not only monovalent antibodies but also multivalent antibodies with two or more valencies. The multivalent antibodies of the present invention include multivalent antibodies whose antigen binding sites are all the same and multivalent antibodies whose antigen binding sites are partially or completely different.

[0160] In a preferred embodiment, the above-mentioned antibody of (199) is an antibody with no modified CDRs. For example, the "antibody that comprises one or more amino acid substitutions, deletions, additions, and/or insertions in the antibody of (1), which has equivalent activity as the antibody of (1)" of the above-mentioned antibody of (199) is preferably "an antibody that has equivalent activity as the antibody of (1), and comprises one or more amino acid substitutions, deletions, additions, and/or insertions in the antibody of (1), and comprises an H chain having the amino acid sequence of SEQ ID NO: 6 as CDR1, the amino acid sequence of SEQ ID NO: 8 as CDR2, and the amino acid sequence of SEQ ID NO: 10 as CDR3". Another preferred antibody of the above-mentioned antibody of (199) can be expressed in a similar manner.

[0161] However, the above-mentioned antibody of (199) does not exclude an antibody in which CDR(s) is/are modified. Those skilled in the art can modify a CDR amino acid

sequence without losing an equivalent activity. Amino acid mutations without losing an equivalent activity can be predicted, for example, using molecular modeling techniques.

[0162] Therefore, for the above-mentioned antibody of (199), an antibody having an equivalent activity as an antibody having an H-chain CDR and/or L-chain CDR of:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody,

is expressed as follows:

an antibody that has equivalent activity as an antibody comprising an H chain having the amino acid sequence of SEQ ID NO: a as CDR1, the amino acid sequence of SEQ ID NO: b as CDR2, and the amino acid sequence of SEQ ID NO: c as CDR3, wherein the "antibody that has equivalent activity" comprises an H chain having:

as CDR1, the amino acid sequence of SEQ ID NO: a, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: a;

as CDR2, the amino acid sequence of SEQ ID NO: b, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: b;

as CDR3, the amino acid sequence of SEQ ID NO: c, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: c;

an antibody that has equivalent activity as an antibody comprising an L chain having the amino acid sequence of SEQ ID NO: d as CDR1, the amino acid sequence of SEQ ID NO: e as CDR2, and the amino acid sequence of SEQ ID NO: f as CDR3, wherein the "antibody that has equivalent activity" comprises an L chain having:

as CDR1, the amino acid sequence of SEQ ID NO: d, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: d;

as CDR2, the amino acid sequence of SEQ ID NO: e, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: e;

as CDR3, the amino acid sequence of SEQ ID NO: f, or an amino acid sequence with

one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: f; or

an antibody that has equivalent activity as an antibody comprising an H chain having the amino acid sequence of SEQ ID NO: a as CDR1, the amino acid sequence of SEQ ID NO: b as CDR2, and the amino acid sequence of SEQ ID NO: c as CDR3, and an L chain having the amino acid sequence of SEQ ID NO: d as CDR1, the amino acid sequence of SEQ ID NO: e as CDR2, and the amino acid sequence of SEQ ID NO: f as CDR3, wherein the "antibody that has equivalent activity" comprises:

an H chain having:

as CDR1, the amino acid sequence of SEQ ID NO: a, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: a;

as CDR2, the amino acid sequence of SEQ ID NO: b, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: b;

as CDR3, the amino acid sequence of SEQ ID NO: c, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: c

and

an L chain having:

as CDR1, the amino acid sequence of SEQ ID NO: d, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: d;

as CDR2, the amino acid sequence of SEQ ID NO: e, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: e;

as CDR3, the amino acid sequence of SEQ ID NO: f, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: f.

[0163] The antibody of (199) for each of the above antibodies can be expressed by referring to the amino acid SEQ ID NO of H chain CDR1 for "a" above, the amino acid SEQ ID NO of H chain CDR2 for "b" above, the amino acid SEQ ID NO of H chain CDR3 for "c" above, the amino acid SEQ ID NO of L chain CDR1 for "d" above, the amino acid SEQ ID NO of L chain CDR2 for "e" above, the amino acid SEQ ID NO of L chain CDR3 for "f" above. For example, the antibody of (199) for an antibody having equivalent activity as an antibody that has the H chain CDR and/or L chain CDR of the AL-201 antibody can be expressed as follows:

an antibody that has equivalent activity as an antibody comprising an H chain having

the amino acid sequence of SEQ ID NO: 6 as CDR1, the amino acid sequence of SEQ ID NO: 8 as CDR2, and the amino acid sequence of SEQ ID NO: 10 as CDR3, wherein the "antibody that has equivalent activity" comprises an H chain having:
as CDR1, the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 6;
as CDR2, the amino acid sequence of SEQ ID NO: 8, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 8;
as CDR3, the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 10;
an antibody that has equivalent activity as an antibody comprising an L chain having the amino acid sequence of SEQ ID NO: 12 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2, and the amino acid sequence of SEQ ID NO: 16 as CDR3, wherein the "antibody that has equivalent activity" comprises an L chain having:
as CDR1, the amino acid sequence of SEQ ID NO: 12, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 12;
as CDR2, the amino acid sequence of SEQ ID NO: 14, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 14;
as CDR3, the amino acid sequence of SEQ ID NO: 16, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 16; or
an antibody that has equivalent activity as an antibody comprising an H chain having the amino acid sequence of SEQ ID NO: 6 as CDR1, the amino acid sequence of SEQ ID NO: 8 as CDR2, and the amino acid sequence of SEQ ID NO: 10 as CDR3, and an L chain having the amino acid sequence of SEQ ID NO: 12 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2, and the amino acid sequence of SEQ ID NO: 16 as CDR3, wherein the "antibody that has equivalent activity" comprises:
an H chain having:
as CDR1, the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 6;
as CDR2, the amino acid sequence of SEQ ID NO: 8, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 8;

as CDR3, the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 10

and

an L chain having:

as CDR1, the amino acid sequence of SEQ ID NO: 12, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 12;

as CDR2, the amino acid sequence of SEQ ID NO: 14, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 14;

as CDR3, the amino acid sequence of SEQ ID NO: 16, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: 16.

[0164] Furthermore, as mentioned above, regarding the antibodies in the embodiments mentioned below, the antibody of (199) for each of the antibodies can be expressed by referring to the amino acid SEQ ID NOs of VH, VL, CDR of:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody

for "a" to "h".

[0165] In the above antibodies in which CDRs are modified, "several" means, preferably five amino acids or less, more preferably four amino acids or less, more preferably three amino acids or less, more preferably two amino acids. The number of amino acids substituted, deleted, added, and/or inserted between two amino acid sequences can be identified by aligning the amino acid sequences using sequence analysis programs. The programs for alignment include, for example, FASTA(Lipman DJ, Pearson WR (1985) Science 227 (4693):1435-1441; Pearson, WR.,Lipman, DJ (1988) Proc. Natl. Acad. Sci. USA 85 (8): 2444-2448), BLAST(Altschul et al (1990) J. Mol. Biol. 215:403-410;Altschulet al (1997) Nucleic Acids Res. 25: 3389-402).

[0166] It is known to those skilled in the art that, in the binding specificity or affinity of an antibody to an antigen, CDR3 plays a particularly important role. Thus, in the antibodies of (199), the CDR3 sequence is preferably conserved. Therefore, in a

preferred embodiment, the antibody of (199) can be expressed as follows:
an antibody that has equivalent activity as an antibody comprising an H chain having the amino acid sequence of SEQ ID NO: a as CDR1, the amino acid sequence of SEQ ID NO: b as CDR2, and the amino acid sequence of SEQ ID NO: c as CDR3, wherein the "antibody that has equivalent activity" comprises an H chain having:
as CDR1, the amino acid sequence of SEQ ID NO: a, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: a;
as CDR2, the amino acid sequence of SEQ ID NO: b, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: b;
as CDR3, the amino acid sequence of SEQ ID NO: c;
an antibody that has equivalent activity as an antibody comprising an L chain having the amino acid sequence of SEQ ID NO: d as CDR1, the amino acid sequence of SEQ ID NO: e as CDR2, and the amino acid sequence of SEQ ID NO: f as CDR3, wherein the "antibody that has equivalent activity" comprises an L chain having:
as CDR1, the amino acid sequence of SEQ ID NO: d, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: d;
as CDR2, the amino acid sequence of SEQ ID NO: e, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: e;
as CDR3, the amino acid sequence of SEQ ID NO: f; or
an antibody that has equivalent activity as an antibody comprising an H chain having the amino acid sequence of SEQ ID NO: a as CDR1, the amino acid sequence of SEQ ID NO: b as CDR2, and the amino acid sequence of SEQ ID NO: c as CDR3, and an L chain having the amino acid sequence of SEQ ID NO: d as CDR1, the amino acid sequence of SEQ ID NO: e as CDR2, and the amino acid sequence of SEQ ID NO: f as CDR3, wherein the "antibody that has equivalent activity" comprises:
an H chain having:
as CDR1, the amino acid sequence of SEQ ID NO: a, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: a;
as CDR2, the amino acid sequence of SEQ ID NO: b, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: b;
as CDR3, the amino acid sequence of SEQ ID NO: c
and

an L chain having:

as CDR1, the amino acid sequence of SEQ ID NO: d, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: d;

as CDR2, the amino acid sequence of SEQ ID NO: e, or an amino acid sequence with one or several amino acid substitutions, deletions, additions and/or insertions in the amino acid sequence of SEQ ID NO: e;

as CDR3, the amino acid sequence of SEQ ID NO: f.

[0167] Regarding the antibodies of (199), an antibody having equivalent activity as an antibody that has the VH and/or VL of:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody

can be expressed as follows:

an antibody that has equivalent activity as an antibody comprising an H chain having VH comprising the amino acid sequence of SEQ ID NO: g, wherein the "antibody that has equivalent activity" comprises an H chain having VH comprising an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: g;

an antibody that has equivalent activity as an antibody comprising an L chain having VL comprising the amino acid sequence of SEQ ID NO: h, wherein the "antibody that has equivalent activity" comprises an H chain having VL comprising an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: h;

or

an antibody that has equivalent activity as an antibody comprising an H chain having VH comprising the amino acid sequence of SEQ ID NO: g and an L chain having VL comprising the amino acid sequence of SEQ ID NO: h, wherein the "antibody that has equivalent activity" comprises

an H chain having VH comprising the amino acid sequence of SEQ ID NO: g, or an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: g, and

an L chain having VL comprising the amino acid sequence of SEQ ID NO: h, or an

amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: h.

[0168] The antibody of (199) for each of the above antibodies can be expressed by referring to the amino acid SEQ ID NO of VH for "g" above, and the amino acid SEQ ID NO of VL for "h" above. For example, the antibody of (199) for an antibody having equivalent activity as an antibody that has the VH and/or VL chain of the AL-201 antibody can be expressed as follows:

an antibody that has equivalent activity as an antibody comprising an H chain having VH comprising the amino acid sequence of SEQ ID NO: 530, wherein the "antibody that has equivalent activity" comprises an H chain having VH comprising an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: 530;

an antibody that has equivalent activity as an antibody comprising an L chain having VL comprising the amino acid sequence of SEQ ID NO: 532, wherein the "antibody that has equivalent activity" comprises an H chain having VL comprising an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: 532;

or

an antibody that has equivalent activity as an antibody comprising an H chain having VH comprising the amino acid sequence of SEQ ID NO: 530 and an L chain having VL comprising the amino acid sequence of SEQ ID NO: 532, wherein the "antibody that has equivalent activity" comprises

an H chain having VH comprising the amino acid sequence of SEQ ID NO: 530, or an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: 530, and

an L chain having VL comprising the amino acid sequence of SEQ ID NO: 532, or an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: 532.

[0169] In the above antibodies in which VH and/or VL are modified, "several" means, preferably 50 amino acids or less, 30 amino acids or less, 20 amino acids or less, 15 amino acids or less, or 10 amino acids or less, more preferably nine, eight, seven, six, five, four, three, or two amino acids. As long as the equivalent activity is retained, the positions of the modified amino acids are not particularly limited; however, amino acids in FR are preferably modified.

[0170] Thus, in a preferred embodiment, among the antibodies of (199), an antibody having equivalent activity as an antibody that has the VH and/or VL of:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody,

AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody

can be expressed as follows:

an antibody that has equivalent activity as an antibody comprising an H chain having VH comprising the amino acid sequence of SEQ ID NO: a, wherein the "antibody that has equivalent activity" comprises an H chain having VH comprising an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: a, and the amino acid sequence of SEQ ID NO: b as CDR1, the amino acid sequence of SEQ ID NO: c as CDR2, and the amino acid sequence of SEQ ID NO: d as CDR3;

an antibody that has equivalent activity as an antibody comprising an L chain having VL comprising the amino acid sequence of SEQ ID NO: e, wherein the "antibody that has equivalent activity" comprises an L chain having VL comprising an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: e, and the amino acid sequence of SEQ ID NO: f as CDR1, the amino acid sequence of SEQ ID NO: g as CDR2, and the amino acid sequence of SEQ ID NO: h as CDR3;

or

an antibody that has equivalent activity as an antibody comprising an H chain having VH comprising the amino acid sequence of SEQ ID NO: a and VL comprising the amino acid sequence of SEQ ID NO: e, wherein the "antibody that has equivalent activity" comprises:

an H chain having VH comprising the amino acid sequence of SEQ ID NO: a, or an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: a, and the amino acid sequence of SEQ ID NO: b as CDR1, the amino acid sequence of SEQ ID NO: c as CDR2, and the amino acid sequence of SEQ ID NO: d as CDR3,

and

an L chain having VL comprising the amino acid sequence of SEQ ID NO: e, or an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: e, and the amino acid sequence of SEQ ID NO: f as CDR1, the amino acid sequence of SEQ ID NO: g as CDR2, and the amino acid sequence of SEQ ID NO: h as CDR3.

[0171] The antibody of (199) for each of the above antibodies can be expressed by referring

to the amino acid SEQ ID NO of VH for "a" above, the amino acid SEQ ID NO of H chain CDR1 for "b" above, the amino acid SEQ ID NO of H chain CDR2 for "c" above, the amino acid SEQ ID NO of H chain CDR3 for "d" above, the amino acid SEQ ID NO of VL for "e" above, the amino acid SEQ ID NO of L chain CDR1 for "f" above, the amino acid SEQ ID NO of L chain CDR2 for "g" above, the amino acid SEQ ID NO of L chain CDR3 for "h" above. For example, the antibody of (199) for an antibody having equivalent activity as an antibody that has the VH and/or VL of the AL-201 antibody can be expressed as follows:

an antibody that has equivalent activity as an antibody comprising an H chain having VH comprising the amino acid sequence of SEQ ID NO: 530, wherein the "antibody that has equivalent activity" comprises an H chain having VH comprising an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: 530, and the amino acid sequence of SEQ ID NO: 6 as CDR1, the amino acid sequence of SEQ ID NO: 8 as CDR2, and the amino acid sequence of SEQ ID NO: 10 as CDR3;

an antibody that has equivalent activity as an antibody comprising an L chain having VL comprising the amino acid sequence of SEQ ID NO: 532, wherein the "antibody that has equivalent activity" comprises an L chain having VL comprising an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: 532, and the amino acid sequence of SEQ ID NO: 12 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2, and the amino acid sequence of SEQ ID NO: 16 as CDR3;

or

an antibody that has equivalent activity as an antibody comprising an H chain having VH comprising the amino acid sequence of SEQ ID NO: 530 and VL comprising the amino acid sequence of SEQ ID NO: 532, wherein the "antibody that has equivalent activity" comprises:

an H chain having VH comprising the amino acid sequence of SEQ ID NO: 530, or an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: 530, and the amino acid sequence of SEQ ID NO: 6 as CDR1, the amino acid sequence of SEQ ID NO: 8 as CDR2, and the amino acid sequence of SEQ ID NO: 10 as CDR3,

and

an L chain having VL comprising the amino acid sequence of SEQ ID NO: 532, or an amino acid sequence in which one or several amino acids are substituted, deleted, added, and/or inserted in the amino acid sequence of SEQ ID NO: 532, and the amino acid sequence of SEQ ID NO: 12 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2, and the amino acid sequence of SEQ ID NO: 16 as CDR3.

[0172] In the modified antibodies that have the H chain CDR and/or L chain CDR, or VH and/or VL of:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody,

the amino acid modifications are preferably conserved amino acid substitutions. Thus, in a preferred embodiment, in the antibodies described above, "conservative amino acid substitution" can be performed, instead of "substitution, deletion, addition, and/or insertion"

Methods for preparing a polypeptide having activity equivalent to that of a certain polypeptide that are well known to those skilled in the art include methods for introducing mutations into a polypeptide. For example, one skilled in the art can prepare an antibody having activity equivalent to that of an antibody of the present invention by introducing appropriate mutations into the antibody using site-directed mutagenesis (Hashimoto-Gotoh, T. et al. (1995) Gene 152, 271-275; Zoller, MJ, and Smith, M. (1983) Methods Enzymol. 100, 468-500; Kramer, W. et al. (1984) Nucleic Acids Res. 12, 9441-9456; Kramer W, and Fritz HJ (1987) Methods. Enzymol. 154, 350-367; Kunkel, TA (1985) Proc. Natl. Acad. Sci. USA. 82, 488-492; Kunkel (1988) Methods Enzymol. 85, 2763-2766) and such. Amino acid mutations may also occur naturally. The antibodies of the present invention also include an antibody that comprises an amino acid sequence with one or more amino acid mutations in the amino acid sequence of an antibody of the present invention, and which has activity equivalent to that of the antibody of the present invention.

[0173] Amino acid residues are preferably mutated into other amino acids that conserve the properties of the amino acid side chains. For example, amino acids are categorized as follows depending on the side chain properties: hydrophobic amino acids (A, I, L, M, F, P, W, Y, and V), hydrophilic amino acids (R, D, N, C, E, Q, G, H, K, S, and T), amino acids with aliphatic side chains (G, A, V, L, I, and P), amino acids with hydroxyl-containing side chains (S, T, and Y), amino acids with sulfur atom-containing side chains (C and M), amino acids with carboxylic acid- and amide-containing side chains (D, N, E, and Q), amino acids with basic side chains (R, K, and H), and amino acids with aromatic ring-containing side chains (H, F, Y, and W) (amino acids are represented by one-letter codes in parentheses). "Conservative amino

acid substitution" refers to substitution of an amino acid with another amino acid with a conserved amino acid side chain characteristics. In the antibodies of (199), amino acid sequence mutations in an antibody are preferably "conservative amino acid substitutions".

[0174] A polypeptide having an amino acid sequence, in which one or more amino acid residues are modified (deleted, added, and/or substituted with other amino acids) in a certain amino acid sequence, is known to retain its original biological activity (function).

[0175] In addition to the above-mentioned modifications, the antibodies of the present invention may be conjugated to other substances as long as the activity is maintained. Examples of the substances include peptides, lipids, sugars and sugar chains, acetyl groups, and natural and synthetic polymers. These modifications may be performed to confer additional functions to the antibodies, or to stabilize the antibodies.

[0176] Antibodies in which several amino acid residues have been added to the amino acid sequence of an antibody of the present invention include fusion proteins containing the antibody. In the fusion proteins, the antibody is fused with another peptide or protein. Methods for producing a fusion protein can be carried out by ligating a polynucleotide encoding an antibody of the present invention in frame with a polynucleotide encoding another peptide or polypeptide, and inserting this into an expression vector, and expressing the fusion construct in a host. Techniques known to those skilled in the art can be used for this purpose. The peptides or polypeptides fused with an antibody of the present invention include, for example, known peptides such as FLAG (Hopp, T.P. et al., BioTechnology (1988) 6, 1204-1210), 6x His consisting of six histidine (His) residues, 10x His, Influenza hemagglutinin (HA), human c-myc fragments, VSV-GP fragments, p18HIV fragments, T7-tag, HSV-tag, E-tag, SV40T antigen fragments, lck tag, alpha-tubulin fragments, B-tag, and Protein C fragments; glutathione-S-transferase (GST); immunoglobulin constant regions; beta-galactosidase; and maltose-binding protein (MBP), etc. Commercially available polynucleotides encoding these peptides or polypeptides can be fused with polynucleotides encoding the antibodies of the present invention, and the fusion polypeptides can be produced by expressing the fusion polynucleotides thus prepared.

[0177] The antibodies of the present invention may differ in the amino acid sequence, molecular weight, presence or absence of sugar chains, structure and such, depending on the cell or host producing the antibodies or the purification method. However, as long as the obtained antibody has an activity equivalent to an antibody of the present invention, it is included in the present invention.

[0178] Herein, "equivalent activity" means that the antibody of interest has the same biological or biochemical activity as an antibody of the present invention. The "activity"

of the present invention includes, for example, activity to specifically bind to A beta oligomers but not bind to A beta monomers, anti-neurotoxic activity, A beta amyloid fibril formation suppressing activity, anti-synaptic toxicity activity, anti-memory impairment activity, anti-A beta deposition activity, anti-thioflavin S-positive plaque formation activity, and anti-A beta oligomer acccumulation activity.

[0179] In a preferred embodiment, the "activity" of the present invention is activity to specifically bind to A beta oligomers but not bind to A beta monomers. As shown in the Example, the "activity to specifically bind to A beta oligomers but not bind to A beta monomer" is preferably assessed by dot blot or competitive ELISA. Specific methods of dot blot or competitive ELISA include methods described in the Examples. Furthermore, the binding activity towards A beta oligomers and monomers can be assessed by other immunodetection methods, for example, absorbance measurement, enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), radioimmunoassay (RIA), immunofluorescent method, etc. For example, in ELISA, an antibody is immobilized onto a plate, an antigen for the antibody is added to the plate, and a culture supernatant of antibody-producing cells or a purified antibody is added. Then, a secondary antibody that recognizes a primary antibody and that is tagged with an enzyme such as alkali phosphatase is added, and the plate is incubated. After washing, an enzyme substrate such as p-nitrophenyl phosphate is added to the plate, and the absorbance is measured to assess the antigen-binding ability of a sample of interest. The binding abilities for A beta oligomers and monomers are preferably measured by the same method; however, they can be measured by different methods. For example, the binding to A beta oligomers can be analysed using Biacore (GE Healthcare Sciences).

[0180] When the "activity" of the present invention is anti-neurotoxic activity, this activity can be assessed by, for example, culturing neurons with A beta in the presence or absence of an antibody, and measuring the A beta-induced cytotoxicity level inhibited by the antibody. A beta-induced cytotoxicity can be measured by, for example, live/dead two color fluorescent assay, measurement of the LDH amount derived from dead cells released into a medium. For the measurement of the LDH amount, for example, CytoTox96 (Promega) or such can be used. Specific methods for measuring anti-neurotixic activity include the methods described in the Examples.

[0181] When the "activity" of the present invention is A beta amyloid fibril formation suppressing activity, this activity can be assessed, for example, by incubating an A beta solution with or without an antibody, and detecting the A beta amyloid fibril formation level suppressed by the antibody. The amount of A beta amyloid fibril is assessed, for example, by adding a ThT (Thioflavin T) solution to a culture, and the amount of ThT bound to amyloid fibrils with ThT fluoresence. Specific methods for measuring A beta

amyloid fibril formation suppressing activity include the methods described in the Examples.

[0182] When the "activity" of the present invention is anti-synaptic toxicity activity, this activity can be assessed, for example, by detecting synaptic toxicity suppressing effect by antibody administration to mutant human APP gene-expressing mice (for example, Tg2576 mice, Taconics, USA). The assessment of synaptic toxicity can be performed by mouse memory impairment test, analysis of the number of swollen dystrophic neurites using an anti-synaptophysin antibody, immunofluorescent analysis of mouse brain sections using anti-synaptophysin or anti-drebrin antibodies. When the "activity" of the present invention is anti-memory impairment activity, this activity is assessed by memory impairment test using mutant APP gene-expressing mice. If the "activity" of the present invention is anti-A beta deposition activity, anti-thioflavin S-positive plaque formation activity, or anti-A beta oligomer accumulation activity, these activities can be assessed by antibody administration test using mutant APP gene-expressing mice.

[0183] Specific methods for measuring the anti-memory impairment activity, anti-synaptic toxicity activity, anti-A beta deposition activity, anti-thioflavin S-positive plaque formation activity, and anti-A beta oligomer accumulation activity include the following method.

[0184] Female non-transgenic (non-Tg) mice for control, and Tg2576 mice having and over-expressing the Swedish-type mutant human APP gene with dual mutations (K670N and M671L) derived from familial AD are administered with the antibody of the present invention (dosage within the range of 0.4 to 5.0 mg/kg/w) or PBS into the caudal vein. The mouse age at the initiation of administration is six months or later at which memory and learning impairments are expressed, for monitoring therapeutic effect; or four months for monitoring prophylactic effect. Antibody administration period is two months for monitoring therapeutic effect, and nine months for monitoring prophylactic effect. To measure the anti-memory impairment activity, the following three behavioral paradigms are analysed after the antibody administration period (Mouri A, FASEB J, 21: 2135-2148, 2007): (1) Y-maze test for short-term memory; (2) novel object recognition test; (3) contextual fear conditioning test. To assess the other activities, mice are sacrificed after the behavioral analysis, and the brain hemispheres are sliced into 10 to 30-micro m-thick sagittal sections using a cryotome (RM 2145; Leica, Wetzlar, Germany). To observe thioflavin S-positive plaque formation, thioflavin S staining is performed as described in Wyss-Coray et al., 2001. The formation of swollen dystrophic neurites is observed using an anti-synaptophysin antibody (Chemicon, Temecula, CA). For each mouse, the number of thioflavin S-positive plaques and synaptophysin-positive swollen dystrophic neurites are calculated

in four or five sections from a brain hemisphere at 40-fold magnification. To observe A beta deposition, serial sections briefly pre-treated with formic acid or Protease K are stained using an A beta immunostaining kit (Sigma, St. Louis, MO) or anti-A beta polyclonal antibody (Biosource), and immuno-positive signals are visualized using an ABC elite kit (Vector Laboratories). Images of the cerebral cortex and hippocampus are recorded using a digital camera connected with a microscope, and analyzed using a simple PCI software (Compix Imaging System, Lake Oswego, OR). The number of thioflavin S-positive plaques and synaptophysin-positive swollen dystrophic neurites was determined in a double blind manner. Synaptic degeneration is observed by immunostaining using anti-synaptophysin or anti-drebrin antibodies. To assess the anti-A beta oligomer deposition activity, brain homogenates are prepared from the other brain hemisphere of the same mouse using the method by Kawarabayashi et al., J. Neuroscience 2001), and the amount of A beta oligomers is measured by SDS-PAGE and immunoblot analysis. For detection antibodies, commercially available anti-A beta oligomer monoclonal antibodies (e.g., 6E10, Covance Immuno-Technologies, Dedham, MA) or polyclonal antibodies (e.g., A11, Biosource, Carmarillo, CA) can be used.

[0185] The term "equivalent" in "equivalent activity" means that a value obtained as a biological or biochemical activity differs within 20% between two antibodies compared. The difference of the activity value is, preferably within 15%, within 10%, within 5%, or within 2.5%.Antibodies that bind to an epitope to which an antibody of any one of (1) to (198) above binds can be obtained by methods known to those skilled in the art. For example, the antibodies can be obtained by (i) determining the epitope bound by the antibody of any one of (1) to (198) using a conventional method, and producing the antibodies using a polypeptide comprising an amino acid sequence included in the epitope as an immunogen; or (ii) determining the epitopes of antibodies produced by a conventional method, and selecting antibodies whose epitope is the same as that of the antibody of any one of (1) to (198).

[0186] The above-mentioned antibodies of (1) to (200) also include any type of antibodies such as the above-described minibodies, antibodies with modified amino acid sequences such as humanized antibodies and chimeric antibodies, non-human animal antibodies, human antibodies, modified antibodies conjugated to other molecules (for example, polymers such as polyethylene glycol), and sugar chain-modified antibodies.

[0187] In a preferred embodiment, the antibodies of the present invention include:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody,

AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, and AL-233 antibody. These antibodies can be obtained by the method described in the Examples. Alternatively, the antibodies can be prepared based on their sequence information.

[0188] In a preferred embodiment, the antibodies of the present invention include modified antibodies such as chimeric antibodies or humanized antibodies. In a more preferred embodiment, the chimeric antibodies include antibodies comprise a variable region derived from:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody;

and a constant region derived from human immunoglobulin. In a more preferred embodiment, humanized antibodies include antibodies comprise CDR derived from:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody;

and FR derived from human immunoglobulin, and a constant region derived from human immunoglobulin.

[0189] The above chimeric antibodies can be expressed as follows:

an antibody that comprises an H chain having VH comprising the amino acid sequence of SEQ ID NO: a, and CH of a human antibody;

an antibody that comprises an L chain having VL comprising the amino acid sequence of SEQ ID NO: b, and CL of a human antibody; or

an antibody that comprises an H chain having VH comprising the amino acid sequence of SEQ ID NO: a, and CH of a human antibody, and an L chain having VL comprising the amino acid sequence of SEQ ID NO: b, and CL of a human antibody.

[0190] Preferred embodiments of chimeric antibodies from each of the above antibodies can be expressed by referring to the amino acid SEQ ID NO of VH for "a" above, and the amino acid SEQ ID NO of VL for "b" above. For example, chimeric antibodies for the AL-201 antibody can be expressed as follows:

an antibody that comprises an H chain having VH comprising the amino acid sequence of SEQ ID NO: 530, and CH of a human antibody;

an antibody that comprises an L chain having VL comprising the amino acid sequence of SEQ ID NO: 532, and CL of a human antibody; or

an antibody that comprises an H chain having VH comprising the amino acid sequence of SEQ ID NO: 530, and CH of a human antibody, and an L chain having VL comprising the amino acid sequence of SEQ ID NO: 532, and CL of a human antibody.

[0191] The above humanized antibodies can be expressed as follows:

an antibody that comprises an H chain having CDR of VH comprising the amino acid sequence of SEQ ID NO: a, FR of VH of a human antibody, and CH of a human antibody;

an antibody that comprises an L chain having CDR of VL comprising the amino acid sequence of SEQ ID NO: b, FR of VL of a human antibody, and CL of a human antibody; or

an antibody that comprises an H chain having CDR of VH comprising the amino acid sequence of SEQ ID NO: a, FR of VH of a human antibody, and CH of a human antibody, and an L chain having CDR of VL comprising the amino acid sequence of SEQ ID NO: b, FR of VL of a human antibody, and CL of a human antibody.

[0192] Preferred embodiments of humanized antibodies from each of the above antibodies can be expressed by referring to the amino acid SEQ ID NO of VH for "a" above, and the amino acid SEQ ID NO of VL for "b" above. For example, humanized antibodies for the AL-201 antibody can be expressed as follows:

an antibody that comprises an H chain having CDR of VH comprising the amino acid sequence of SEQ ID NO: 530, FR of VH of a human antibody, and CH of a human antibody;

an antibody that comprises an L chain having CDR of VL comprising the amino acid sequence of SEQ ID NO: 532, FR of VL of a human antibody, and CL of a human antibody; or

an antibody that comprises an H chain having CDR of VH comprising the amino acid sequence of SEQ ID NO: 530, FR of VH of a human antibody, and CH of a human antibody, and an L chain having CDR of VL comprising the amino acid sequence of SEQ ID NO: 532, FR of VL of a human antibody, and CL of a human antibody.

[0193] The above modified antibodies can be produced using known methods.

[0194] Since the antigenicity of a chimeric antibody or a humanized antibody in the human body is reduced, such an antibody is useful for administration to humans for therapeutic purposes or such.

[0195] Chimeric antibodies are produced by combining sequences derived from different animals. Examples of chimeric antibodies include antibodies comprising the heavy-chain and light-chain variable regions of a mouse antibody and the heavy-chain and light-chain constant regions of a human antibody. The production of chimeric antibodies can be carried out using known methods (see, for example, Jones et al., Nature 321:522-5, 1986; Riechmann et al., Nature 332:323-7, 1988; and Presta, Curr. Opin. Struct. Biol. 2:593-6, 1992). For example, first, genes encoding the variable regions or CDRs of the antibody of interest are prepared from the RNAs of antibody-producing cells by polymerase chain reaction (PCR) or such (see, for example, Larrick et al., "Methods: a Companion to Methods in Enzymology", Vol. 2: 106, 1991; Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies" in Monoclonal Antibodies: Production, Engineering and Clinical Application; Ritter et al. (eds.), page 166, Cambridge University Press, 1995, and Ward et al., "Genetic Manipulation and Expression of Antibodies" in Monoclonal Antibodies: Principles and Applications; and Birch et al. (eds.), page 137, Wiley-Liss, Inc., 1995). To prepare chimeric antibodies from any one of the AL-201 to AL-333 antibodies, a gene encoding a variable region or CDR can be synthesized based on the sequence information of each of the antibodies disclosed herein. The prepared genes encoding the variable regions or CDRs are linked to genes encoding the constant regions (e.g., human antibody constant regions) or framework regions (e.g., human antibody framework regions). The genes encoding the constant regions or framework regions may be determined in a manner similar to that for the variable region-encoding or CDR-encoding genes, or alternatively, they can be prepared based on the sequence information of known antibodies. DNA sequences encoding chimeric products and CDR-grafted products may be synthesized completely or partially using oligonucleotide synthesis techniques. For example, the oligonucleotide synthesis described by Jones et al. (Nature 321:522-5, 1986) may be performed. Furthermore, in some cases, site-directed mutagenesis and polymerase chain reaction techniques may be appropriately used. Techniques for oligonucleotide-specific mutagenesis of known variable regions described by Verhoeyen et al. (Science 239: 1534-6, 1988) and Riechmann et al. (Nature 332: 323-7, 1988) may be used for modifying the variable region sequences, for example, to enhance the binding ability of chimeric antibodies. Furthermore, if necessary, enzymatic fill-in of gapped oligonucleotides using T4 DNA polymerase may be performed, for example, as described by Queen et al. (Proc. Natl. Acad. Sci. USA 86: 10029-33, 1989; and WO 90/07861).

[0196] For example, CDR-grafting techniques are known in the art ("Immunoglobulin genes", Academic Press (London), pp 260-74, 1989; and Michael A et al., Proc. Natl. Acad. Sci. USA 91: 969-73, 1994). Using the techniques, the CDRs of a certain antibody are replaced with the CDRs of another antibody. Through such replacement, the binding specificity of the former antibody is changed to that of the latter antibody. Among such chimeric antibodies, those in which the framework amino acids are derived from a human antibody are called "humanized antibodies (CDR-grafted antibodies)". When using antibodies to treat humans, human antibodies or humanized antibodies are preferably utilized.

[0197] Generally, chimeric antibodies comprise the variable regions of a non-human mammal-derived antibody and the constant regions derived from a human antibody. On the other hand, humanized antibodies comprise the complementarity-determining regions (CDR) of a non-human mammal-derived antibody and the framework regions and constant regions derived from a human antibody.

[0198] After producing the chimeric antibodies or humanized antibodies, amino acids in the variable regions (for example, FRs) or the constant regions may be substituted with other amino acids.

[0199] The origin of the variable regions of the chimeric antibodies or the CDRs of the humanized antibodies is not particularly limited.

[0200] Human antibody-derived C-regions are used for the C-regions of the chimeric antibodies and humanized antibodies. For example, C gamma1, C gamma2, C gamma3, C gamma4, C mu, C delta, C alpha1, C alpha2, and C epsilon can be used for the H-chain C-regions, and C kappa and C lambda can be used for the L-chain C-regions. Their sequences are known. Furthermore, the human antibody C regions can be modified to improve the stability of the antibodies or their production.

[0201] The present invention provides polynucleotides encoding the above antibodies of the present invention or antigen-binding fragments thereof.

[0202] The polynucleotides of the present invention are not particularly limited as long as they encode the antibodies of the present invention, and may be a DNA or RNA. Furthermore, they may include a non-natural base. The polynucleotides of the present invention can be used for producing the antibodies of the present invention by genetic engineering techiniques.

[0203] The polynucleotides of the present invention can be obtained by isolating mRNA from antibody-producing cells that produce an antibody of the present invention, obtaining cDNA by reverse transcription reaction, and amplifying the obtained cDNA by PCR or such, as described in the Examples.

[0204] In a preferred embodiment, the polynucleotides of the present invention include a polynucleotide encoding an antibody comprising the H chain CDR and/or L chain

CDR of each of the following antibodies, or antigen-binding fragments thereof: AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody.

[0205] In another embodiment, the polynucleotides of the present invention include a polynucleotide encoding an antibody comprising the VH and/or VL of each of the following antibodies, or antigen-binding fragments thereof:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, or AL-233 antibody.

[0206] In the above embodiments, the polynucleotides can be obtained by synthesizing the polynucleotides based on the amino acid sequence information of each of the above antibodies described herein.

[0207] Furthermore, the present invention provides vectors comprising the polynucleotides of the present invention. The vectors of the present invention are preferably expression vectors for expressing an antibody of the present invention in a host cell. The vectors of the present invention may be used for producing the antibodies of the present invention.

[0208] The vectors of the present invention preferably comprise a promoter sequence that enables expression in a host cell, in addition to a polypeptide of the present invention. Furthermore, they may comprise a signal sequence for secretion of an antibody of the present invention. Furthermore, they may comprise a marker gene for selection of a host cell into which a vector of the present invention has been introduced. The components comprised in the vectors are not limited thereto, and may be a suitable component appropriately selected by those skilled in the art.

[0209] For example, expression vectors for expression in E. coli include vectors that have "ori" for amplification in E. coli, and have a promoter such as lacZ promoter (Ward et al., Nature (1989) 341, 544-546;FASEB J. (1992) 6, 2422-2427), araB promoter

(Better et al., Science (1988) 240, 1041-1043), or T7 promoter, and a marker gene such as a drug-resistance gene against ampicillin, tetracycline, kanamycin, chloramphenicol, etc. The vectors include M13 vectors, pUC vectors, pBR322, pBluescript, pCR-Script, etc. Furthermore, for a signal sequence, the pelB signal sequence (Lei, S. P. et al J. Bacteriol. (1987) 169, 4379) or such can be used.

[0210] The vectors of the present invention other than E. coli expression vectors include, for example, mammal-derived expression vectors (e.g., pcDNA3 (Invitrogen), pEGF-BOS (Nucleic Acids. Res. 1990, 18(17), p5322), pEF, pCDM8), insect cell-derived expression vectors (e.g, Bac-to-BAC baculovirus expression system (Gibco BRL), pBacPAK8), plant-derived expression vectors (e.g., pMH1, pMH2), animal virus-derived expression vectors (e.g., pHSV, pMV, pAdexLcw), retrovirus-derived expression vectors (e.g., pZIPneo), yeast-derived expression vectors (e.g., Pichia Expression Kit (Invitrogen)), pNV11, SP-Q01), and Bacillus-derived expression vectors (e.g., pPL608, pKTH50).

[0211] Expression vectors for expression in animal cells such as CHO cells, COS cells, NIH3T3 cells include vectors that have a promoter such as SV40 promoter (Mulligan et al., Nature (1979) 277, 108), MMTV-LTR promoter, EF1 alpha promoter (Mizushima et al., Nucleic Acids Res. (1990) 18, 5322), CMV promoter, or such; and a marker gene such as s drug-resistance gene against neomycin, G418, etc. These vectors include, for example, pMAM, pDR2, pBK-RSV, pBK-CMV, pOPRSV, pOP13, etc. As a signal sequence, any one of those described in the Examples can be used.

[0212] Furthermore, the present invention provides host cells that produce an antibody of the present invention or antigen-binding fragment thereof. The host cells include cells that have a polynucleotide of the present invention or a vector of the present invention. The host cells of the present invention may be used to produce the antibodies or antigen-binding fragments of the present invention.

[0213] The host cells of the present invention are not limited to hybridomas that produce an antibody of the present invention, and may be prokaryotes or eukaryotes into which a vector of the present invention has been introduced. When eukaryotes are used as host cells, for example, animal cells, plant cells, or fungal cells can be used. Animal cells include mammal cells (CHO (J. Exp. Med. (1995) 108, 945), COS, 3T3, myeloma, BHK (baby hamster kidney), HeLa, Vero cells, etc.), amphibian cells (Xenopus oocytes (Valle, et al., Nature (1981) 291, 358-340), etc.), insect cells (Sf9, Sf21, Tn5, etc.). As plant cells, for example, cells derived from Nicotiana tabacum are known as a protein expression system, and they may be cultured into callus and used. Fungal cells include, for example, yeast (e.g., the genus Saccharomyces (Saccharomyces cerevisiae, Saccharomyces pombe, etc.), filamentous fungi (e.g., the genus Aspergillus (Aspergillus niger, etc.). Prokaryotic cells include, for example, E. coli and Bacillus.

Vectors can be introduced into host cell by calcium phosphate methods, DEAE dextran methods, methods using cationic liposome DOTAP (Boehringer Manheim), electroporation methods, lipofection methods, etc.

[0214] Furthermore, the present invention provides antibodies produced from the above host cells.

[0215] Furthermore, the present invention provides compositions comprising the above-mentioned antibody of the present invention and a pharmaceutically acceptable carrier.

[0216] As described below, the present invention strongly suggests that each of the following antibodies are promising candidates for therapeutic antibodies for preventing Alzheimer-like phenotypes:

AL-201 antibody, AL-202 antibody, AL-203 antibody, AL-204 antibody, AL-205 antibody, AL-206 antibody, AL-207 antibody, AL-208 antibody, AL-209 antibody, AL-210 antibody, AL-211 antibody, AL-212 antibody, AL-213 antibody, AL-214 antibody, AL-215 antibody, AL-216 antibody, AL-217 antibody, AL-218 antibody, AL-219 antibody, AL-220 antibody, AL-221 antibody, AL-222 antibody, AL-223 antibody, AL-224 antibody, AL-225 antibody, AL-226 antibody, AL-227 antibody, AL-228 antibody, AL-229 antibody, AL-230 antibody, AL-231 antibody, AL-232 antibody, and AL-233 antibody. Memory deterioration has been shown to be related to synaptic dysfunction caused by soluble A beta oligomers (Klein WL, 2001, Trends Neurosci; and Selkoe DJ, 2002, Science). Excessive accumulation and deposition of A beta oligomers may trigger the complicated downstream cascades that cause Alzheimer's disease. Thus, therapeutic intervention using a composition comprising an antibody or antigen-binding fragment of the present invention and a pharmaceutically acceptable carrier could be effective for blocking the pathologic cascades, and thus this could enable the treatment of Alzheimer's disease (WO2009/051220, WO2009/099176, US 12/533,294, and US 12/533,348).

[0217] The "treatment" or "prevention" of the present invention does not necessarily have complete therapeutic or preventive effects against organs or tissues exhibiting symptoms of disorders or diseases, but may have partial effects or effects of suppressing the progression of symptoms.

[0218] "Treatment of Alzheimer's disease" in the present invention means amelioration or suppression of the progression of a symptom of at least one symptom that may be caused by Alzheimer's disease, and examples include amelioration or suppression of cognitive impairment, amelioration or suppression of senile plaque formation, amelioration or suppression of synaptic dysfunction, and reduction or suppression of A beta accumulation in brain tissues, blood, or such. Herein, "cognitive impairment" includes, for example, memory impairment including long term/short term memory impairment, object recognition memory impairment, spatial memory impairment, and

associative and emotional memory impairment. Herein, "prevention of Alzheimer's disease" means suppression of at least one symptom that may be caused by Alzheimer's disease, and includes suppression of development of cognitive impairment, suppression of senile plaque formation, suppression of development of synaptic dysfunction, suppression of A beta accumulation in brain tissues, blood, or such.

[0219] The present invention provides pharmaceutical compositions or pharmaceutical agents which comprise as an active ingredient the above-described composition comprising an antibody or antigen-binding fragment of the present invention and a pharmaceutically acceptable carrier. The above pharmaceutical compositions or pharmaceutical agents are expressed as "pharmaceutical compositions or pharmaceutical agents containing a pharmaceutically acceptable carrier that comprise an antibody or antigen-binding fragment of the present invention as an active ingredient".

[0220] In the present invention, the phrase "comprising as an active ingredient the above-described composition comprising an antibody or antigen-binding fragment of the present invention and a pharmaceutically acceptable carrier", and "comprising as an active ingredient the above-described an antibody or antigen-binding fragment" mean comprising the above-described composition comprising an antibody or antigen-binding fragment of the present invention and a pharmaceutically acceptable carrier, or an antibody or antigen-binding fragment of the present invention as a major ingredient or a component that shows physiological activity or pharmacological function, but does not limit its content rate.

[0221] Examples of the above-mentioned pharmaceutical compositions include agents against cognitive impairment, Alzheimer's disease therapeutic agents, agents for suppressing the progression of Alzheimer's disease, agents for suppressing senile plaque formation, agents for suppressing A beta accumulation, anti-neurotoxic agents (agents for neutralizing neurotoxicity), agents for inhibiting A beta amyloid fibril formation, and anti-synaptic toxicity agents (agents for neutralizing synaptic toxicity).

[0222] The above-mentioned pharmaceutical composition of the present invention can be expressed, for example, as "methods for suppressing Alzheimer's disease" which comprise the step of administering to a subject (individual) the above-described composition comprising an antibody or antigen-binding fragment of the present invention and a pharmaceutically acceptable carrier. Alternatively, it can be expressed, for example, as "methods for suppressing Alzheimer's disease" which comprise the step of administering to a subject a therapeutically effective amount of the above-described antibody or antigen-binding fragment of the present invention. In other embodiments, examples include methods for suppressing cognitive impairment, methods for suppressing the progression of Alzheimer's disease, methods for suppressing senile plaque

formation, methods for suppressing A beta accumulation, methods for neutralizing (suppressing) neurotoxic activity, methods for inhibiting A beta amyloid fibril formation, and methods for neutralizing (suppressing) synaptic toxicity. In further embodiments, examples include methods for preventing and/or treating cognitive impairment, and methods for preventing and/or treating Alzheimer's disease.

[0223] The present invention also provides use of a composition comprising the above-described antibody or antigen-binding fragment of the present invention and a pharmaceutically acceptable carrier in the production of the above-mentioned pharmaceutical composition. The present invention further provides use of the above-described antibody or antigen-binding fragment of the present invention in the production of the above-described pharmaceutical composition.

[0224] Furthermore, the present invention relates to the following antibodies or antigen-binding fragments.

- The above-described antibody or antigen-binding fragment of the present invention and a pharmaceutically acceptable carrier for use in preventing and/or treating cognitive impairment.
- The above-described antibody or antigen-binding fragment of the present invention for use in preventing and/or treating Alzheimer's disease.
- The above-described antibody or antigen-binding fragment of the present invention for use in suppressing the progression of Alzheimer's disease.
- The above-described antibody or antigen-binding fragment of the present invention for use in suppressing senile plaque formation.
- The above-described antibody or antigen-binding fragment of the present invention for use in suppressing A beta accumulation.
- The above-described antibody or antigen-binding fragment of the present invention for use in neutralizing (suppressing) neurotoxic activity.
- The above-described antibody or antigen-binding fragment of the present invention for use in inhibiting A beta amyloid fibril formation.
- The above-described antibody or antigen-binding fragment of the present invention for use in neutralizing (suppressing) synaptic toxicity.

[0225] The present invention also relates to the following:

- Use of the above-described antibody or antigen-binding fragment of the present invention for preventing and/or treating cognitive impairment.
- Use of the above-described antibody or antigen-binding fragment of the present invention for preventing and/or treating Alzheimer's disease.
- Use of the above-described antibody or antigen-binding fragment of the present invention for suppressing the progression of Alzheimer's disease.
- Use of the above-described antibody or antigen-binding fragment of the present

invention for suppressing senile plaque formation.

- Use of the above-described antibody or antigen-binding fragment of the present invention for suppressing A beta accumulation.
- Use of the above-described antibody or antigen-binding fragment of the present invention for neutralizing (suppressing) neurotoxicity.
- Use of the above-described antibody or antigen-binding fragment of the present invention for inhibiting A beta amyloid fibril formation.
- Use of the above-described antibody or antigen-binding fragment of the present invention for neutralizing (suppressing) synaptic toxicity.

[0226] The above-mentioned pharmaceutical compositions or agents of the present invention can be administered to humans or other animals. In the present invention, non-human animals to which the pharmaceutical compositions or agents are administered include mice, rats, guinea pigs, rabbits, chickens, cats, dogs, sheep, pigs, cattle, monkeys, baboons, and chimpanzees. These animals preferably exhibit at least one symptom selected from, for example, cognitive impairment, senile plaque formation, synaptic dysfunction, A beta accumulation in brain tissues or blood, etc.

[0227] Antibodies or antigen-binding fragments contained in the pharmaceutical compositions of the present invention are not particularly limited as long as they are included in the above-mentioned antibodies or antigen-binding fragments of the present invention, and examples include the antibodies or antigen-binding fragments described herein.

[0228] When using the above-mentioned antibodies or antigen-binding fragments of the present invention for pharmaceutical compositions, they may be formulated by methods known to those skilled in the art. For example, as necessary, they can be prepared in the form of injectable sterile solutions or suspensions using water or another pharmaceutically acceptable liquid, and can be administered parenterally. For example, the antibodies or antigen-binding fragments to be included in the pharmaceutical compositions can be combined with pharmaceutically acceptable carriers or media, specifically, sterile water, physiological saline, vegetable oils, emulsifiers, suspensions, surfactants, stabilizers, flavoring agents, excipients, solvents, preservatives, binders, or such, and mixed into a unit dose form required for generally accepted pharmaceutical practice. The phrase "pharmaceutically acceptable" indicates that the substance is inactive, and contains conventional substances used as diluents or vehicles for pharmaceuticals. Suitable excipients and their formulations are described, for example, in Remington's Pharmaceutical Sciences, 16th ed. (1980) Mack Publishing Co., ed. Oslo et al.

[0229] Physiological saline and other isotonic solutions containing glucose or adjuvants (for example, D-sorbitol, D-mannose, D-mannitol, and sodium chloride) can be used as

aqueous solutions for injection. They can be used together with appropriate solubilizers such as alcohols, more specifically, ethanol and polyalcohols (propylene glycol, polyethylene glycol, and such), and non-ionic surfactants (Polysorbate 80™, HCO-50, and such).

[0230] Sesame oil or soybean oil can be used as an oleaginous liquid, and benzyl benzoate or benzyl alcohol can be used in combination as a solubilizer. Buffers (for example, phosphate buffer and sodium acetate buffer), soothing agents (for example, procaine hydrochloride), stabilizers (for example, benzyl alcohol and phenol), and antioxidants can be used for the formulations. Prepared injection solutions can be filled into appropriate ampules.

[0231] The administration is preferably parenteral administration, and specific examples include administration by injection, transnasal administration, transpulmonary administration, and transdermal administration. Examples of administration by injection include systemic and local administration by intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection, and such.

[0232] The pharmaceutical compositions contain a pharmaceutically effective amount of the active component (the above-mentioned antibody of the present invention). "Pharmaceutically effective amount (of a compound)" refers to an amount sufficient for treating and/or preventing disorders in which antigens for the above-mentioned antibodies of the present invention play an important role. For example, "a pharmaceutically acceptable amount" may be an amount required for reducing A beta accumulation, neutralizing A beta-induced toxicity, reducing A beta fibril formation, or such, thereby treating or preventing conditions caused by Alzheimer's disease, when the compound is administered to individuals (patients). The reduction or neutralization may be, for example, a reduction or neutralization of at least approximately 5%, 10%, 20%, 30%, 40%, 50%, 75%, 80%, 90%, 95%, 99%, or 100%.

[0233] Assessment for determining such a pharmaceutically effective amount of the above-mentioned antibodies or antigen-binding fragments of the present invention may be carried out using a standard clinical protocol including histopathological diagnosis.

[0234] A suitable administration method may be selected depending on the age and symptoms of the patient. The dosage of an antibody-containing pharmaceutical composition may be selected, for example, within the range of 0.0001 mg to 1000 mg per kilogram body weight for each administration. Alternatively, for example, the dosage for each patient may be selected within the range of 0.001 to 100,000 mg/body; however, the dosage is not necessarily limited to these ranges. Although the dosage and administration methods vary depending on the patient's body weight, age, symptoms, and such, one skilled in the art can appropriately select them. The dosage may be selected based on the high-dose intravenous immunoglobulin therapy (400 mg/

kg) covered by health insurance for humans.

[0235] In the present invention, the pharmaceutical compositions or agents comprising an antibody or antigen-binding fragment may be included in products and kits containing materials useful for treating pathological conditions of a subject. The products may comprise any labeled container for a compound. Suitable containers include bottles, vials, and test tubes. The containers may be formed from a variety of materials such as glass and plastic. The label on the container surface should indicate that the composition is used to treat or prevent one or more conditions of the disease. The label may also indicate descriptions for administration, and such.

[0236] In addition to the above-mentioned container, a kit containing a pharmaceutical composition or agent comprising an antibody or antigen-binding fragment may optionally include a second container that stores a pharmaceutically acceptable diluent. The kit may further include other materials desirable from a commercial and user's standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with descriptions for use.

[0237] If necessary, the pharmaceutical compositions may be provided in a pack or dispenser device that may contain one or more unit dosage forms comprising an active ingredient. The pack may comprise metal or plastic foil, and, for example, it is a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

[0238] In the above-mentioned pharmaceutical agents and kits, besides the antibody or antigen-binding fragment of the present invention that is an active ingredient, sterile water, physiological saline, vegetable oils, surfactants, lipids, solubilizing agents, buffers, protein stabilizers (BSA, gelatin, etc.), preservatives, blocking solutions, reaction solutions, reaction quenching solutions, reagents for treating samples, and such, may be mixed as necessary.

[0239] Furthermore, the present invention provides methods for detecting A beta oligomers (examples include A beta40 (A beta 1-40), A beta42 (A beta 1-42) oligomers, and A beta40/A beta42 oligomers) in samples (specimens). Examples of "samples" of the present invention include samples collected from subjects, cell culture supernatants, cell extracts, samples collected from subject animals, or such; however, they are not particularly limited as long as they contain A beta oligomers. Specifically, the present methods include the step of detecting A beta oligomers contained in a sample (e.g., a sample collected from a subject) using an antibody or antigen-binding fragment of the present invention. A beta oligomers in a sample can be detected by common immunological detection methods, for example, using ELISA (sandwich solid-phase enzyme immunoassay methods that use chemiluminescence (chemiluminescence ELISA), etc.), RIA, immunoprecipitation methods that use the obtained antibodies, im-

munoblotting, flow cytometry, mass spectrometry, and immunohistochemical analysis.

[0240] When A beta oligomers are detected in a sample collected from a subject by the above-mentioned measurement methods, the subject is a possible Alzheimer's disease patient (WO2009/051220, WO2009/099176, US 12/533,294, and US 12/533,348). Thus, the present invention also provides methods of diagnosing whether a subject is a possible Alzheimer's disease patient. For example, when the amount of A beta oligomers in a sample collected from a subject is compared with that from a healthy individual, and if the amount of A beta oligomers is greater in the subject than in the healthy individual, the subject is determined to be a possible Alzheimer's disease patient. Whether or not a subject is a possible Alzheimer's disease patient is diagnosed usually by physicians (including individuals under instructions from physicians; same herein below). Data on the amount of A beta oligomers in samples collected from a subject and a healthy individual, which are obtained by the present methods of diagnosis, will be useful for diagnosis by physicians. Therefore, the present methods of diagnosis can be expressed as methods of collecting and presenting data useful for diagnosis by physicians. Furthermore, "a method of diagnosing whether or not a subject is a possible Alzheimer's disease patient" is alternatively expressed as "a method of diagnosing whether or not a subject suffers from Alzheimer's disease, or is at a risk of developing Alzheimer's disease".Specifically, the present invention provides methods for diagnosing whether or not a subject is a possible Alzheimer's disease patient, wherein the methods comprise detecting A beta oligomers in a sample collected from the subject using an antibody or antigen-binding fragment of the present invention.

[0241] More specifically, the present invention provides a method of diagnosing whether or not a subject is a possible Alzheimer's disease patient, which comprises the steps of:

(a) contacting a sample collected from a subject with the antibody or antigen-binding fragment of the present invention; and

(b) measuring the amount of A beta oligomer in the sample,

wherein the subject is determined to be a possible Alzheimer's disease patient, when the amount measured in step (b) is higher than that of a healthy individual. Step (b) above can be alternatively expressed as "the step of detecting an A beta oligomer in the sample via the antibody or antigen-binding fragment of the present invention that has bound to an A beta oligomer in the sample".

[0242] Furthermore, the present invention provides methods of diagnosing whether or not a subject is a possible Alzheimer's disease patient, which comprise the steps of:

(a) contacting a sample collected from a subject with an antibody or antigen-binding fragment of the present invention and an antibody or antigen-binding fragment that binds to an A beta monomer; and

(b) measuring the ratio of A beta oligomer to A beta monomer in the sample,
wherein the subject is determined to be a possible Alzheimer's disease patient, if the ratio measured in step (b) is higher than that of a healthy individual.

[0243] First, in the present methods, a sample collected from a subject is contacted with an antibody or antigen-binding fragment of the present invention and an antibody or antigen-binding fragment that binds to an A beta monomer. Herein, "contact" may be carried out, for example, by adding each of the above-mentioned antibodies or antigen-binding fragments to a sample collected from a subject, which is placed in a test tube. In this case, the antibody or antigen-binding fragment is added suitably in the form of a solution, a solid obtained by freeze-drying, or such. When adding the antibody as an aqueous solution, the solution may purely contain the antibody alone, or may contain, for example, surfactants, excipients, coloring agents, flavors, preservatives, stabilizers, buffers, suspending agents, tonicity agents, binding agents, disintegrants, lubricants, fluidity promoters, or corrigents. The concentration at which the antibody is added is not particularly limited. For example, as with human immunoglobulin formulations, 500-mg, 1000-mg, and 2500-mg freeze-dried formulations and such may be suitably used. "Contact" may be performed, for example, by adding a sample to a carrier on which the above antibody or antigen-binding fragment has been immobilized. Preferred examples of the carrier on which the above antibody or antigen-binding fragment is immobilized include, for example, microplates, beads (magnetic beads, Sepharose beads, etc.

[0244] Next, the ratio of A beta oligomer to A beta monomer (herein, this is also referred to as "O/M index") in the aforementioned sample is measured. To measure this ratio, the measurement can be carried out using a method of comparing the oligomer and monomer ELISA values obtained from the same sample.

[0245] Then, this ratio is compared with the ratio for a healthy individual. When the ratio is higher in the subject than in the healthy individual, the subject is determined to be a possible Alzheimer's disease patient.

[0246] The methods of diagnosis of the present invention can be performed both in vitro and in vivo, but they are preferably performed in vitro.

[0247] Preferably, the "sample collected from a subject" of the present invention is not particularly limited as long as it is a tissue derived from a subject. Examples include the brain (brain parenchyma, and such), organs, and body fluids (blood, cerebrospinal fluid, and such) of a subject. In the present invention, the sample is preferably blood (more preferably, plasma) or cerebrospinal fluid. The "sample collected from a subject" includes a sample treated with an enzyme, treated using a column, treated by centrifugation, treated by extraction, after collection.

[0248] When the sample is a brain tissue, frozen tissue samples from the brain tissue may be

homogenized and subjected to ultracentrifugation or such, to separate buffer-soluble fractions and buffer-insoluble fractions and measure A beta oligomers. For example, a brain tissue is homogenized in nine volumes of Tris-buffered saline (TS) containing a protease inhibitor cocktail, and the homogenates are ultracentrifuged at 265,000 x g for 20 minutes. Then, a collected supernatant as a soluble fraction of the brain tissue can be used as a sample for immunoblotting, ELISA, RIA, immunoprecipitation, etc. A buffer-insoluble fraction may be solublized by formic acid (e.g., 70%) extraction, and used as a sample for immunoblotting, ELISA, RIA, immunoprecipitation, etc. Formic acid extracts may be appropriately neutralized or diluted with a buffer (e.g., 1 M Tris-HCl (pH 8.0)).

[0249] When A beta oligomers present in a brain tissue are visualized and measured by immunohistochemical methods, brain tissue sections from a subject can be used as samples. To enhance the immunoreactivity, the brain tissue sections can be pre-treated with Protease K. In immunohistochemical methods, it is not essential to quantify A beta oligomers in brain tissues. For example, if A beta deposition is observed, the subject is determined to be a possible Alzheimer's disease patient.

[0250] To increase the accuracy of A beta oligomer measurements, lipoproteins may be removed from a subject-derived sample. The depletion of lipoproteins can be performed by, for example, combining ultracentrifugation, ultrafiltration, and affinity chromatography. A specific method of depleting lipoproteins from a sample is exemplified below.

[0251] The density of a sample is adjusted to 1.25 g/ml with KBr. The sample is ultracentrifuged at 100,000 rpm and 16degrees C for eight hours. Lipoproteins floating at a density of 1.25 g/ml and lipoprotein-depleted clarified fluid are subjected to ultrafiltration using a 3 kDa cut-off membrane (Microcon 3; Arnicon, Inc), and then frozen and stored, or stored at 4degrees C, until use. Lipoproteins are also removed by affinity chromatography using PHML-LIPOSORB (Calbiochem, La Jolla, CA). A sample and PHML-LIPOSORB (Calbiochem, La Jolla, CA) are combined at a ratio of 1.5:1, and mixed for 60 seconds. Then, the mixture is centrifuged at 3,000 rpm for ten minutes. The resulting supernatants can be used as lipoprotein-free samples. The lipoprotein-bound samples bound to PHML-LIPOSORB are eluted using 20 mM sodium deoxycholate. The removal of specific lipoproteins can be confirmed by 1% agarose gel electrophoresis, followed by staining with FAST-RED 7B (Wako, Osaka, Japan).

[0252] Furthermore, by size fractionation of A beta oligomers in a sample using size exclusion chromatography, ultrafiltration, or such, and subsequent detection of A beta oligomers in each fraction using the antibody or antigen-binding fragment of the present invention, the amount of A beta oligomer of each size in the sample can be measured. Fractionation by size exclusion chromatography can be performed by con-

centrating a subject-derived sample about ten-fold using a Microcon 3 kDa molecular weight cut-off filter (Millipore Corp.), and then applying the sample to a Superose 12 size exclusion column (1 cm x 30 cm; Pharmacia Biotech., Uppsala, Sweden; flow rate of 0.5 ml/min) equilibrated with a phosphate buffer. Alternatively, fractionation by ultrafiltration can be performed by sequential ultrafiltration using Microcon 3 kDa, 10 kDa, 30 kDa, and 100 kDa cut-off membranes. The amount of A beta oligomer contained in each fraction can be measured by ELISA, RIA, immunoblotting, immunoprecipitation, etc.

[0253] The methods of measuring an A beta oligomer of the present invention are not particularly limited as long as they comprise the step of detecting an A beta oligomer in a sample using the antibodies or antigen-binding fragments of the present invention. Preferable methods include sandwich ELISA. When sandwich ELISA is performed, an antibody or antigen-binding fragment of the present invention may be immobilized or labeled. Alternatively, an antibody or antigen-binding fragment of the present invention may be used as a primary antibody, and a labeled secondary antibody can be bound to it. The other antibody used in sandwich ELISA may be an antibody or antigen-binding fragment of the present invention, or may be a commercially available anti-A beta antibody. A specific method of detecting A beta oligomers in a sample by sandwich ELISA is exemplified below.

[0254] Microplates are coated with an antibody or antigen-binding fragment of the present invention, and 100 micro l of a sample is added and incubated continuously for 24 hours at 4degrees C. Then, horseradish peroxidase-conjugated BA27 Fab' fragment (anti-A beta1-40 specific to A beta40; Wako pure chemical, Osaka, Japan) or horseradish peroxidase-conjugated BCO5 Fab' fragment (anti-A beta35-43 specific to A beta42; Wako pure chemical, Osaka, Japan) is added and incubated at 4degrees C for 24 hours. The chemiluminescence generated using SuperSignal ELISA Pico Chemiluminescent Substrate (Pierce, Rockford, IL, USA) is quantified by a Veritas Microplate Luminometer (Promega).

[0255] Furthermore, if a sample is immunoprecipitated using an antibody of the present invention, and then immunoblotting analysis is performed, the size of A beta oligomer contained in a sample can be identified without carrying out size fractionation by size exclusion chromatography, ultrafiltration, or such. A specific method is exemplified below.

[0256] Immunoprecipitation is conducted by incubating a sample with an antibody of the present invention and Protein G-Sepharose. The immunoprecipitated A beta oligomers are separated using an NuPAGE 4-12% Bis-Tris-Glycine gel, and transferred onto a nitrocellulose membrane or Immobilon P (Millipore) using 10 mM 3-cyclohexylamino-1-propane sulfonic acid (pH 11) containing 10% methanol at 400

mA for one hour. Non-specific binding sites on the membrane were blocked with a phosphate buffer containing 5% low-fat milk, 1% BSA, and 0.05% Tween-20 at room temperature for three hours. The A beta oligomers are detected by reaction with an antibody of the present invention, or a commercially available anti-A beta antibody such as 4G8 or 6E10 (Covance Immuno-Technologies, Dedham, MA).

[0257] Furthermore, to quantify the amount of A beta oligomer in a sample, a calibration curve may be prepared using standard samples containing a known concentration of A beta oligomer. A beta oligomers used for preparation of standard samples can be prepared by diluting a synthetic A beta (HCl form) dissolved in an HCl solution with PBS or such to a suitable concentration (e.g., 0.1 mg/ml), and incubating at 37degrees C for an hour. The incubation temperature and time for synthetic A beta can be suitably selected. In the methods of the present invention, to obtain the ratio of A beta oligomer to A beta monomer, a calibration curve may be also prepared for A beta monomers. A beta monomers used for preparation of standard A beta monomer samples can be prepared by diluting a synthetic A beta (TFA form) dissolved in TFA (trifluoroacetic acid) with PBS or such to a suitable concentration (e.g., 0.1 mg/ml). For synthetic A beta, A beta1-40, A beta1-42, or such can be used.

[0258] Furthermore, the present invention provides pharmaceutical agents (reagents) or kits for use in the above-mentioned methods of measuring A beta oligomers in a sample, or methods of diagnosing whether or not a subject is a possible Alzheimer's disease patient.

[0259] The pharmaceutical agents for use in the above-mentioned methods of measuring A beta oligomers, or methods of diagnosing whether or not a subject is a possible Alzheimer's disease patient include pharmaceutical agents comprising an antibody or antigen-binding fragment of the present invention. In a preferred embodiment, the pharmaceutical agents include antibody solutions and immobilized antibodies; however, they are not limited thereto. When the pharmaceutical agents are in a form of antibody solution, an antibody or antigen-binding fragment of the present invention is being dissolved in a suitable solvent. Those skilled in the art can select suitable solvents for dissolving the antibody or antigen-binding fragment of the present invention such as water, physiological saline, phosphate buffer, Tris buffer, etc. The above antibody solution of the present invention may comprise, in addition to an antibody of the present invention, a buffer, protein stabilizing agent, preservative agent, blocking agent, surfactant, solubilizing agent, or such, as necessary.

[0260] When the pharmaceutical agent of the present invention is an immobilized antibody, the antibody or antigen-binding fragment of the present invention is being carried by a suitable carrier. Examples of the carrier include microplates, beads (magnetic beads, Sepharose beads, etc.), nitrocellulose membranes, and such; however, they are not

limited thereto. Those skilled in the art can select suitable carriers for immobilizing the antibodies of the present invention. Antibodies or antigen-binding fragments of the present invention can be bound to carriers using known methods.

[0261] Antibodies or antigen-binding fragments of the present invention comprised in the pharmaceutical agents may be suitably labeled with an enzyme label, radioactive label, fluorescent label, dye label, chemical luminescence label, etc.

[0262] The kits for use in the above-mentioned methods of measuring A beta oligomers, or methods of diagnosing whether or not a subject is a possible Alzheimer's disease patient include kits comprising pharmaceutical agents comprising an antibody or antigen-binding fragment of the present invention. Preferable examples of pharmaceutical agents comprising an antibody or antigen-binding fragment of the present invention are as mentioned above. The kits may comprise an antibody or antigen-binding fragment of the present invention in a form of lymphilized powder. In this case, kit users dissolve the lymphilized powder of antibody or antigen-binding fragment with a suitable solvent. The kits may comprise such a solvent for dissolving the antibody or antigen-binding fragment. The kits further comprise a dilution solution for diluting the above-mentioned antibody solutions.

[0263] The kits may comprise, in addition to a pharmaceutical agent comprising an antibody or antigen-binding fragment of the present invention, a reagent such as blocking agent, chromogenic reagent, chromogenic substrate, reaction termination solution, washing solution, buffer, primary antibody, secondary antibody, or such, as necessary. Those skilled in the art can select a suitable reagent depending on the A beta oligomer measurement method. For example, a sandwich ELISA kit comprising a microplate on which the antibody is immobilized may further comprise a labeled anti-A beta antibody, chromogenic substrate, reaction termination solution, washing solution, plate seal, etc. Furthermore, in a sandwich ELISA kit comprising an antibody solution of the present invention may further comprise a microplate on which an anti-A beta antibody is immobilized, chromogenic substrate, reaction termination solution, washing solution, plate seal, labeled secondary antibody (if the antibody of the present invention is not labeled), etc.

[0264] The kits may further comprise a standard sample for preparing a calibration curve of A beta oligomer. The standard sample may be a solution containing a known concentration of A beta oligomer. The kits may comprise a diluting solution for stepwise dilution of the standard solution. Alternatively, lymphilized powder of A beta oligomers may be included, and a solvent for dissolving the lymphilized powder may be comprised. Furthermore, the kits may comprise a solution or lymphilized powder of an A beta monomer, and kit uses may prepare an A beta oligomer standard solution by incubating the A beta monomer solution to polymerize A beta monomers.

[0265] When the kits are for use in methods of diagnosing whether or not a subject is a possible Alzheimer's disease patient, they may comprise a sample (a brain tissue, cerebrospinal fluid, blood, plasma, etc.) collected from a healthy individual as a negative control, and a sample collected from a AD brain patient as a positive control.

[0266] The kit may further include other materials desirable from a commercial and user's standpoint, including buffers, diluents, filters, needles, syringes, and attached documents including descriptions for use (instructions, CD-ROM, etc.). The pharmaceutical agents comprise a kit may be included in a container with a label. Such a container includes a bottle, vial, test tube, microtube, etc.

[0267] All prior art references cited herein are incorporated by reference into this description.

Examples

[0268] Hereinbelow, the present invention is specifically described with reference to the Examples, but it is not to be construed as being limited thereto.

[0269] Methods:

Preparation of antigens

Synthetic A beta1-42 (Peptide Institute, Inc., Osaka) was dissolved in distilled deionized water or 10 mM phosphate buffer, and incubated at 37degrees C for 18 hours. Then, the peptides were separated using a NuPAGE 4-12% Tris-Glycine Gel SDS-PAGE, and after visualization by CBB staining, just the A beta1-42 tetramer was excised without contamination of the A beta1-42 monomer. Antigen was prepared by finely crushing the gel containing the tetramer or extracting the tetramer from the gel.

[0270] Preparation of antibody-producing hybridomas

BALB/c mice were immunized by injecting the antigen prepared by the method described above into their foot pads or abdominal cavities. Then, booster immunization was carried out six times. Hybridomas were prepared from inguinal lymph node cells or spleen cells by fusion with Sp2/O-Ag14 cells using Polyethylene Glycol 1500.

[0271] ELISA screening (primary screening)

Hybridoma culture supernatants were added to ELISA plates immobilized with A beta oligomers and reacted. Color development was carried out using TMB solution after reacting with HRP-conjugated anti-mouse IgG antibody. A beta oligomers used in this method is A beta1-40 (HCl form) after one hour incubation or above-described extracted antigens of A beta1-42 tetramer.

[0272] Dot blot analysis (secondary screening)

Dot blot analysis was carried out for hybridomas that gave positive result for primary screening. In this analysis, 0.1 micro g/dot of three types of A beta; synthesized A beta 1-40 (TFA form) as A beta monomer, synthesized A beta1-40 (HCl form) after 1 hour

incubation as A beta oligomer, and synthesized A beta1-42, were immobilized onto nitrocellulose membrane and used. The membrane was blocked with Tris Buffer containing 5% low-fat milk and 0.05% Tween-20, and reacted with hybridoma culture supernatants and detected with chemiluminescence kit (ECL) after reacting with HRP-conjugated anti-mouse IgG antibody.

[0273] Antibody isotyping

Isotyping of purified immunoglobulins were carried out using a Serotec (Oxford, UK) Mouse Monoclonal Antibody Isotyping Test Kit.

[0274] Identification of antibody sequences

RNAs were purified from hybridomas (1 x 10^6 cells) produced by the method described above using FastPure RNA Kit (TaKaRa, Japan). Using the RNAs as templates, cDNAs were synthesized using 5' RACE System (Invitrogen, USA) and primers specific to H chains or L chains of antibodies that are produced from each hybridomas. 3' side primer sequences that were used for cDNA syntheses are shown below.

H chain (G1) mIGC1Rv: AAGGCTTACAACCACAATCCCT (SEQ ID NO: 707)

H chain (G2a) mIGC2aRv: TGCTGGGCATTTGCATGGA (SEQ ID NO: 708)

H chain (G2b) mIGC2bRv: TGGGCATTTGTGACACTCC (SEQ ID NO: 709)

H chain (G3) mIGC3Rv: ACTGGGCTTGGGTATTCTAGG (SEQ ID NO: 710)

L chain (kappa) mIKCNRv1: GTCCAACTGTTCAGGACGCCATTTTGTCGTT (SEQ ID NO: 711)

L chain (lambda) mILCNRv1: TCCACAGTGTGACCTTCATGAGTGACC (SEQ ID NO: 712)

[0275] Furtherore, using the cDNAs, VH and VL resions were amplified by PCR method. 3' side primer sequences specific to H chains or L chains used for PCR are shown below.

H chain mIGCNRv: ACAGGGATCCAGAGTTCCA (SEQ ID NO: 713)

L chain (kappa) mIKCNRv2: TAACTGCTCACTGGATGG (SEQ ID NO: 714)

L chain (lambda) mILCNRv2: AGTGTGGCCTTGTTAGTCTCGAGC (SEQ ID NO: 715)

[0276] cDNA syntheses and PCR were carried out according to the manual attached to the product, and primers attached to the product (AAP: GGCCACGCGTCGACTAG-TACGGGGGGGGGG (SEQ ID NO: 716), AUAP: GGCCACGCGTCGACTAGTAC (SEQ ID NO: 717)) were used as 5' side primers. Moreoer, Taq DNA polymerase High Fidelity (Invitrogen, USA) was used for PCR.

[0277] VH and VL region fragments amplified by PCR was ligated with linear vector (pGEMTM-T Easy Vector (Promega, USA)) for one hour and transformed into E. coli DH5 alpha strain. Formed colonies were cultured overnight in a liquid selection medium and plasmids were purified using High Purity Plasmid Miniprep System

(MARIGEN BIOSCIENCES, USA). Antibody sequences were detemined by gene sequence analysis using BigDye Terminator V3.1 Cycle Sequence Kit (Applied Biosystems) and 3730xl DNA Analyzer (Applied Biosystems). Two primers described below were used for sequence analysis.

SP6: CGCCAGGGTTTTCCCAGTCACGAC (SEQ ID NO: 718)

M13Rv: TCACACAGGAAACAGCTATGAC (SEQ ID NO: 719)

[0278] Control antibodies

Anti-A beta antibody 6E10 was used as a control antibody to compare to the antibodies of the present invention. Anti-A beta antibody 6E10 (Covance Immuno-Technologies, Dedham, MA) is a mouse monoclonal antibody that recognizes a sequence in A beta1-16 as an epitope, and has no selectivity against A beta oligomer (binds to A beta monomer).

[0279] Competitive ELISA

A beta oligomer antigens were prepared by diluting synthetic A beta1-40 (HCl form) at 0.1 mg/ml with PBS and incubating at 37degrees C for one hour. A beta monomer was prepared by diluting synthetic A beta1-40 (TFA form) at 0.1 mg/ml with PBS. First, 400 ng/well of A beta oligomer was immobilized onto 96-well immunopate and the plate was blocked with BSA. Next, antibodies of the present invention or a control anti-A beta antibody (6E10) were each mixed with serially-diluted A beta monomer or A beta oligomer at a range of 100 pg/ml to 100 micro g/ml and incubated for two hours, then each mixture was added to 96-well immunoplate and incubated at room temperature for ten minutes. Binding abilities of each antibodies to immobilized A beta oligomer were detected by reacting with HRP-conjugated anti-mouse IgG antibody and visualized by measuring absorbance at 450 nm using TMB solution. In the present method, two types of A beta1-40 (A beta1-40 monomer and A beta1-40 oligomer), which have the same sequence but have different structure and polymerization characters due to their structure, was compared as competitive substance. Accordingly, the method can compare the binding difference of the antibodies only derived from the existence of A beta1-40 polymerization, and thus can obtain extremely reliable results.

[0280] Analysis of affinity to A beta oligomer

The analysis was carried out by Surface Plasmon Resonance (SPR) using Biacore 3000 (GE Healthcare Sciences). A beta oligomer was immobilized onto a sensor chip (CM5) as a ligand and antibodies of the present invention and control 6E10 antibody were used as analyte, kinetics analysis was carried out. Analysis was conducted at analyte antibodies at the following five concentrations: 1.25, 2.50, 5.00, 10.00, and 20.00 micro g/ml, and association rate constant (ka), dissociaton rate constant (kd), and dissociation constant (KD) was calculated using BiaEvaluation software. A beta oligomer used in the analysis was prepared by diluting synthetic A beta1-40 (HCl

form) at 0.1 mg/ml with PBS and incubating at 37degrees C for one hour.

[0281] A beta-induced neurotoxicity assay

Human neuroblastoma cell (SH-SY5Y cell) was plated into 24-well plates at a density of 150,000 cells/well, and cultured for 24 hours in DMEM containing 10% FBS. Then, the medium was replaced a serum-free medium containing 12.5 micro M A beta1-42 in the presence or absence of antibodies and cells were cultured for another 24 hours. To determine the cytotoxicity induced by A beta1-42, LDH contents released into the medium from dead cells was determined using CytoTox96 Kit (manufactured by Promega).

[0282] Activity of suppressing A beta amyloid fibril formation

A beta1-42 solution diluted to 12.5 micro M with cell culture medium was incubated in the presence or absence of antibodies of the present invention at 37degrees C for 24 hours. Then, the solutions were mixed with Thioflavin T (ThT) solution (5 micro M ThT, 50 mM Glycine-NaOH, pH8.5), ThT fluorescence intensity, which is correlated with A beta amyloid fibril contents,were determined using fluorescence spectrophotometer (RF-5300PC; Shimadzu Co., Kyoto, Japan). Excitation and emission wavelengths were set at 446 nm and 490 nm, respectively. Fluorescence intensity was measured immediately after the mixture was prepared.

[0283] Immunoblotting

Brain homogenates of Tg2576 or wild type mice were used for APP binding assay. The homogenates were electrophoresed in NuPAGE Tris-Glycine 4-12% gel and transferred to a PVDF membrane. The membrane was reacted to each antibody after blocking by PVDF blocking reagent (TOYOBO). The binding ability was detected by an HRP-conjugated anti-mouse IgG antibody and chemiluminescent reagent (Immobilon western, Millipore).

[0284] Result:

Selection of anti-A beta olilgomer antibodies

67 mice were immunized with A beta tetramer antigen and inguinal lympho node or spleen were isolated from each mice. Cells derived from each organs were fused with myeloma (Sp2/O-Ag14) and dispensed into seven plates of 96-well plate per mice and cultured. Hybridomas producing the antibodies of interest were selected by adding culture supernatant from the 96-well plate onto ELISA plates immobilized with A beta oligomer, and reacting them to analyze. As a result, 45 positive cells were selected from 45,024 wells ((67 mice) x (7 plates) x (96 wells)).

[0285] The above-described ELISA screening also select antibodies that do not specifically bind to A beta oligomer (antibodies that bind to ELISA plate other than A beta oligomer). By performing dot blot analysis, these non-specific antibodies can be excluded. Accordingly, dot blot analysis using ELISA-positive cells were carried out.

For dot blot analysis, two types of oligomers and A beta monomer were spotted and excluded non-specific antibodies (antibodies that do not bind to the spotted A beta oligomer were excluded), as well as specificity against A beta oligomer (absence of binding to A beta monomer) was confirmed. As a result, 33 positive antibodies among 45 ELISA-positive cells were selected (Fig. 1).

[0286] Identification of antibody sequences

The variable region sequences were analyzed by the above-mentioned method, for 33 antibodies (i.e., AL-201 to AL-233) selected by the above dot blot analysis. As a result, the following nucleotide sequences of regions comprising VH CDR1, CDR2, and were obtained:

SEQ ID NO: 1(AL-201), SEQ ID NO: 17(AL-202), SEQ ID NO: 33(AL-203), SEQ ID NO: 49(AL-204), SEQ ID NO: 65(AL-205), SEQ ID NO: 81(AL-206), SEQ ID NO: 97(AL-207), SEQ ID NO: 113(AL-208), SEQ ID NO: 129(AL-209), SEQ ID NO: 145(AL-210), SEQ ID NO: 161(AL-211), SEQ ID NO: 177(AL-212), SEQ ID NO: 193(AL-213), SEQ ID NO: 209(AL-214), SEQ ID NO: 225(AL-215), SEQ ID NO: 241(AL-216), SEQ ID NO: 257(AL-217), SEQ ID NO: 273(AL-218), SEQ ID NO: 289(AL-219), SEQ ID NO: 305(AL-220), SEQ ID NO: 321(AL-221), SEQ ID NO: 337(AL-222), SEQ ID NO: 353(AL-223), SEQ ID NO: 369(AL-224), SEQ ID NO: 385(AL-225), SEQ ID NO: 401(AL-226), SEQ ID NO: 417(AL-227), SEQ ID NO: 433(AL-228), SEQ ID NO: 449(AL-229), SEQ ID NO: 465(AL-230), SEQ ID NO: 481(AL-231), SEQ ID NO: 497(AL-232), and SEQ ID NO: 513(AL-233). From the above nucleotide sequence, the following amino acid sequences were obtained:

SEQ ID NO: 2(AL-201), SEQ ID NO: 18(AL-202), SEQ ID NO: 34(AL-203), SEQ ID NO: 50(AL-204), SEQ ID NO: 66(AL-205), SEQ ID NO: 82(AL-206), SEQ ID NO: 98(AL-207), SEQ ID NO: 114(AL-208), SEQ ID NO: 130(AL-209), SEQ ID NO: 146(AL-210), SEQ ID NO: 162(AL-211), SEQ ID NO: 178(AL-212), SEQ ID NO: 194(AL-213), SEQ ID NO: 210(AL-214), SEQ ID NO: 226(AL-215), SEQ ID NO: 242(AL-216), SEQ ID NO: 258(AL-217), SEQ ID NO: 274(AL-218), SEQ ID NO: 290(AL-219), SEQ ID NO: 306(AL-220), SEQ ID NO: 322(AL-221), SEQ ID NO: 338(AL-222), SEQ ID NO: 354(AL-223), SEQ ID NO: 370(AL-224), SEQ ID NO: 386(AL-225), SEQ ID NO: 402(AL-226), SEQ ID NO: 418(AL-227), SEQ ID NO: 434(AL-228), SEQ ID NO: 450(AL-229), SEQ ID NO: 466(AL-230), SEQ ID NO: 482(AL-231), SEQ ID NO: 498(AL-232), and SEQ ID NO: 514(AL-233).

[0287] Furthermore, the following nucleotide sequences of regions comprising VL CDR1, CDR2, and were obtained:

SEQ ID NO: 3(AL-201), SEQ ID NO: 19(AL-202), SEQ ID NO: 35(AL-203), SEQ ID NO: 51(AL-204), SEQ ID NO: 67(AL-205), SEQ ID NO: 83(AL-206), SEQ ID NO: 99(AL-207), SEQ ID NO: 115(AL-208), SEQ ID NO: 131(AL-209), SEQ ID NO:

147(AL-210), SEQ ID NO: 163(AL-211), SEQ ID NO: 179(AL-212), SEQ ID NO: 195(AL-213), SEQ ID NO: 211(AL-214), SEQ ID NO: 227(AL-215), SEQ ID NO: 243(AL-216), SEQ ID NO: 259(AL-217), SEQ ID NO: 275(AL-218), SEQ ID NO: 291(AL-219), SEQ ID NO: 307(AL-220), SEQ ID NO: 323(AL-221), SEQ ID NO: 339(AL-222), SEQ ID NO: 355(AL-223), SEQ ID NO: 371(AL-224), SEQ ID NO: 387(AL-225), SEQ ID NO: 403(AL-226), SEQ ID NO: 419(AL-227), SEQ ID NO: 435(AL-228), SEQ ID NO: 451(AL-229), SEQ ID NO: 467(AL-230), SEQ ID NO: 483(AL-231), SEQ ID NO: 499(AL-232), and SEQ ID NO: 515(AL-233). From the above nucleotide sequence, the following amino acid sequences were obtained: SEQ ID NO: 4(AL-201), SEQ ID NO: 20(AL-202), SEQ ID NO: 36(AL-203), SEQ ID NO: 52(AL-204), SEQ ID NO: 68(AL-205), SEQ ID NO: 84(AL-206), SEQ ID NO: 100(AL-207), SEQ ID NO: 116(AL-208), SEQ ID NO: 132(AL-209), SEQ ID NO: 148(AL-210), SEQ ID NO: 164(AL-211), SEQ ID NO: 180(AL-212), SEQ ID NO: 196(AL-213), SEQ ID NO: 212(AL-214), SEQ ID NO: 228(AL-215), SEQ ID NO: 244(AL-216), SEQ ID NO: 260(AL-217), SEQ ID NO: 276(AL-218), SEQ ID NO: 292(AL-219), SEQ ID NO: 308(AL-220), SEQ ID NO: 324(AL-221), SEQ ID NO: 340(AL-222), SEQ ID NO: 356(AL-223), SEQ ID NO: 372(AL-224), SEQ ID NO: 388(AL-225), SEQ ID NO: 404(AL-226), SEQ ID NO: 420(AL-227), SEQ ID NO: 436(AL-228), SEQ ID NO: 452(AL-229), SEQ ID NO: 468(AL-230), SEQ ID NO: 484(AL-231), SEQ ID NO: 500(AL-232), and SEQ ID NO: 516(AL-233).

[0288] CDR sequences were determined from the amino acid sequences, based on the definition by Kabat (Kabat, Elvin A., Sequences of proteins of immunological interest 5th ed., National Institutes of Health, 1991). The CDR sequences of the antibodies are shown in Table 1. In Table 1, "Name" shows the name of each antibody, "class" shows the IgG subclass of each antibody, "chain" shows whether the chain is an H or L chain, and "(na)" means "nucleic acid". The L chain of AL-233 was a lambda chain, while that of the other antibodies was kappa chain.

[0289]

[Table 1]

Name	class	chain	CDR1	SEQ ID NO	SEQ ID NO (na)	CDR2	SEQ ID NO	SEQ ID NO (na)	CDR3	SEQ ID NO	SEQ ID NO (na)
AL-201	2b	H	SYWMH	6	5	EINPSNGRTNYNEKFKS	8	7	QGYRHGVFAY	10	9
		L	KASQSVSNDVA	12	11	YASNRYT	14	13	QQDYSSPT	16	15
AL-202	2a	H	SYGMS	22	21	TISSGGSYTYYPDSVKG	24	23	PLYYRHGVFAY	26	25
		L	RASKSISKYLA	28	27	SGSTLQS	30	29	QQHNEYPWT	32	31
AL-203	I	H	DYYMY	38	37	TISDGGSYTYYPDSVKG	40	39	AKYYRYDGGGAYAMDY	42	41
		L	KSSQSVLYSSNQKNYLA	44	43	WASTRES	46	45	HQYLSSYT	48	47
AL-204	I	H	DYYMY	54	53	TISDGGSYTYYPDSVKG	56	55	AKYYRYDGGGAYAMDY	58	57
		L	KSSQSVLYSSNQKNYLA	60	59	WASTRES	62	61	HQYLSSYT	64	63
AL-205	2a	H	NYWMN	70	69	EIRLKSNNYATHYAESVKG	72	71	GTRVWLRREAWFAY	74	73
		L	RASESVDNYGISFMN	76	75	AASNQGS	78	77	QQSKEVPWT	80	79
AL-206	2b	H	SDYAWN	86	85	YISYSGTTRYNPSLKS	88	87	YGSSYYWYFDV	90	89
		L	TASSSVSSSYLH	92	91	STSNLAS	94	93	HQYHRSPPT	96	95
AL-207	2b	H	TSGMGVG	102	101	HIWWDDDEYYNPSLKS	104	103	RAIHYYGYDAMDY	106	105
		L	TASSSVSSSYLH	108	107	STSNLAS	110	109	HQYHRSPPT	112	111
AL-208	2b	H	SYWMH	118	117	EINPSNGRTNYNEKFKS	120	119	QGYRHGVFAY	122	121
		L	TASSSVSSSYLH	124	123	STSNLAS	126	125	HQYHRSPPT	128	127
AL-209	2a	H	TSGMGVS	134	133	HIYWDDDKRYNPSLKS	136	135	YAKGFAY	138	137
		L	KASQDINKYIA	140	139	YTSTLQP	142	141	LQYDNLYT	144	143
AL-210	2a	H	TSGMGVS	150	149	HIYWDDDKRYNPSLKS	152	151	RGDFDY	154	153
		L	RSSQSLVHSNGNTYLH	156	155	KVSNRFS	158	157	SQSTHVPPT	160	159
AL-211	2b	H	TSGMGVG	166	165	HIWWDDDKYYNPSLKS	168	167	RSLSRDYFDY	170	169
		L	RSSQSLVHSNGNTYLH	172	171	KVSNRFS	174	173	SQSTHVPLT	176	175
AL-212	2b	H	TSGMGVG	182	181	HIWWDDDKYYNPSLKS	184	183	STMITTFAY	186	185
		L	RSSQSLVHSNGNTYLH	188	187	KVSNRFS	190	189	SQSTHVPLT	192	191
AL-213	2b	H	SYGVH	198	197	VIWRGGSTDYNAAFMS	200	199	NRYERGGYYAMDY	202	201
		L	RSSQSIVHSNGNTYLE	204	203	KVSNRFS	206	205	FQGSHVPLT	208	207
AL-214	2b	H	SYGVH	214	213	VIWRGGSTDYNAAFMS	216	215	NRYERGGYYAMDY	218	217
		L	RSSQSIVHSNGNTYLE	220	219	KVSNRFS	222	221	FQGSHVPLT	224	223
AL-215	2a	H	TSGMGVS	230	229	HIYWDDDKRYNPSLKS	232	231	YGNSFAY	234	233
		L	RSSQSIVHSNGNTYLE	236	235	KVSNRFS	238	237	FQGSHVPLT	240	239
AL-216	2b	H	SYWMH	246	245	EINPSNGRTNYNEKFKS	248	247	EHYYGYGAY	250	249
		L	RSSQSIVHSNGNTYLE	252	251	KVSNRFS	254	253	FQGSHVPLT	256	255
AL-217	1	H	TSGMGVS	262	261	HIYWDDDKRYNPSLKS	264	263	RGPSYYRYRDYFDY	266	265
		L	RSSQSIVHSNGNTYLE	268	267	KVSNRFS	270	269	FQGSHVPLT	272	271
AL-218	2b	H	TSGMGVG	278	277	HIWWDDDKYYNPSLKS	280	279	RALYGYDAMDY	282	281
		L	RSSQSIVHSNGNTYLE	284	283	KVSNRFS	286	285	FQGSHVPLT	288	287
AL-219	2b	H	TSGMGVS	294	293	HIYWDDDKRYNPSLKS	296	295	YRSGFAY	298	297
		L	RSSQSIVHSNGNTYLE	300	299	KVSNRFS	302	301	FQGSHVPLT	304	303
AL-220	2b	H	SYWMH	310	309	EINPSNGRTNYNEKFKS	312	311	EHYYGYGAY	314	313
		L	RSSQSIVHSNGNTYLE	316	315	KVSNRFS	318	317	FQGSHVPYT	320	319
AL-221	2b	H	TSGMGVG	326	325	HIWWDDDKYYNPSLKS	328	327	RSLSRDYFDY	330	329
		L	RSSQSIVHSNGNTYLE	332	331	KVSNRFS	334	333	FQGSHVPLT	336	335
AL-222	2b	H	TAGMGVG	342	341	HIWWDDDKYYNPSLKS	344	343	RGLYYGNYDAMDY	346	345
		L	RSSQSIVHSNGNTYLE	348	347	KVSTRFS	350	349	FQGSRVPLT	352	351
AL-223	2a	H	TSGMGVG	358	357	HIWWDDDKYYNPSLKS	360	359	RALITTRDYFDY	362	361
		L	RSSQSIVHSNGNTYLE	364	363	KVSNRFS	366	365	FQGSHVPLT	368	367
AL-224	2a	H	SFGMH	374	373	YISSGSSTIYYADTVKG	376	375	YGNYAMDY	378	377
		L	RSSQSIVHSNGNTYLE	380	379	KVSNRFS	382	381	FQGSHVPPT	384	383
AL-225	2a	H	TSGMGVG	390	389	HIWWDDDKYYNPSLKS	392	391	RGLIRQDYFDY	394	393
		L	RSSQSIVHSNGNTYLE	396	395	KVSNRFS	398	397	FQGSHVPLT	400	399
AL-226	2b	H	TSGMGVS	406	405	HIYWDDDKRYNPSLKS	408	407	GDYRYDGAY	410	409
		L	RSSQSLVHSNGNTYLH	412	411	KVSNRFS	414	413	SQSTHVPLT	416	415
AL-227	2a	H	TSGMGVS	422	421	HIYWDDDKRYNPSLKS	424	423	CYGNYGAMDY	426	425
		L	RSSQSLVHSNGNTYLH	428	427	KVSNRFS	430	429	SQSTHVPLT	432	431
AL-228	2a	H	TSGMGVG	438	437	HIWWDDDKYYNPSLKS	440	439	RALLRLQGDYFDY	442	441
		L	RSSQSIVHSNGNTYLE	444	443	KVSNRFS	446	445	FQGSHVPLT	448	447
AL-229	2b	H	TSGMGVS	454	453	HIYWDDDKRYNPSLKS	456	455	RGDFDY	458	457
		L	RSSQSLVHSNGNTYLH	460	459	KVSNRFS	462	461	SQSTHVPPT	464	463
AL-230	2b	H	TSGMGVS	470	469	HIYWDDDKRYNPSLKS	472	471	YYYGLY	474	473
		L	RSSQSIVHSNGNTYLE	476	475	KVSNRFS	478	477	FQGSHVPLT	480	479
AL-231	2a	H	TSGMGVG	486	485	HIWWDDDKYYNPSLKS	488	487	RALNWDVFDY	490	489
		L	RSSQSIVHSNGNTYLE	492	491	KVSNRFS	494	493	FQGSHVPLT	496	495
AL-232	3	H	TSGMGVG	502	501	HIWWDDDKYYNPSLKS	504	503	RALYDYDAMDY	506	505
		L	RSSQSIVHSNGNTYLE	508	507	KVSNRFS	510	509	FQGSHVPLT	512	511
AL-233	2b λ	H	SGYSWH	518	517	YIHYSGSTNYNPSLKS	520	519	RGYDGYYSWFAY	522	521
		L	RSSTGAVTTSNYAN	524	523	GTNNRAP	526	525	ALWYSNHWV	528	527

[0290] Some of the obtained VH and VL sequences contained signal peptides or lacked N-terminal or C-terminal sequences. If sequences are lacked, they are supplemented.

Thus, the VH and VL sequences without signal sequences were determined based on the homology with previously-reported antibody sequences.

[0291] The VH amino acid sequences, excluding signal peptides, of each antibody are shown in the following sequence ID numbers:

SEQ ID NO: 530(AL-201), SEQ ID NO: 534(AL-202), SEQ ID NO: 538(AL-203), SEQ ID NO: 542(AL-204), SEQ ID NO: 546(AL-205), SEQ ID NO: 550(AL-206), SEQ ID NO: 554(AL-207), SEQ ID NO: 558(AL-208), SEQ ID NO: 562(AL-209), SEQ ID NO: 566(AL-210), SEQ ID NO: 570(AL-211), SEQ ID NO: 574(AL-212), SEQ ID NO: 578(AL-213), SEQ ID NO: 582(AL-214), SEQ ID NO: 586(AL-215), SEQ ID NO: 590(AL-216), SEQ ID NO: 594(AL-217), SEQ ID NO: 598(AL-218), SEQ ID NO: 602(AL-219), SEQ ID NO: 606(AL-220), SEQ ID NO: 610(AL-221), SEQ ID NO: 614(AL-222), SEQ ID NO: 618(AL-223), SEQ ID NO: 622(AL-224), SEQ ID NO: 626(AL-225), SEQ ID NO: 630(AL-226), SEQ ID NO: 634(AL-227), SEQ ID NO: 638(AL-228), SEQ ID NO: 642(AL-229), SEQ ID NO: 646(AL-230), SEQ ID NO: 650(AL-231), SEQ ID NO: 654(AL-232), and SEQ ID NO: 658(AL-233). The nucleotide sequences corresponding to the above amino acid sequences are shown in the following sequence ID numbers:

SEQ ID NO: 529(AL-201), SEQ ID NO: 533(AL-202), SEQ ID NO: 537(AL-203), SEQ ID NO: 541(AL-204), SEQ ID NO: 545(AL-205), SEQ ID NO: 549(AL-206), SEQ ID NO: 553(AL-207), SEQ ID NO: 557(AL-208), SEQ ID NO: 561(AL-209), SEQ ID NO: 565(AL-210), SEQ ID NO: 569(AL-211), SEQ ID NO: 573(AL-212), SEQ ID NO: 577(AL-213), SEQ ID NO: 581(AL-214), SEQ ID NO: 585(AL-215), SEQ ID NO: 589(AL-216), SEQ ID NO: 593(AL-217), SEQ ID NO: 597(AL-218), SEQ ID NO: 601(AL-219), SEQ ID NO: 605(AL-220), SEQ ID NO: 609(AL-221), SEQ ID NO: 613(AL-222), SEQ ID NO: 617(AL-223), SEQ ID NO: 621(AL-224), SEQ ID NO: 625(AL-225), SEQ ID NO: 629(AL-226), SEQ ID NO: 633(AL-227), SEQ ID NO: 637(AL-228), SEQ ID NO: 641(AL-229), SEQ ID NO: 645(AL-230), SEQ ID NO: 649(AL-231), SEQ ID NO: 653(AL-232), and SEQ ID NO: 657(AL-233).

[0292] The VL amino acid sequences, excluding signal peptides, of each antibody are shown in the following sequence ID numbers:

SEQ ID NO: 532(AL-201), SEQ ID NO: 536(AL-202), SEQ ID NO: 540(AL-203), SEQ ID NO: 544(AL-204), SEQ ID NO: 548(AL-205), SEQ ID NO: 552(AL-206), SEQ ID NO: 556(AL-207), SEQ ID NO: 560(AL-208), SEQ ID NO: 564(AL-209), SEQ ID NO: 568(AL-210), SEQ ID NO: 572(AL-211), SEQ ID NO: 576(AL-212), SEQ ID NO: 580(AL-213), SEQ ID NO: 584(AL-214), SEQ ID NO: 588(AL-215), SEQ ID NO: 592(AL-216), SEQ ID NO: 596(AL-217), SEQ ID NO: 600(AL-218), SEQ ID NO: 604(AL-219), SEQ ID NO: 608(AL-220), SEQ ID NO: 612(AL-221),

SEQ ID NO: 616(AL-222), SEQ ID NO: 620(AL-223), SEQ ID NO: 624(AL-224), SEQ ID NO: 628(AL-225), SEQ ID NO: 632(AL-226), SEQ ID NO: 636(AL-227), SEQ ID NO: 640(AL-228), SEQ ID NO: 644(AL-229), SEQ ID NO: 648(AL-230), SEQ ID NO: 652(AL-231), SEQ ID NO: 656(AL-232), and SEQ ID NO: 660(AL-233). The nucleotide sequences corresponding to the above amino acid sequences are shown in the following sequence ID numbers:
SEQ ID NO: 531(AL-201), SEQ ID NO: 535(AL-202), SEQ ID NO: 539(AL-203), SEQ ID NO: 543(AL-204), SEQ ID NO: 547(AL-205), SEQ ID NO: 551(AL-206), SEQ ID NO: 555(AL-207), SEQ ID NO: 559(AL-208), SEQ ID NO: 563(AL-209), SEQ ID NO: 567(AL-210), SEQ ID NO: 571(AL-211), SEQ ID NO: 575(AL-212), SEQ ID NO: 579(AL-213), SEQ ID NO: 583(AL-214), SEQ ID NO: 587(AL-215), SEQ ID NO: 591(AL-216), SEQ ID NO: 595(AL-217), SEQ ID NO: 599(AL-218), SEQ ID NO: 603(AL-219), SEQ ID NO: 607(AL-220), SEQ ID NO: 611(AL-221), SEQ ID NO: 615(AL-222), SEQ ID NO: 619(AL-223), SEQ ID NO: 623(AL-224), SEQ ID NO: 627(AL-225), SEQ ID NO: 631(AL-226), SEQ ID NO: 635(AL-227), SEQ ID NO: 639(AL-228), SEQ ID NO: 643(AL-229), SEQ ID NO: 647(AL-230), SEQ ID NO: 651(AL-231), SEQ ID NO: 655(AL-232), and SEQ ID NO: 659(AL-233).

[0293] The amino acid sequences of H-chain signal peptides of each antibody are shown in the following sequence ID numbers:

SEQ ID NO: 662(AL-213, AL-214), SEQ ID NO: 664(AL-207), SEQ ID NO: 667(AL-211, AL-212, AL-215, AL-218, AL-221, AL-222, AL-223, AL-225, AL-227, AL-228, AL-229, AL-231, AL-232), SEQ ID NO: 669(AL-209), SEQ ID NO: 671(AL-224), SEQ ID NO: 673(AL-201, AL-208, AL-216, AL-220), SEQ ID NO: 675(AL-202), SEQ ID NO: 677(AL-203, AL-204), SEQ ID NO: 679(AL-210, AL-217, AL-219, AL-226, AL-230), SEQ ID NO: 681(AL-233), SEQ ID NO: 683(AL-206), and SEQ ID NO: 685(AL-205). The nucleotide sequences encoding H-chain signal peptides of each antibody are shown in the following sequence ID numbers:

SEQ ID NO: 661(AL-213, AL-214), SEQ ID NO: 663(AL-207), SEQ ID NO: 665(AL-215, AL-227, AL-229), SEQ ID NO: 666(AL-211, AL-212, AL-218, AL-221, AL-222, AL-223, AL-225, AL-228, AL-231, AL-232), SEQ ID NO: 668(AL-209), SEQ ID NO: 670(AL-224), SEQ ID NO: 672(AL-201, AL-208, AL-216, AL-220), SEQ ID NO: 674(AL-202), SEQ ID NO: 676(AL-203, AL-204), SEQ ID NO: 678(AL-210, AL-217, AL-219, AL-226, AL-230), SEQ ID NO: 680(AL-233), SEQ ID NO: 682(AL-206), and SEQ ID NO: 684(AL-205).

[0294] The amino acid sequences of L-chain signal peptides of each antibody are shown in the following sequence ID numbers:

SEQ ID NO: 687(AL-233), SEQ ID NO: 689(AL-206, AL-207, AL-208), SEQ ID NO: 691(AL-205), SEQ ID NO: 694(AL-203, AL-204), SEQ ID NO: 696(AL-228), SEQ ID NO: 698(AL-222), SEQ ID NO: 700(AL-210, AL-211, AL-212, AL-213, AL-214, AL-215, AL-216, AL-217, AL-218, AL-220, AL-221, AL-223, AL-224, AL-225, AL-226, AL-227, AL-229, AL-230, AL-231, AL-232), SEQ ID NO: 702(AL-201), SEQ ID NO: 704(AL-202), and SEQ ID NO: 706(AL-209). The nucleotide sequences encoding L-chain signal peptides of each antibody are shown in the following sequence ID numbers:
SEQ ID NO: 686(AL-233), SEQ ID NO: 688(AL-206, AL-207, AL-208), SEQ ID NO: 690(AL-205), SEQ ID NO: 692(AL-204), SEQ ID NO: 693(AL-203), SEQ ID NO: 695(AL-228), SEQ ID NO: 697(AL-222), SEQ ID NO: 699(AL-210, AL-211, AL-212, AL-213, AL-214, AL-215, AL-216, AL-217, AL-218, AL-220, AL-221, AL-223, AL-224, AL-225, AL-226, AL-227, AL-229, AL-230, AL-231, AL-232), SEQ ID NO: 701(AL-201), SEQ ID NO: 703(AL-202), and SEQ ID NO: 705(AL-209). The L-chain signal peptide sequence of AL-291 was not determined. An N-terminal portion of the L-chain signal peptide sequence of AL-228 was not determined.

[0295] Competitive ELISA analysis

Dot blot anlysis is a method for analyzing a reactivity against A beta monomer or oligomer immobilized onto nitrocellulose membtane. However, A betas are solubilized into fluids such as interstitial fluid, cerebral fluid, or blood. Then, the present analysis was carried out for investigating specific binding to A beta oligomers in solutions and difference of selectivity to A beta monomer. Competitive ELISA is a method for determining oligomer specificity by preliminarily reacting with antibodies to be measured and serially-diluted A beta monomer or oligomer in solutions, and carrying out ELISA by adding the solutions to a plate immobilized with A beta oligomer. When an antibody is an A beta oligomer-specific antibody, ELISA reaction decreases in an A beta oligomer concentration-dependent manner in a solution reacted with A beta oligomer, but does not decrease in a solution reacted with A beta monomer or decreases when A beta concentration becomes higher than the oligomer concentration. 19 antibodies were analyzed and the result shown in Fig. 2 was obtained. Eight antibodies (AL-213, 217, 220, 224, 225, 226, 229, and 233) showed high binding specificity even in the solution. Meanwhile, antibody that react with both A beta monomer and oligomer (6E10) used as a control showed equivalent ELISA reactivity against monomer and oligomer. IC_{50} and A beta oligomer selectivity over A beta monomer (A beta monomer IC_{50}/A beta oligomer IC_{50}) calculated by the competitive ELISA are shown in Table 2.

[0296]

[Table 2]

Antibody Name	IC_{50} (nmol/L)		Selectivity (vs monomer)
	monomer	oligomer	
AL-209	532	87	6.1
AL-210	1680	361	4.7
AL-213	2200	74	29.7
AL-215	1644	575	2.9
AL-217	>2200	4.48	>491
AL-218	1794	202	8.9
AL-219	999	199	5.0
AL-220	>2200	1958	>1.1
AL-221	49	56	0.9
AL-222	16	26	0.6
AL-223	269	74	3.6
AL-224	>2200	3.8	>579
AL-225	>2200	10.3	>214
AL-226	>2200	24.5	>90
AL-228	1073	56.5	19.0
AL-229	>2200	9.2	>239
AL-231	1652	561	2.9
AL-232	1524	248	6.1
AL-233	>2200	31	>71
Control (6E10)	6.84	7.58	0.9

[0297] Analysis of affinity for A beta oligomer

To investigate the binding ability of the antibodies of the present invention to A beta oligomer, affinity was analyzed (see Methods). From eight antibodies that exhibit high specificity by the competitive ELISA, three antibodies were analyzed and results shown in Fig. 3 was obtained. Calculated association rate constant (ka), dissociation rate constant (kd), and dissociation constant (KD) was shown in Table 3.

[0298]

[Table 3]

Antibody Name	Kinetics assay (five dose)		
	ka ($M^{-1}s^{-1}$)	kd (s^{-1})	KD=kd/ka (M)
AL-217	1.91E+05	1.23E-03	6.44E-09
AL-224	2.85E+05	0.155	5.44E-07
AL-225	1.52E+05	0.0192	1.26E-07
6E10	5.78E+04	1.68E-04	2.91E-09

[0299] Assay of neutralizaion ability of anti-A beta oligomer antibodies against A beta-induced cytotoxicity

A beta oligomers cause cytotoxicity to neuronal cells. To assess whether the present anti-A beta oligomer antibodies neurtlize A beta-induced cytotoxicity, in vitro assay using human neuroblastoma cells (SH-SY5Y cells) was performed. Three kinds of anti-A beta oligomer antibodies (AL-217, AL-224 and AL-225) were examined. They neurtlized the A beta-induced cytotoxicity (Fig. 4). By contrast, non-A beta IgG which was used as a negative control antibody did not neurtlize the cytotoxicity. In the graphs, the value of Y axis indicates the relative rate to the cytotoxicity of A beta only (no antibody).

[0300] Assay of inhibtion ability of anti-A beta oligomer antibodies against A beta-fibril formation

A beta monomers form fibrils as a result of multimerization when they are incubated in neutral pH buffer. To assess whether the present antibodies inhibit the fibril formation, an antibody and A beta were mixed and incubated for 24 hours and the mixture were measured by fluorescence of ThioflavinT which reflects the amount of fibrils. Three kinds fo anti-A beta oligomer antibodies (AL-217, AL-224 and AL-225) were examined. They inhibited formation of A beta fibrils compared to non-A beta IgG which was used as a negative control antibody (Fig. 5). In the graph, the values of Y axis indicates the relative rate to the fibril formation of A beta only (no antibody).

[0301] Immunoblotting to confirm that anti-A beta oligomer antibodies do not bind to APP (amyloid precursor protein)

It is important for escape of side effect that anti-A beta antibodies do not bind APP which is a physiological protein expressed in a healthy body. Anti-A beta oligomer antibodies are expected not to bind to APP because they recognaize a conformational domain of A beta oligomer that does not present in APP. Therefore, the present inventor performed immunoblotting to assess whether the present anti-A beta oligomer

antibodies do not bind to APP. Three antibodies (AL-217, AL-224 and AL-225) were examined, and the results showed that they do not bind to APP (Fig. 6).

Industrial Applicability

[0302] The antibodies provided by the present invention are expected to contribute to the establishment of preventive/therapeutic methods selective to molecules responsible for evoking pathological conditions of Alzheimer's disease, and the establishment of early diagnostic markers for Alzheimer's disease.

Claims

[Claim 1] An antibody that recognizes an isolated A beta tetramer as an antigen, wherein the antibody does not bind to an A beta monomer.

[Claim 2] The antibody of claim 1, which is any one of (1) to (99) below:

(1) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 530;

(2) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 532;

(3) an antibody that comprises the H chain of (1) and the L chain of (2);

(4) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 534;

(5) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 536;

(6) an antibody that comprises the H chain of (4) and the L chain of (5);

(7) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 538;

(8) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 540;

(9) an antibody that comprises the H chain of (7) and the L chain of (8);

(10) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 542;

(11) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 544;

(12) an antibody that comprises the H chain of (10) and the L chain of (11);

(13) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 546;

(14) an antibody that comprises an L chain having CDR1, CDR2, and

CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 548;

(15) an antibody that comprises the H chain of (13) and the L chain of (14);

(16) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 550;

(17) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 552;

(18) an antibody that comprises the H chain of (16) and the L chain of (17);

(19) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 554;

(20) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 556;

(21) an antibody that comprises the H chain of (19) and the L chain of (20);

(22) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 558;

(23) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 560;

(24) an antibody that comprises the H chain of (22) and the L chain of (23);

(25) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 562;

(26) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 564;

(27) an antibody that comprises the H chain of (25) and the L chain of (26);

(28) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence

of SEQ ID NO: 566;
(29) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 568;
(30) an antibody that comprises the H chain of (28) and the L chain of (29);
(31) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 570;
(32) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 572;
(33) an antibody that comprises the H chain of (31) and the L chain of (32);
(34) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 574;
(35) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 576;
(36) an antibody that comprises the H chain of (34) and the L chain of (35);
(37) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 578;
(38) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 580;
(39) an antibody that comprises the H chain of (37) and the L chain of (38);
(40) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 582;
(41) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 584;
(42) an antibody that comprises the H chain of (40) and the L chain of (41);

(43) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 586;
(44) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 588;
(45) an antibody that comprises the H chain of (43) and the L chain of (44);
(46) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 590;
(47) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 592;
(48) an antibody that comprises the H chain of (46) and the L chain of (47);
(49) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 594;
(50) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 596;
(51) an antibody that comprises the H chain of (49) and the L chain of (50);
(52) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 598;
(53) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 600;
(54) an antibody that comprises the H chain of (52) and the L chain of (53);
(55) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 602;
(56) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 604;

(57) an antibody that comprises the H chain of (55) and the L chain of (56);
(58) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 606;
(59) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 608;
(60) an antibody that comprises the H chain of (58) and the L chain of (59);
(61) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 610;
(62) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 612;
(63) an antibody that comprises the H chain of (61) and the L chain of (62);
(64) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 614;
(65) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 616;
(66) an antibody that comprises the H chain of (64) and the L chain of (65);
(67) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 618;
(68) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 620;
(69) an antibody that comprises the H chain of (67) and the L chain of (68);
(70) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 622;
(71) an antibody that comprises an L chain having CDR1, CDR2, and

CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 624;

(72) an antibody that comprises the H chain of (70) and the L chain of (71);

(73) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 626;

(74) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 628;

(75) an antibody that comprises the H chain of (73) and the L chain of (74);

(76) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 630;

(77) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 632;

(78) an antibody that comprises the H chain of (76) and the L chain of (77);

(79) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 634;

(80) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 636;

(81) an antibody that comprises the H chain of (79) and the L chain of (80);

(82) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 638;

(83) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 640;

(84) an antibody that comprises the H chain of (82) and the L chain of (83);

(85) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence

of SEQ ID NO: 642;
(86) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 644;
(87) an antibody that comprises the H chain of (85) and the L chain of (86);
(88) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 646;
(89) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 648;
(90) an antibody that comprises the H chain of (88) and the L chain of (89);
(91) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 650;
(92) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 652;
(93) an antibody that comprises the H chain of (91) and the L chain of (92);
(94) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 654;
(95) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 656;
(96) an antibody that comprises the H chain of (94) and the L chain of (95);
(97) an antibody that comprises an H chain having CDR1, CDR2, and CDR3, which are identified in VH comprising the amino acid sequence of SEQ ID NO: 658;
(98) an antibody that comprises an L chain having CDR1, CDR2, and CDR3, which are identified in VL comprising the amino acid sequence of SEQ ID NO: 660; and
(99) an antibody that comprises the H chain of (97) and the L chain of (98);

[Claim 3] The antibody of claim 1, which is any one of (1) to (200) below:
(1) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 6 as CDR1, the amino acid sequence of SEQ ID NO: 8 as CDR2, and the amino acid sequence of SEQ ID NO: 10 as CDR3;
(2) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 12 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2, and the amino acid sequence of SEQ ID NO: 16 as CDR3;
(3) an antibody that comprises the H chain of (1) and the L chain of (2);
(4) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 530 as VH;
(5) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 532 as VL;
(6) an antibody that comprises the H chain of (4) and the L chain of (5);
(7) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 22 as CDR1, the amino acid sequence of SEQ ID NO: 24 as CDR2, and the amino acid sequence of SEQ ID NO: 26 as CDR3;
(8) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 28 as CDR1, the amino acid sequence of SEQ ID NO: 30 as CDR2, and the amino acid sequence of SEQ ID NO: 32 as CDR3;
(9) an antibody that comprises the H chain of (7) and the L chain of (8);
(10) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 534 as VH;
(11) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 536 as VL;
(12) an antibody that comprises the H chain of (10) and the L chain of (11);
(13) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 38 as CDR1, the amino acid sequence of SEQ ID NO: 40 as CDR2, and the amino acid sequence of SEQ ID NO: 42 as CDR3;
(14) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 44 as CDR1, the amino acid sequence of SEQ ID NO: 46 as CDR2, and the amino acid sequence of SEQ ID NO: 48 as CDR3;

(15) an antibody that comprises the H chain of (13) and the L chain of (14);
(16) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 538 as VH;
(17) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 540 as VL;
(18) an antibody that comprises the H chain of (16) and the L chain of (17);
(19) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 54 as CDR1, the amino acid sequence of SEQ ID NO: 56 as CDR2, and the amino acid sequence of SEQ ID NO: 58 as CDR3;
(20) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 60 as CDR1, the amino acid sequence of SEQ ID NO: 62 as CDR2, and the amino acid sequence of SEQ ID NO: 64 as CDR3;
(21) an antibody that comprises the H chain of (19) and the L chain of (20);
(22) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 542 as VH;
(23) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 544 as VL;
(24) an antibody that comprises the H chain of (22) and the L chain of (23);
(25) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 70 as CDR1, the amino acid sequence of SEQ ID NO: 72 as CDR2, and the amino acid sequence of SEQ ID NO: 74 as CDR3;
(26) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 76 as CDR1, the amino acid sequence of SEQ ID NO: 78 as CDR2, and the amino acid sequence of SEQ ID NO: 80 as CDR3;
(27) an antibody that comprises the H chain of (25) and the L chain of (26);
(28) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 546 as VH;
(29) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 548 as VL;

(30) an antibody that comprises the H chain of (28) and the L chain of (29);
(31) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 86 as CDR1, the amino acid sequence of SEQ ID NO: 88 as CDR2, and the amino acid sequence of SEQ ID NO: 90 as CDR3;
(32) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 92 as CDR1, the amino acid sequence of SEQ ID NO: 94 as CDR2, and the amino acid sequence of SEQ ID NO: 96 as CDR3;
(33) an antibody that comprises the H chain of (31) and the L chain of (32);
(34) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 550 as VH;
(35) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 552 as VL;
(36) an antibody that comprises the H chain of (34) and the L chain of (35);
(37) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 102 as CDR1, the amino acid sequence of SEQ ID NO: 104 as CDR2, and the amino acid sequence of SEQ ID NO: 106 as CDR3;
(38) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 108 as CDR1, the amino acid sequence of SEQ ID NO: 110 as CDR2, and the amino acid sequence of SEQ ID NO: 112 as CDR3;
(39) an antibody that comprises the H chain of (37) and the L chain of (38);
(40) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 554 as VH;
(41) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 556 as VL;
(42) an antibody that comprises the H chain of (40) and the L chain of (41);
(43) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 118 as CDR1, the amino acid sequence of SEQ ID NO: 120 as CDR2, and the amino acid sequence of SEQ ID NO: 122 as CDR3;

(44) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 124 as CDR1, the amino acid sequence of SEQ ID NO: 126 as CDR2, and the amino acid sequence of SEQ ID NO: 128 as CDR3;
(45) an antibody that comprises the H chain of (43) and the L chain of (44);
(46) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 558 as VH;
(47) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 560 as VL;
(48) an antibody that comprises the H chain of (46) and the L chain of (47);
(49) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 134 as CDR1, the amino acid sequence of SEQ ID NO: 136 as CDR2, and the amino acid sequence of SEQ ID NO: 138 as CDR3;
(50) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 140 as CDR1, the amino acid sequence of SEQ ID NO: 142 as CDR2, and the amino acid sequence of SEQ ID NO: 144 as CDR3;
(51) an antibody that comprises the H chain of (49) and the L chain of (50);
(52) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 562 as VH;
(53) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 564 as VL;
(54) an antibody that comprises the H chain of (52) and the L chain of (53);
(55) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 150 as CDR1, the amino acid sequence of SEQ ID NO: 152 as CDR2, and the amino acid sequence of SEQ ID NO: 154 as CDR3;
(56) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 156 as CDR1, the amino acid sequence of SEQ ID NO: 158 as CDR2, and the amino acid sequence of SEQ ID NO: 160 as CDR3;
(57) an antibody that comprises the H chain of (55) and the L chain of (56);

(58) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 566 as VH;
(59) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 568 as VL;
(60) an antibody that comprises the H chain of (58) and the L chain of (59);
(61) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 166 as CDR1, the amino acid sequence of SEQ ID NO: 168 as CDR2, and the amino acid sequence of SEQ ID NO: 170 as CDR3;
(62) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 172 as CDR1, the amino acid sequence of SEQ ID NO: 174 as CDR2, and the amino acid sequence of SEQ ID NO: 176 as CDR3;
(63) an antibody that comprises the H chain of (61) and the L chain of (62);
(64) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 570 as VH;
(65) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 572 as VL;
(66) an antibody that comprises the H chain of (64) and the L chain of (65);
(67) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 182 as CDR1, the amino acid sequence of SEQ ID NO: 184 as CDR2, and the amino acid sequence of SEQ ID NO: 186 as CDR3;
(68) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 188 as CDR1, the amino acid sequence of SEQ ID NO: 190 as CDR2, and the amino acid sequence of SEQ ID NO: 192 as CDR3;
(69) an antibody that comprises the H chain of (67) and the L chain of (68);
(70) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 574 as VH;
(71) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 576 as VL;
(72) an antibody that comprises the H chain of (70) and the L chain of (71);

(73) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 198 as CDR1, the amino acid sequence of SEQ ID NO: 200 as CDR2, and the amino acid sequence of SEQ ID NO: 202 as CDR3;
(74) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 204 as CDR1, the amino acid sequence of SEQ ID NO: 206 as CDR2, and the amino acid sequence of SEQ ID NO: 208 as CDR3;
(75) an antibody that comprises the H chain of (73) and the L chain of (74);
(76) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 578 as VH;
(77) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 580 as VL;
(78) an antibody that comprises the H chain of (75) and the L chain of (76);
(79) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 214 as CDR1, the amino acid sequence of SEQ ID NO: 216 as CDR2, and the amino acid sequence of SEQ ID NO: 218 as CDR3;
(80) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 220 as CDR1, the amino acid sequence of SEQ ID NO: 222 as CDR2, and the amino acid sequence of SEQ ID NO: 224 as CDR3;
(81) an antibody that comprises the H chain of (79) and the L chain of (80);
(82) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 582 as VH;
(83) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 584 as VL;
(84) an antibody that comprises the H chain of (82) and the L chain of (83);
(85) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 230 as CDR1, the amino acid sequence of SEQ ID NO: 232 as CDR2, and the amino acid sequence of SEQ ID NO: 234 as CDR3;
(86) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 236 as CDR1, the amino acid sequence of

SEQ ID NO: 238 as CDR2, and the amino acid sequence of SEQ ID NO: 240 as CDR3;

(87) an antibody that comprises the H chain of (85) and the L chain of (86);

(88) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 586 as VH;

(89) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 588 as VL;

(90) an antibody that comprises the H chain of (88) and the L chain of (89);

(91) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 246 as CDR1, the amino acid sequence of SEQ ID NO: 248 as CDR2, and the amino acid sequence of SEQ ID NO: 250 as CDR3;

(92) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 252 as CDR1, the amino acid sequence of SEQ ID NO: 254 as CDR2, and the amino acid sequence of SEQ ID NO: 256 as CDR3;

(93) an antibody that comprises the H chain of (91) and the L chain of (92);

(94) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 590 as VH;

(95) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 592 as VL;

(96) an antibody that comprises the H chain of (94) and the L chain of (95);

(97) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 262 as CDR1, the amino acid sequence of SEQ ID NO: 264 as CDR2, and the amino acid sequence of SEQ ID NO: 266 as CDR3;

(98) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 268 as CDR1, the amino acid sequence of SEQ ID NO: 270 as CDR2, and the amino acid sequence of SEQ ID NO: 272 as CDR3;

(99) an antibody that comprises the H chain of (97) and the L chain of (98);

(100) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 594 as VH;

(101) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 596 as VL;
(102) an antibody that comprises the H chain of (100) and the L chain of (101);
(103) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 278 as CDR1, the amino acid sequence of SEQ ID NO: 280 as CDR2, and the amino acid sequence of SEQ ID NO: 282 as CDR3;
(104) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 284 as CDR1, the amino acid sequence of SEQ ID NO: 286 as CDR2, and the amino acid sequence of SEQ ID NO: 288 as CDR3;
(105) an antibody that comprises the H chain of (103) and the L chain of (104);
(106) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 598 as VH;
(107) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 600 as VL;
(108) an antibody that comprises the H chain of (106) and the L chain of (107);
(109) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 294 as CDR1, the amino acid sequence of SEQ ID NO: 296 as CDR2, and the amino acid sequence of SEQ ID NO: 298 as CDR3;
(110) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 300 as CDR1, the amino acid sequence of SEQ ID NO: 302 as CDR2, and the amino acid sequence of SEQ ID NO: 304 as CDR3;
(111) an antibody that comprises the H chain of (109) and the L chain of (110);
(112) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 602 as VH;
(113) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 604 as VL;
(114) an antibody that comprises the H chain of (112) and the L chain of (113);
(115) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 310 as CDR1, the amino acid sequence of

SEQ ID NO: 312 as CDR2, and the amino acid sequence of SEQ ID NO: 314 as CDR3;
(116) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 316 as CDR1, the amino acid sequence of SEQ ID NO: 318 as CDR2, and the amino acid sequence of SEQ ID NO: 320 as CDR3;
(117) an antibody that comprises the H chain of (115) and the L chain of (116);
(118) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 606 as VH;
(119) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 608 as VL;
(120) an antibody that comprises the H chain of (118) and the L chain of (119);
(121) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 326 as CDR1, the amino acid sequence of SEQ ID NO: 328 as CDR2, and the amino acid sequence of SEQ ID NO: 330 as CDR3;
(122) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 332 as CDR1, the amino acid sequence of SEQ ID NO: 334 as CDR2, and the amino acid sequence of SEQ ID NO: 336 as CDR3;
(123) an antibody that comprises the H chain of (121) and the L chain of (122);
(124) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 610 as VH;
(125) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 612 as VL;
(126) an antibody that comprises the H chain of (124) and the L chain of (125);
(127) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 342 as CDR1, the amino acid sequence of SEQ ID NO: 344 as CDR2, and the amino acid sequence of SEQ ID NO: 346 as CDR3;
(128) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 348 as CDR1, the amino acid sequence of SEQ ID NO: 350 as CDR2, and the amino acid sequence of SEQ ID NO: 352 as CDR3;

(129) an antibody that comprises the H chain of (127) and the L chain of (128);
(130) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 614 as VH;
(131) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 616 as VL;
(132) an antibody that comprises the H chain of (130) and the L chain of (131);
(133) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 358 as CDR1, the amino acid sequence of SEQ ID NO: 360 as CDR2, and the amino acid sequence of SEQ ID NO: 362 as CDR3;
(134) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 364 as CDR1, the amino acid sequence of SEQ ID NO: 366 as CDR2, and the amino acid sequence of SEQ ID NO: 368 as CDR3;
(135) an antibody that comprises the H chain of (133) and the L chain of (134);
(136) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 618 as VH;
(137) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 620 as VL;
(138) an antibody that comprises the H chain of (136) and the L chain of (137);
(139) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 374 as CDR1, the amino acid sequence of SEQ ID NO: 376 as CDR2, and the amino acid sequence of SEQ ID NO: 378 as CDR3;
(140) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 380 as CDR1, the amino acid sequence of SEQ ID NO: 382 as CDR2, and the amino acid sequence of SEQ ID NO: 384 as CDR3;
(141) an antibody that comprises the H chain of (139) and the L chain of (140);
(142) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 622 as VH;
(143) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 624 as VL;

(144) an antibody that comprises the H chain of (142) and the L chain of (143);
(145) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 390 as CDR1, the amino acid sequence of SEQ ID NO: 392 as CDR2, and the amino acid sequence of SEQ ID NO: 394 as CDR3;
(146) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 396 as CDR1, the amino acid sequence of SEQ ID NO: 398 as CDR2, and the amino acid sequence of SEQ ID NO: 400 as CDR3;
(147) an antibody that comprises the H chain of (145) and the L chain of (146);
(148) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 626 as VH;
(149) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 628 as VL;
(150) an antibody that comprises the H chain of (148) and the L chain of (149);
(151) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 406 as CDR1, the amino acid sequence of SEQ ID NO: 408 as CDR2, and the amino acid sequence of SEQ ID NO: 410 as CDR3;
(152) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 412 as CDR1, the amino acid sequence of SEQ ID NO: 414 as CDR2, and the amino acid sequence of SEQ ID NO: 416 as CDR3;
(153) an antibody that comprises the H chain of (151) and the L chain of (152);
(154) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 630 as VH;
(155) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 632 as VL;
(156) an antibody that comprises the H chain of (154) and the L chain of (155);
(157) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 422 as CDR1, the amino acid sequence of SEQ ID NO: 424 as CDR2, and the amino acid sequence of SEQ ID NO: 426 as CDR3;

(158) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 428 as CDR1, the amino acid sequence of SEQ ID NO: 430 as CDR2, and the amino acid sequence of SEQ ID NO: 432 as CDR3;
(159) an antibody that comprises the H chain of (157) and the L chain of (158);
(160) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 634 as VH;
(161) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 636 as VL;
(162) an antibody that comprises the H chain of (160) and the L chain of (161);
(163) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 438 as CDR1, the amino acid sequence of SEQ ID NO: 440 as CDR2, and the amino acid sequence of SEQ ID NO: 442 as CDR3;
(164) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 444 as CDR1, the amino acid sequence of SEQ ID NO: 446 as CDR2, and the amino acid sequence of SEQ ID NO: 448 as CDR3;
(165) an antibody that comprises the H chain of (163) and the L chain of (164);
(166) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 638 as VH;
(167) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 640 as VL;
(168) an antibody that comprises the H chain of (166) and the L chain of (167);
(169) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 454 as CDR1, the amino acid sequence of SEQ ID NO: 456 as CDR2, and the amino acid sequence of SEQ ID NO: 458 as CDR3;
(170) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 460 as CDR1, the amino acid sequence of SEQ ID NO: 462 as CDR2, and the amino acid sequence of SEQ ID NO: 464 as CDR3;
(171) an antibody that comprises the H chain of (169) and the L chain of (170);

(172) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 642 as VH;
(173) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 644 as VL;
(174) an antibody that comprises the H chain of (172) and the L chain of (173);
(175) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 470 as CDR1, the amino acid sequence of SEQ ID NO: 472 as CDR2, and the amino acid sequence of SEQ ID NO: 474 as CDR3;
(176) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 476 as CDR1, the amino acid sequence of SEQ ID NO: 478 as CDR2, and the amino acid sequence of SEQ ID NO: 480 as CDR3;
(177) an antibody that comprises the H chain of (175) and the L chain of (176);
(178) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 646 as VH;
(179) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 648 as VL;
(180) an antibody that comprises the H chain of (178) and the L chain of (179);
(181) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 486 as CDR1, the amino acid sequence of SEQ ID NO: 488 as CDR2, and the amino acid sequence of SEQ ID NO: 490 as CDR3;
(182) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 492 as CDR1, the amino acid sequence of SEQ ID NO: 494 as CDR2, and the amino acid sequence of SEQ ID NO: 496 as CDR3;
(183) an antibody that comprises the H chain of (181) and the L chain of (182);
(184) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 650 as VH;
(185) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 652 as VL;
(186) an antibody that comprises the H chain of (184) and the L chain of (185);

(187) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 502 as CDR1, the amino acid sequence of SEQ ID NO: 504 as CDR2, and the amino acid sequence of SEQ ID NO: 506 as CDR3;
(188) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 508 as CDR1, the amino acid sequence of SEQ ID NO: 510 as CDR2, and the amino acid sequence of SEQ ID NO: 512 as CDR3;
(189) an antibody that comprises the H chain of (187) and the L chain of (188);
(190) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 654 as VH;
(191) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 656 as VL;
(192) an antibody that comprises the H chain of (190) and the L chain of (191);
(193) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 518 as CDR1, the amino acid sequence of SEQ ID NO: 520 as CDR2, and the amino acid sequence of SEQ ID NO: 522 as CDR3;
(194) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 524 as CDR1, the amino acid sequence of SEQ ID NO: 526 as CDR2, and the amino acid sequence of SEQ ID NO: 528 as CDR3;
(195) an antibody that comprises the H chain of (193) and the L chain of (194);
(196) an antibody that comprises an H chain having the amino acid sequence of SEQ ID NO: 658 as VH;
(197) an antibody that comprises an L chain having the amino acid sequence of SEQ ID NO: 660 as VL;
(198) an antibody that comprises the H chain of (196) and the L chain of (197);
(199) an antibody that comprises one or more amino acid substitutions, deletions, additions, and/or insertions in the antibody of any one of (1) to (198), which has equivalent activity to the antibody of any one of (1) to (198); and
(200) an antibody that binds to the epitope bound by the antibody of any one of (1) to (198).

[Claim 4] The antibody of any one of claims 1 to 3, wherein the antibody is a chimeric antibody or a humanized antibody.

[Claim 5] An antigen-binding fragment of the antibody of any one of claims 1 to 4.

[Claim 6] A pharmaceutical composition comprising the antibody of any one of claims 1 to 4 or the antigen-binding fragment of claim 5, and a pharmaceutically acceptable carrier.

[Claim 7] The composition of claim 6, which comprises an agent against cognitive impairment, a therapeutic agent for Alzheimer's disease, an agent for suppressing the progression of Alzheimer's disease, an agent for suppressing senile plaque formation, an agent for suppressing A beta accumulation, an anti-neurotoxic agent, an agent for inhibiting A beta amyloid fibril formation, or an agent against synaptic toxicity.

[Claim 8] A method for detecting an A beta oligomer, which comprises the step of detecting an A beta oligomer contained in a sample using the antibody of any one of claims 1 to 4 or the antigen-binding fragment of claim 5.

[Claim 9] A method of diagnosing whether or not a subject is a possible Alzheimer's disease patient, which comprises using the antibody of any one of claims 1 to 4 or the antigen-binding fragment of claim 5, to detect an A beta oligomer in a sample collected from a subject.

[Claim 10] A method of diagnosing whether or not a subject is a possible Alzheimer's disease patient, which comprises the steps of:
(a) contacting a sample collected from a subject with the antibody of any one of claims 1 to 4 or the antigen-binding fragment of claim 5; and
(b) measuring the amount of A beta oligomer in the sample,
wherein the subject is determined to be a possible Alzheimer's disease patient, when the amount measured in step (b) is higher than that of a healthy individual.

[Claim 11] A method of diagnosing whether or not a subject is a possible Alzheimer's disease patient, which comprises the steps of:
(a) contacting a sample collected from a subject with the antibody of any one of claims 1 to 4 or the antigen-binding fragment of claim 5, and an antibody that binds to an A beta monomer; and
(b) measuring the ratio of A beta oligomer to A beta monomer in the sample,
wherein the subject is determined to be a possible Alzheimer's disease

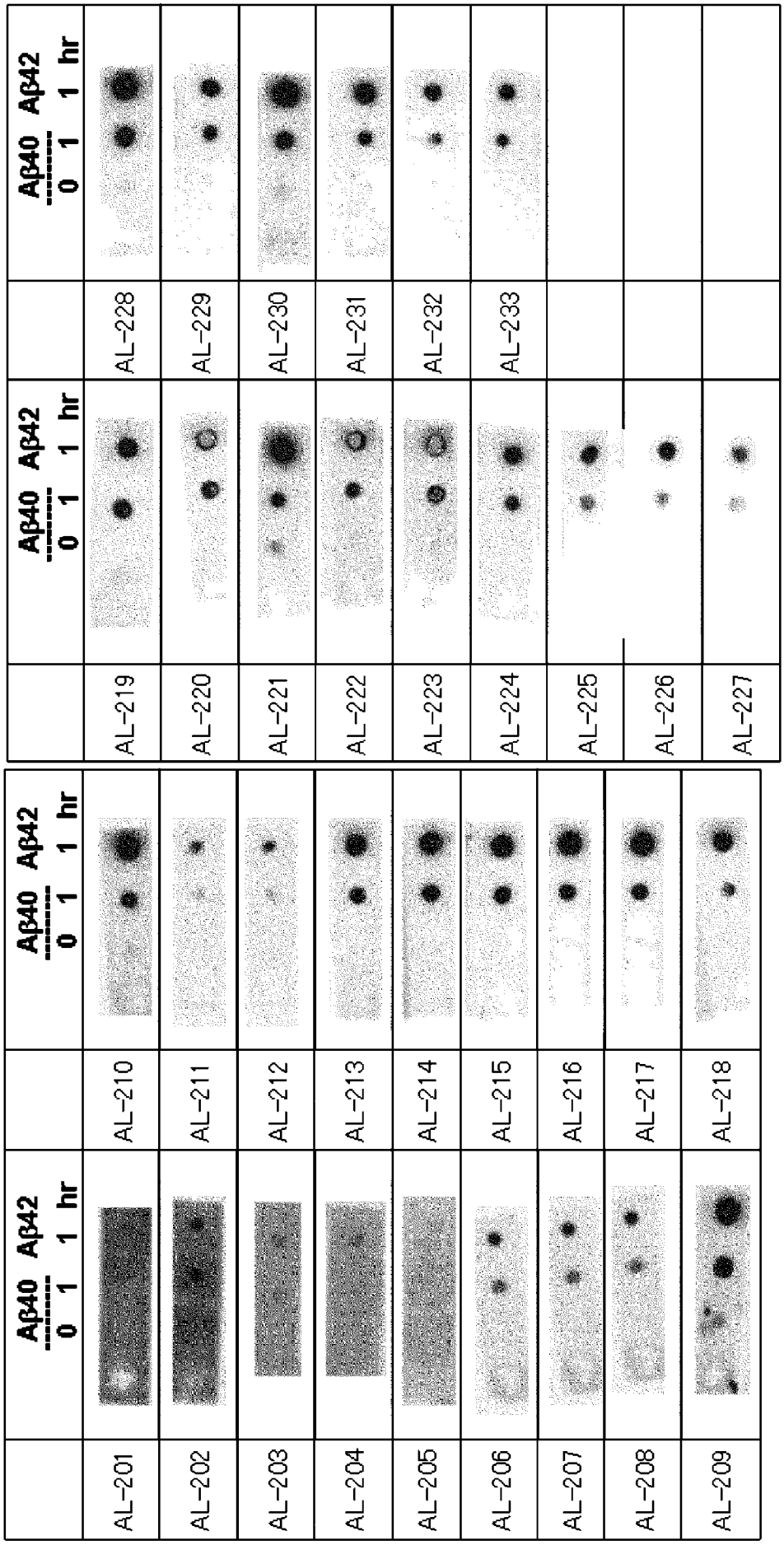
patient, when the ratio measured in step (b) is higher than that of a healthy individual.

[Claim 12] The method of any one of claims 8 to 11, wherein the sample is blood or cerebrospinal fluid.

[Claim 13] A pharmaceutical agent for use in the method of any one of claims 8 to 12.

[Claim 14] A kit for use in the method of any one of claims 8 to 12.

[Fig. 1]


Aβ40 Aβ42
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AL-201
AL-202
AL-203
AL-204
AL-205
AL-206
AL-207
AL-208
AL-209
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AL-212
AL-213
AL-214
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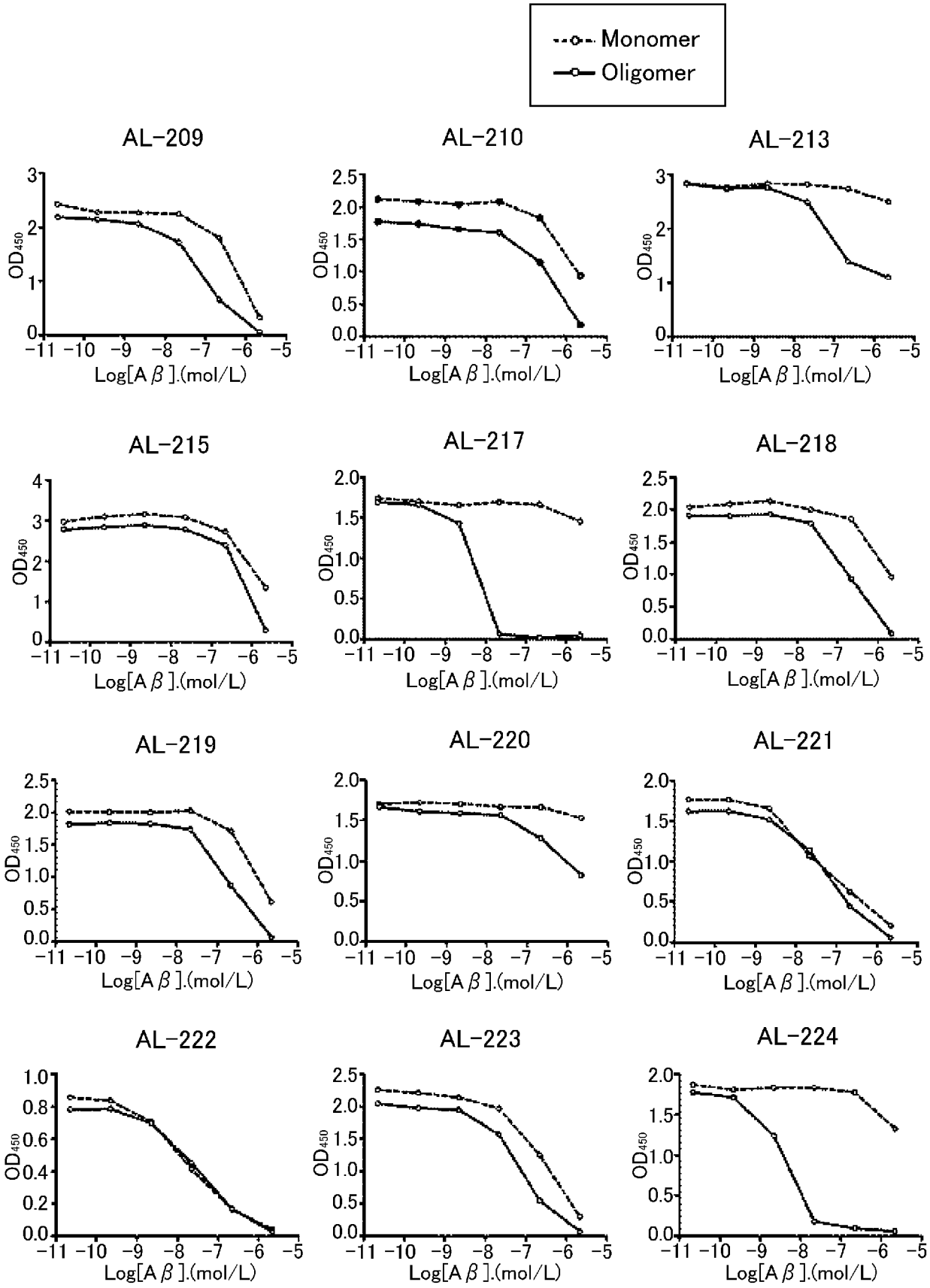
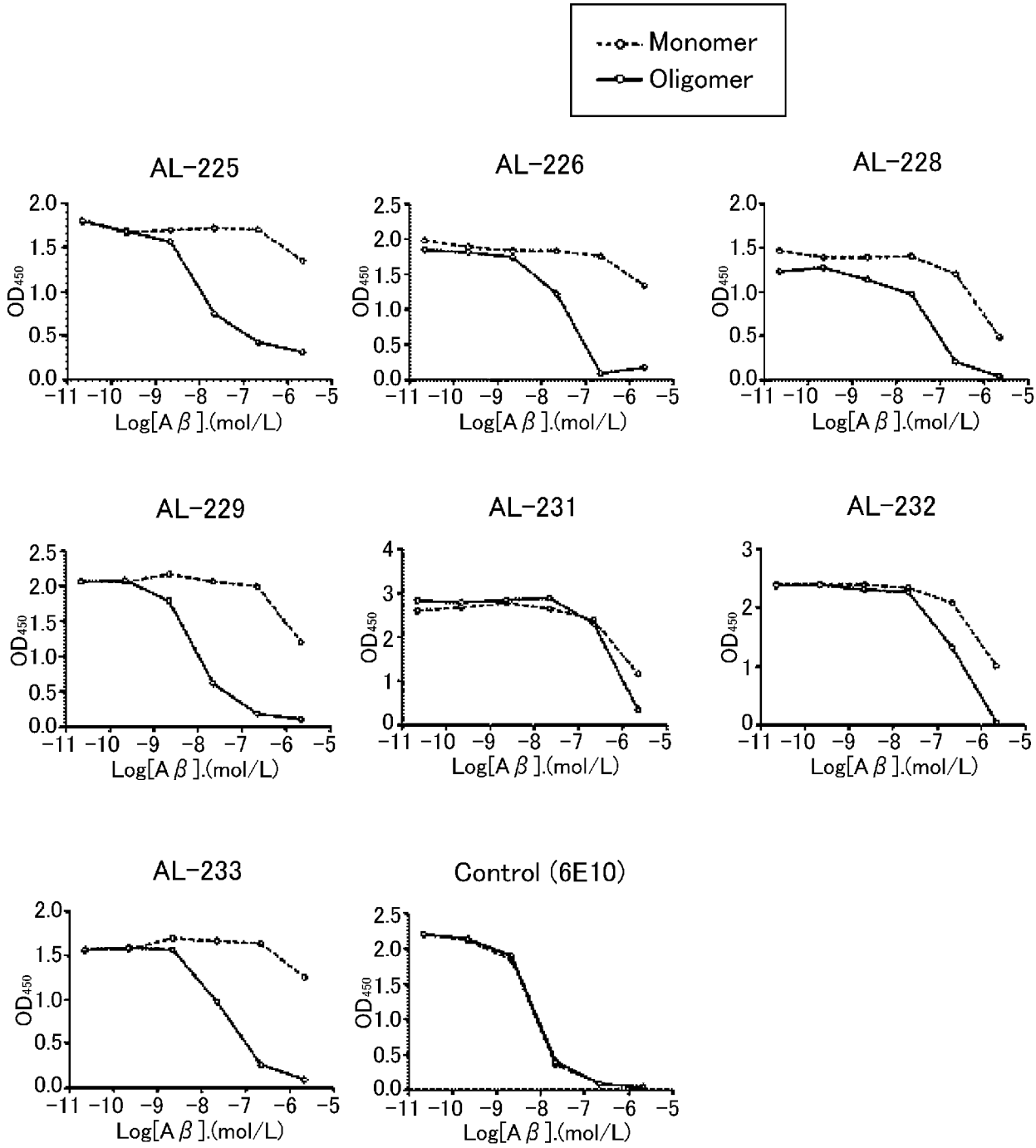
AL-219
AL-220
AL-221
AL-222
AL-223
AL-224
AL-225
AL-226
AL-227
AL-228
AL-229
AL-230
AL-231
AL-232
AL-233

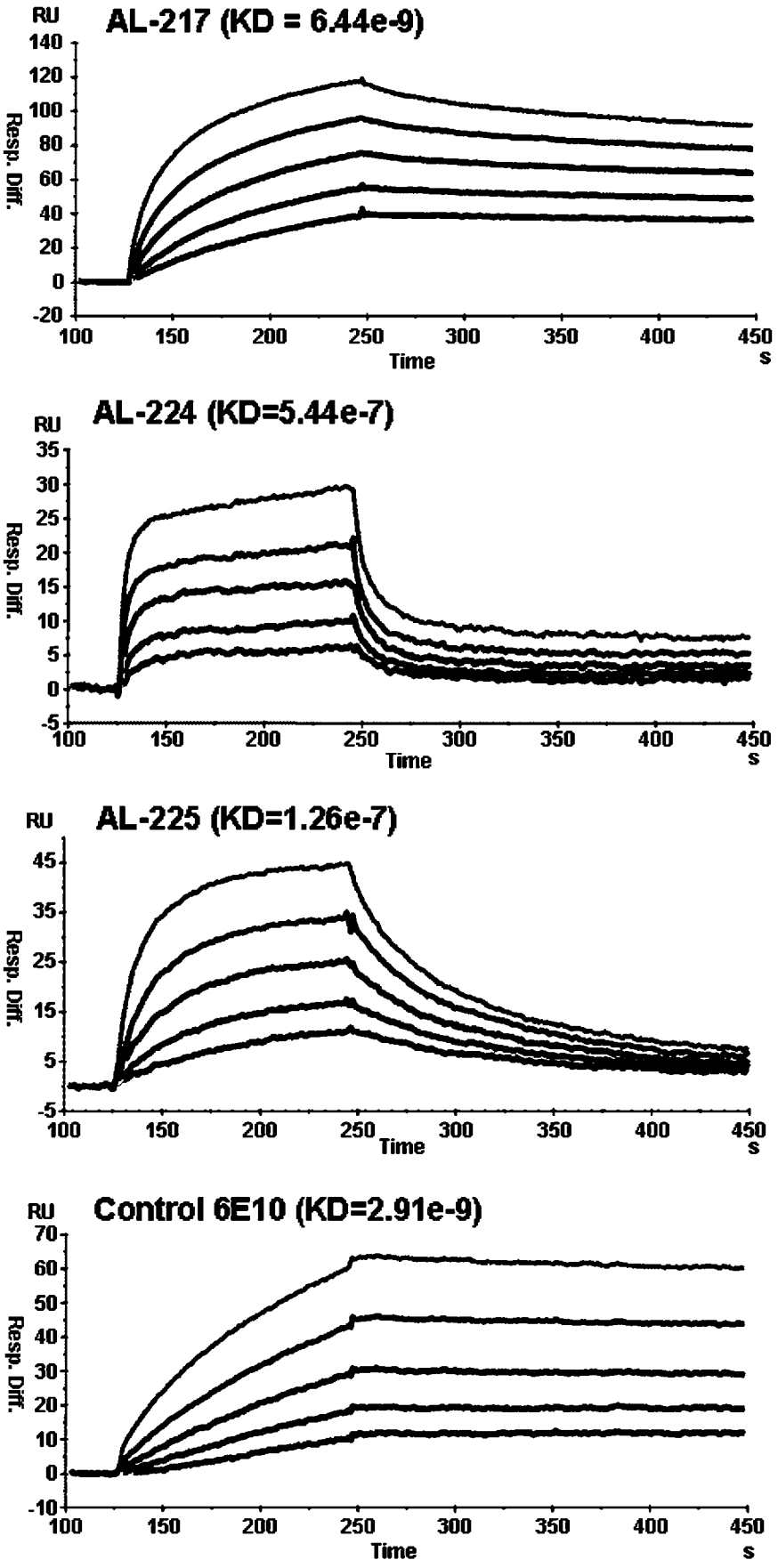
[Fig. 2-1]


Monomer
Oligomer
AL-209
AL-210
AL-213
AL-215
AL-217
AL-218
AL-219
AL-220
AL-221
AL-222
AL-223
AL-224
OD450
Log[Aβ].(mol/L)

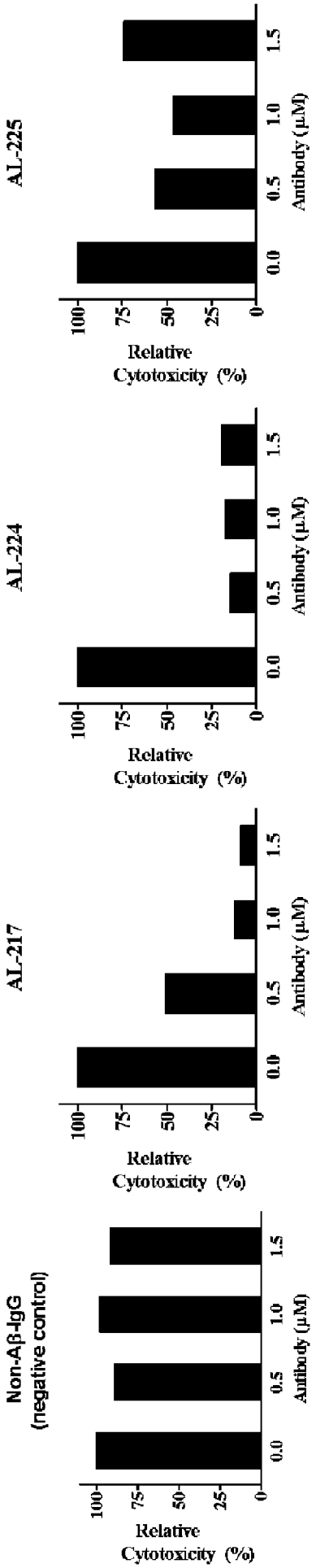
[Fig. 2-2]


Monomer
Oligomer
AL-225
AL-226
AL-228
AL-229
AL-231
AL-232
AL-233
Control (6E10)
OD450
Log[Aβ].(mol/L)

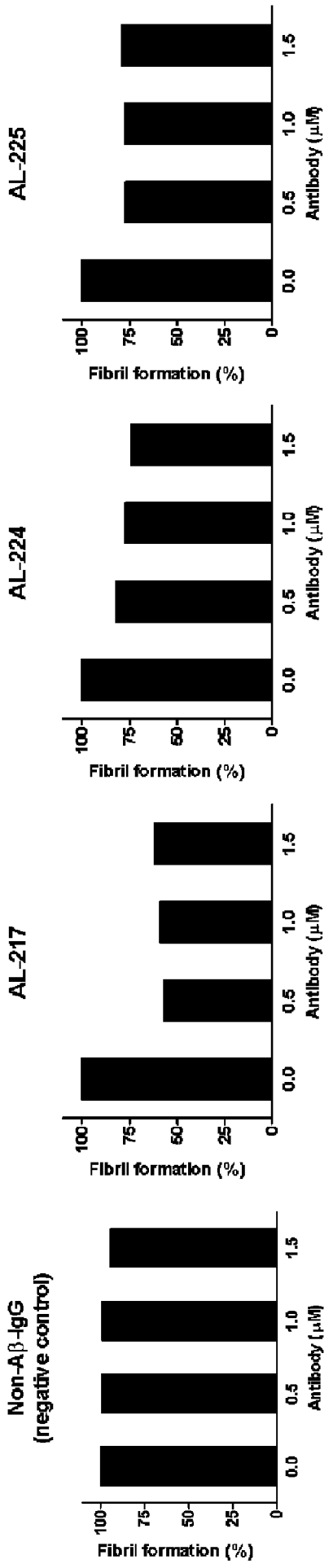
[Fig. 3]


AL-217 (KD = 6.44e-9)
RU
Resp. Diff.
Time
s
AL-224 (KD=5.44e-7)
AL-225 (KD=1.26e-7)
Control 6E10 (KD=2.91e-9)

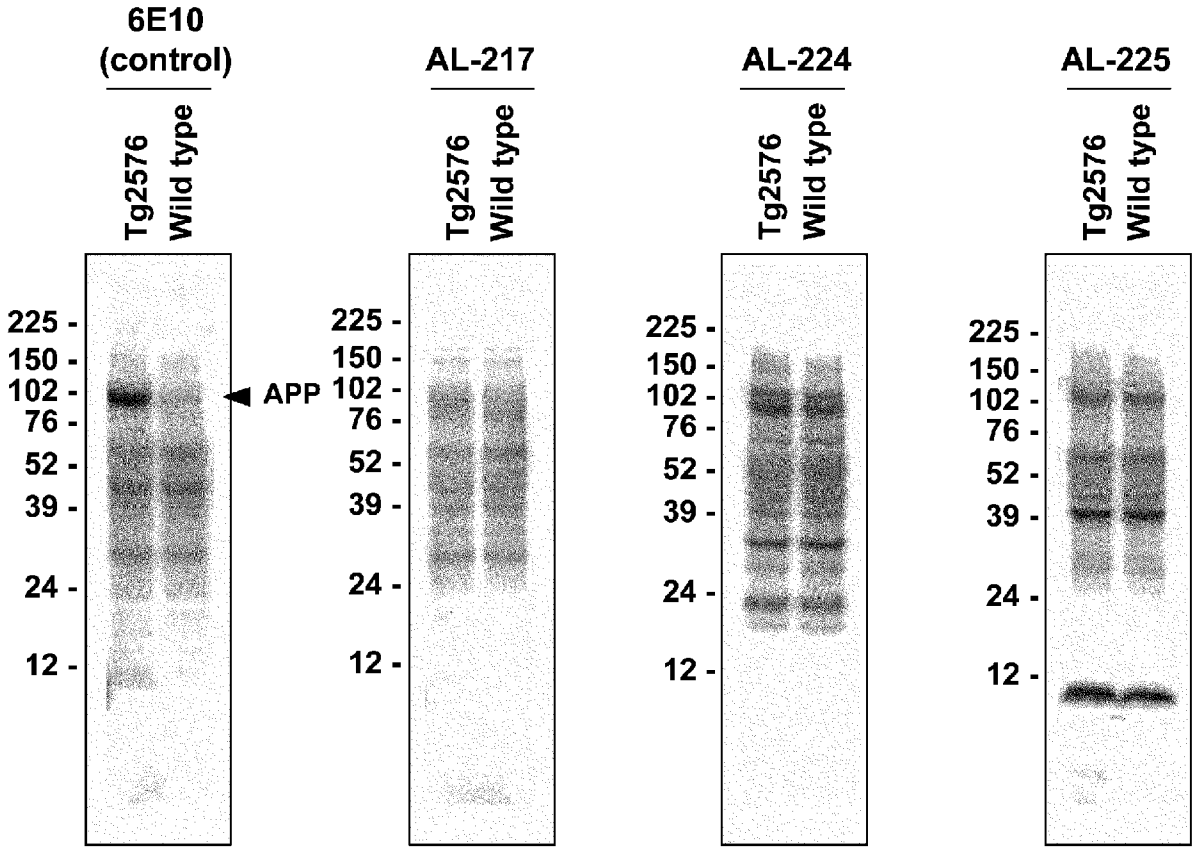
[Fig. 4]


AL-225
Relative Cytotoxicity (%)
100
75
50
25
0
0.0
0.5
1.0
1.5
Antibody (μM)
AL-224
Relative Cytotoxicity (%)
100
75
50
25
0
0.0
0.5
1.0
1.5
Antibody (μM)
AL-217
Relative Cytotoxicity (%)
100
75
50
25
0
0.0
0.5
1.0
1.5
Antibody (μM)
Non-Aβ-IgG (negative control)
Relative Cytotoxicity (%)
100
75
50
25
0
0.0
0.5
1.0
1.5
Antibody (μM)

[Fig. 5]


AL-225
Fibril formation (%)
100
75
50
25
0
0.0
0.5
1.0
1.5
Antibody (μM)
AL-224
Fibril formation (%)
AL-217
Fibril formation (%)
Non-Aβ-IgG
(negative control)
Fibril formation (%)

[Fig. 6]


6E10
(control)
AL-217
AL-224
AL-225
Tg2576
Wild type
225
150
102
76
52
39
24
12
APP

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2010/002771

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. C07K16/18(2006.01)i, A61K39/395(2006.01)i, A61P25/28(2006.01)i, C12N15/09(2006.01)i, G01N33/53(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. C07K16/18, A61K39/395, A61P25/28, C12N15/09, G01N33/53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA/BIOSIS/MEDLINE/WPIDS(STN), JSTPlus/JMEDPlus/JST7580(JDreamII), GenBank/EMBL/DDBJ/GeneSeq, UniProt/GeneSeq

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/150946 A1 (ABBOTT LABORATORIES) 2008.12.11, Example I and page 3 line 12 to page 7 line 2 & EP 2148888 A & US 2009/232801 A1 & CA 2687411 A	1-8, 13, 14
X	WO 2003/104437 A2 (NORTHWESTERN UNIVERSITY & UNIVERSITY OF SOUTHERN CALIFORNIA) 2003.12.18, Example 22, page 2 line 29 to page 3 line 16 & page 7 lines 3-22 & JP 2006-509721 A & US 2003/0068316 A1 & EP 1551447 A	1-8, 13, 14
X	WO 2006/055178 A2 (MERCK & CO., INC. et al.) 2006.05.26, Examples 1-2, page 2 lines 8-25, page 3 lines 12-25, and page 24 line 23 to page 35 line 17 & JP 2008-520553 A & US 2006/0228349 A1 & US 2007/0081998 A1 & US 2007/0148167 A1 & EP 1812062 A & WO 2007/050359 A2 & KR 10-2007-0094890 A & CN 101137394 A	1-8, 13, 14
X	WANG XP. et al., Conformation-dependent single-chain variable fragment antibodies specifically recognize	1-8, 13, 14

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07.07.2010	20.07.2010

Name and mailing address of the ISA/JP	Authorized officer
Japan Patent Office 3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan	Satoshi Ishimaru 4B 3777 Telephone No. +81-3-3581-1101 Ext. 3448

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2010/002771

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	beta-amyloid oligomers., FEBS Lett. (Epub. 20 Jan. 2009) vol. 583, pages 579-584, page 581 '3.2. Binding specificity of selected scFv's to Ab oligomers'	
X/ A	MA QL et al., Antibodies against β-amyloid reduce Aβ oligomers, glycogen synthase kinase-3β activation and tau phosphorylation in vivo and in vitro., J. Neurosci. Res. (2006) vol. 83, pages 374-384, page 374 'Abstract'	1, 8, 13, 14/ 2-7
X/ A	KAYED R. et al., Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis., Science (2003) vol. 300, pages 486-489, page 486 right column	1, 8, 13, 14/ 2-7
P, X	WO 2009/051220 A1 (IMMUNAS PHARMA INC.) 2009.04.23, & CA 2702880 A	1-8, 13, 14
P, X	WO 2010/012004 A2 (THE REAGENTS OF THE UNIVERSITY OF CALIFORNIA) 2010.01.28, (No Family)	1-8, 13, 14
A	JP 2008-527005 A (The REAGENTS OF THE UNIVERSITY OF CALIFOLNIA) 2008.07.24, & EP 1853299 A & WO 2006/083533 A2 & CA 2593846 A	1-8, 13, 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2010/002771

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: 9-12
because they relate to subject matter not required to be searched by this Authority, namely:
a method for diagnosis of human [See PCT Rule 67.1(iv)].

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

专利名称(译)	特异性结合β寡聚体的抗体及其用途		
公开(公告)号	EP2419447A1	公开(公告)日	2012-02-22
申请号	EP2010764291	申请日	2010-04-16
申请(专利权)人(译)	IMMUNAS PHARMA，INC.		
当前申请(专利权)人(译)	IMMUNAS PHARMA，INC.		
[标]发明人	YOKOSEKI TATSUKI OKAMOTO YASUHIDE UMEDA MAKOTO ITO TOSHIYUKI IMAI YUKIHO FUJII SHINOBU TAKAMATSU NAOFUMI		
发明人	YOKOSEKI, TATSUKI OKAMOTO, YASUHIDE UMEDA, MAKOTO ITO, TOSHIYUKI IMAI, YUKIHO FUJII, SHINOBU TAKAMATSU, NAOFUMI		
IPC分类号	C07K16/18 A61K39/395 A61P25/28 C12N15/09 G01N33/53 G01N33/68		
CPC分类号	A61P25/00 A61P25/28 C07K16/18 C07K2317/33 C07K2317/76 C07K2317/92 G01N33/6896 G01N2333/4709 G01N2800/2821		
优先权	61/212986 2009-04-17 US 61/282549 2010-02-26 US		
其他公开文献	EP2419447A4 EP2419447B1		
外部链接	Espacenet		

摘要(译)

本发明人成功地产生了仅对可溶性Aβ寡聚体特异的单克隆抗体，但不识别作为生理分子的可溶性Aβ单体。已证明该抗体可用作阿尔茨海默病的诊断/治疗性单克隆抗体。