

[NPL 9] Igawa et. al. Nat Biotechnol. 2010 Nov;28(11):1203-7

[Summary]

[Technical Problem]

[0010]

5 The invention provides anti-complement component antibodies such as anti-C1s antibodies, pharmaceutical compositions comprising the same, and methods of using the same.

[Solution to Problem]

[0010a]

10 In one aspect, the present disclosure relates to an isolated antibody that comprises an antigen-binding region and an antibody constant region, wherein the antibody promotes dissociation of C1q from C1qrs complex and/or inhibits binding of C1q to C1r2s2, and wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL) selected from the group consisting of 1) to 6) below:

- 15 1) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 59, respectively;
- 2) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 36 and 55, respectively;
- 3) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 55, respectively;
- 20 4) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 47, respectively;
- 5) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 28 and 51, respectively; and
- 6) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 32 and 55, respectively.

[0010b]

 In another aspect, the present disclosure relates to an antibody having binding activity to C1s, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL) selected from the group consisting of 1) to 6) below:

- 30 1) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 59, respectively;
- 2) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 36 and 55, respectively;
- 3) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 55, respectively;
- 35 4) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and

47, respectively;

5) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 28 and 51, respectively; and

6) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 32 and 55, respectively.

[0010c]

In another aspect, the present disclosure relates to an antibody comprising a heavy chain (H chain) and a light chain (L chain) selected from the group consisting of 1) to 6) below:

1) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 66 and 67, respectively;

2) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 68 and 69, respectively;

3) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 70 and 71, respectively;

4) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 72 and 73, respectively;

5) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 74 and 75, respectively; and

6) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 76 and 77, respectively.

[0011]

In one example, the present disclosure provides antibodies that comprise an antigen-binding region and an antibody constant region, have a dissociation promoting function (displacement function) such that the antibody binds to C1qrs complex and promotes dissociation of C1q from C1qrs complex and/or a blocking function such that the antibody binds to C1r2s2 and inhibits the binding of C1q to C1r2s2, and bind to C1s in a pH-dependent manner. In a specific example, the antibodies of the present invention have a mutant constant region comprising at least one amino acid alteration that decreases FcγR-binding activity and/or at least one amino acid alteration that decreases isoelectric point (pI) of an Fc region.

[0012]

Specifically, the present disclosure relates to the following:

[1] An isolated antibody that comprises an antigen-binding region and an antibody constant region,

wherein the antibody promotes dissociation of C1q from C1qrs complex and/or inhibits binding of C1q to C1r2s2, and

wherein the antigen-binding region comprises a combination of HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 selected from the group consisting of 1) to 6)

5 below:

1) HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 that comprise the amino acid sequences consisting of SEQ ID NOs: 25, 26, 27, 60, 61, and 62, respectively;

2) HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 that comprise the amino acid sequences consisting of SEQ ID NOs: 37, 38, 39, 56, 57, and 58, respectively;

10 3) HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 that comprise the amino acid sequences consisting of SEQ ID NOs: 25, 26, 27, 56, 57, and 58, respectively;

4) HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 that comprise the amino acid sequences consisting of SEQ ID NOs: 25, 26, 27, 48, 49, and 50, respectively;

15 5) HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 that comprise the amino acid sequences consisting of SEQ ID NOs: 29, 30, 31, 52, 53, and 54, respectively; and

[CLAIMS]

1. An isolated antibody that comprises an antigen-binding region and an antibody constant region,
5 wherein the antibody promotes dissociation of C1q from C1qrs complex and/or inhibits binding of C1q to C1r2s2, and
wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL) selected from the group consisting of 1) to 6) below:
 - 1) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and
10 59, respectively;
 - 2) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 36 and 55, respectively;
 - 3) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 55, respectively;
 - 15 4) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 47, respectively;
 - 5) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 28 and 51, respectively; and
 - 6) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 32 and
20 55, respectively.
2. The antibody of claim 1, wherein a ratio of a KD value in pH 6.0 to a KD value in pH 7.4, $KD(pH\ 6.0)/KD(pH\ 7.4)$, is 107 or more.
- 25 3. The antibody of any one of claims 1 to 2, wherein the antigen-binding region can specifically bind to a CUB1-EGF-CUB2 domain of human C1s.
4. The antibody of any one of claims 1 to 3, wherein the antibody has a mutant constant region comprising at least one amino acid alteration that decreases Fc γ receptor-binding
30 activity.
5. The antibody of claim 4, wherein the mutant constant region comprises an amino acid alteration at at least one of positions 235 and 236 according to EU numbering.
- 35 6. The antibody of any one of claims 1 to 5, wherein the antibody has a mutant constant region comprising at least one amino acid alteration, and wherein the amino acid alteration

decreases isoelectric point (pI) of the mutant constant region as compared to that of a parent constant region.

7. The antibody of claim 6, wherein the mutant constant region comprises an amino acid alteration at at least one of positions 137, 268, 274, 355, and 419 according to EU numbering.
8. The antibody of any one of claims 1 to 7, wherein pI is 7.8 or less.
9. The antibody of any one of claims 1 to 7, wherein the constant region comprises a heavy chain constant region comprising the amino acid sequence consisting of SEQ ID NO: 45 and a light chain constant region comprising the amino acid sequence consisting of SEQ ID NO: 23.
10. An antibody having binding activity to C1s, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL) selected from the group consisting of 1) to 6) below:
 - 1) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 59, respectively;
 - 2) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 36 and 55, respectively;
 - 3) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 55, respectively;
 - 4) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 24 and 47, respectively;
 - 5) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 28 and 51, respectively; and
 - 6) a VH and VL that comprise the amino acid sequences consisting of SEQ ID NOs: 32 and 55, respectively.
11. The antibody of claim 10, wherein the antibody constant region comprises an H chain constant region comprising the amino acid sequence consisting of SEQ ID NO: 45 and an L chain constant region comprising the amino acid sequence consisting of SEQ ID NO: 23.
12. An antibody comprising a heavy chain (H chain) and a light chain (L chain) selected from the group consisting of 1) to 6) below:

- 1) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 66 and 67, respectively;
- 2) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 68 and 69, respectively;
- 5 3) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 70 and 71, respectively;
- 4) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 72 and 73, respectively;
- 5) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 74 and 75, respectively; and
- 10 6) an H chain and L chain that comprise the amino acid sequences consisting of SEQ ID NOs: 76 and 77, respectively.