

- 9) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 122, the HVR-H2 sequence of SEQ ID NO: 130, the HVR-H3 sequence of SEQ ID NO: 138, the HVR-L1 sequence of SEQ ID NO: 146, the HVR-L2 sequence of SEQ ID NO: 154, and the HVR-L3 sequence of SEQ ID NO: 162,
 - 10) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 123, the HVR-H2 sequence of SEQ ID NO: 131, the HVR-H3 sequence of SEQ ID NO: 139, the HVR-L1 sequence of SEQ ID NO: 147, the HVR-L2 sequence of SEQ ID NO: 155, and the HVR-L3 sequence of SEQ ID NO: 163,
 - 11) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 124, the HVR-H2 sequence of SEQ ID NO: 132, the HVR-H3 sequence of SEQ ID NO: 140, the HVR-L1 sequence of SEQ ID NO: 148, the HVR-L2 sequence of SEQ ID NO: 156, and the HVR-L3 sequence of SEQ ID NO: 164,
 - 12) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 125, the HVR-H2 sequence of SEQ ID NO: 133, the HVR-H3 sequence of SEQ ID NO: 141, the HVR-L1 sequence of SEQ ID NO: 149, the HVR-L2 sequence of SEQ ID NO: 157, and the HVR-L3 sequence of SEQ ID NO: 165, and
 - 13) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 126, the HVR-H2 sequence of SEQ ID NO: 134, the HVR-H3 sequence of SEQ ID NO: 142, the HVR-L1 sequence of SEQ ID NO: 150, the HVR-L2 sequence of SEQ ID NO: 158, and the HVR-L3 sequence of SEQ ID NO: 166,
- wherein the antigen-binding activity of the antibody is lower at pH 5.8 than at pH 7.4,

wherein the antibody comprises an Fc region that has at least one amino acid modification in the region so as to enhance the reduction of plasma antigen concentration, and

wherein the Fc region is a human Fc region that has a binding activity selected from the following group consisting of:

- a) a binding activity to an activating Fc gamma receptor is stronger than the binding activity of an Fc region of the native human IgG1,
- b) a binding activity to an inhibitory Fc gamma receptor is stronger than to an activating Fc gamma receptor, and
- c) a binding activity to an FcRn at neutral pH is stronger than the binding activity of an Fc region of the native human IgG1.

[0012] In some examples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present disclosure is an antibody binding to C1qrs complex on a BIAcore (registered trademark) chip and promotes dissociation of C1q from C1qrs complex. In further examples, the antibody of the present disclosure can be determined as an antibody having a displacement function when a value of response unit (RU) in presence of the antibody is lower than a value of response unit (RU) in the absence of the antibody as determined by a BIAcore (registered trademark) assay when a sufficient time passed.

[0013] In some examples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present disclosure can be determined as an antibody having a displacement function when the time point of crossover is within 60s, 100s, 150s, 200s, 500s, 700s, 1000s, 1500s, or 2000s after the time point of the start of antibody injection as determined by a BIAcore (registered trademark) assay using the following conditions: The capture levels of C1r2s2 complex and

C1q are at 200 resonance unit (RU) and 200 resonance unit (RU), respectively, and the antibody as an analyte is injected at 500 nM at 10 microliter (micro L)/min.

- [0014] In some examples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present disclosure can be determined as an antibody having a displacement function when almost all of C1q are dissociated from C1qrs complex within 100s, 300s, 500s, 700s, 1000s, 1500s, 2000s, 3000s, 5000s, 7000s, or 10000s after the time point of the start of antibody injection as determined by a BIACORE (registered trademark) assay using the following conditions: The capture levels of C1r2s2 complex and C1q are at 200 resonance unit (RU) and 200 resonance unit (RU), respectively, and the antibody as an analyte is injected at 500 nM at 10 micro L/min.
- [0015] In some examples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present disclosure is an antibody having a neutralizing activity for human serum complement of at least 70% in an RBC assay.
- [0016] In some examples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present disclosure is an antibody that specifically binds to C1s or an antibody that specifically binds to C1r.
- [0017] In some examples, an isolated antibody that inhibits the interaction between C1q

Claims

- [Claim 1] An isolated antibody that inhibits the interaction between C1q and C1r2s2 complex,
 wherein the antibody specifically binds to an epitope within a CUB1-EGF-CUB2 domain of C1s, and competes for binding to the epitope with an antibody selected from the group consisting of 1)-5) below:
- 1) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 32, the HVR-H2 sequence of SEQ ID NO: 33, the HVR-H3 sequence of SEQ ID NO: 34, the HVR-L1 sequence of SEQ ID NO: 35, the HVR-L2 sequence of SEQ ID NO: 36, and the HVR-L3 sequence of SEQ ID NO: 37,
 - 2) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 38, the HVR-H2 sequence of SEQ ID NO: 39, the HVR-H3 sequence of SEQ ID NO: 40, the HVR-L1 sequence of SEQ ID NO: 41, the HVR-L2 sequence of SEQ ID NO: 42, and the HVR-L3 sequence of SEQ ID NO: 43,
 - 3) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 44, the HVR-H2 sequence of SEQ ID NO: 45, the HVR-H3 sequence of SEQ ID NO: 46, the HVR-L1 sequence of SEQ ID NO: 47, the HVR-L2 sequence of SEQ ID NO: 48, and the HVR-L3 sequence of SEQ ID NO: 49,
 - 4) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 50, the HVR-H2 sequence of SEQ ID NO: 51, the HVR-H3 sequence of SEQ ID NO: 52, the HVR-L1 sequence of SEQ ID NO: 53, the HVR-L2 sequence of SEQ ID NO: 54, and the HVR-L3 sequence of SEQ ID NO: 55, and
 - 5) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 56, the HVR-H2 sequence of SEQ ID NO: 57, the HVR-H3 sequence of SEQ ID NO: 58, the HVR-L1 sequence of SEQ ID NO: 59, the HVR-L2 sequence of SEQ ID NO: 60, and the HVR-L3 sequence of SEQ ID NO: 61, or
- wherein the antibody specifically binds to an epitope within a CUB1-EGF-CUB2 domain of C1r, and competes for binding to the epitope with an antibody selected from the group consisting of 6)-13) below:
- 6) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 119, the HVR-H2 sequence of SEQ ID NO: 127, the HVR-H3 sequence of SEQ ID NO: 135, the HVR-L1 sequence of SEQ ID NO: 143, the HVR-L2 sequence of SEQ ID NO: 151, and the HVR-L3 sequence of SEQ ID NO: 159,
 - 7) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 120, the HVR-H2 sequence of SEQ ID NO: 128, the HVR-H3 sequence of SEQ ID NO: 136, the HVR-L1 sequence of SEQ ID NO: 144, the HVR-L2 sequence of SEQ ID NO: 152, and the HVR-L3 sequence of SEQ ID NO: 160,
 - 8) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 121, the HVR-H2 sequence of SEQ ID NO: 129, the HVR-H3 sequence of SEQ ID NO: 137, the HVR-L1 sequence of SEQ ID NO: 145, the HVR-L2 sequence of SEQ ID NO: 153, and the HVR-L3 sequence of SEQ ID NO: 161,
 - 9) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 122, the HVR-H2 sequence of SEQ ID NO: 130, the HVR-H3 sequence of SEQ ID NO: 138, the HVR-L1 sequence of SEQ ID NO: 146, the HVR-L2 sequence of SEQ ID NO: 154, and the HVR-L3 sequence of SEQ ID NO: 162,

10) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 123, the HVR-H2 sequence of SEQ ID NO: 131, the HVR-H3 sequence of SEQ ID NO: 139, the HVR-L1 sequence of SEQ ID NO: 147, the HVR-L2 sequence of SEQ ID NO: 155, and the HVR-L3 sequence of SEQ ID NO: 163,
 11) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 124, the HVR-H2 sequence of SEQ ID NO: 132, the HVR-H3 sequence of SEQ ID NO: 140, the HVR-L1 sequence of SEQ ID NO: 148, the HVR-L2 sequence of SEQ ID NO: 156, and the HVR-L3 sequence of SEQ ID NO: 164,
 12) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 125, the HVR-H2 sequence of SEQ ID NO: 133, the HVR-H3 sequence of SEQ ID NO: 141, the HVR-L1 sequence of SEQ ID NO: 149, the HVR-L2 sequence of SEQ ID NO: 157, and the HVR-L3 sequence of SEQ ID NO: 165, and
 13) an antibody comprising the HVR-H1 sequence of SEQ ID NO: 126, the HVR-H2 sequence of SEQ ID NO: 134, the HVR-H3 sequence of SEQ ID NO: 142, the HVR-L1 sequence of SEQ ID NO: 150, the HVR-L2 sequence of SEQ ID NO: 158, and the HVR-L3 sequence of SEQ ID NO: 166,
 wherein the antigen-binding activity of the antibody is lower at pH 5.8 than at pH 7.4,

wherein the antibody comprises an Fc region that has at least one amino acid modification in the region so as to enhance the reduction of plasma antigen concentration, and

wherein the Fc region is a human Fc region that has a binding activity selected from the following group consisting of:

- a) a binding activity to an activating Fc gamma receptor is stronger than the binding activity of an Fc region of the native human IgG1,
- b) a binding activity to an inhibitory Fc gamma receptor is stronger than to an activating Fc gamma receptor, and
- c) a binding activity to an FcRn at neutral pH is stronger than the binding activity of an Fc region of the native human IgG1.

[Claim 2] The antibody of claim 1, wherein the antibody binds to C1qrs complex on a chip for surface plasmon resonance assay and promotes dissociation of C1q from C1qrs complex, wherein a value of response unit (RU) in presence of the antibody is lower than a value of response unit (RU) in the absence of the antibody as determined by a surface plasmon resonance assay.

[Claim 3] The antibody of claim 2, wherein the time point of crossover in the surface plasmon resonance assay is within 1000s after the time point of the start of antibody injection as determined by the surface plasmon resonance assay using the following conditions: the capture levels of C1r2s2 complex and C1q are at 200 resonance unit (RU) and 200 resonance unit (RU), respectively, and the antibody as an analyte is injected at 500 nM at 10 microliter/min.

[Claim 4] The antibody of claim 2, wherein almost all of C1q are dissociated from C1qrs complex within 2000s after the time point of the start of antibody injection as determined by the surface plasmon resonance assay using the following conditions: the capture levels of C1r2s2 complex and C1q are at 200 resonance unit (RU) and 200 resonance unit (RU), respectively, and the antibody as an analyte is injected at 500 nM at 10 microliter/min.

- [Claim 5] The antibody of any one of claims 1 to 4, wherein the antibody has a neutralizing activity for human serum complement of at least 70% in a red blood cell assay.
- [Claim 6] The antibody of any one of claims 1-5, wherein the antibody binds to C1s or C1r with a lower affinity at acidic pH than at neutral pH as described in (i) or (ii) below:
- (i) when measured at a high calcium concentration at both neutral and acidic pH, the ratio of the KD value for C1s-binding activity at acidic pH to the KD value for C1s-binding activity at neutral pH ($KD(\text{acidic pH})/KD(\text{neutral pH})$) is 2 or more,
 - (ii) when measured at a high calcium concentration at neutral pH and at a low calcium concentration at acidic pH, the ratio of the KD value for C1s-binding activity at acidic pH to the KD value for C1s-binding activity at neutral pH ($KD(\text{acidic pH})/KD(\text{neutral pH})$) is 2 or more.
- [Claim 7] The antibody of any one of claims 1 to 6, wherein the antibody binds to both cynomolgus C1s and human C1s, or to both cynomolgus C1r and human C1r.
- [Claim 8] A pharmaceutical formulation comprising the antibody of any one of claims 1 to 7 and a pharmaceutically acceptable carrier.