

- [0005] HI532, an antibody which binds to the beta domain of C1s, was reported to be able inhibit the interaction of C1r2s2 with C1q (NPL 8). However, this antibody was not able to completely neutralize hemolytic activity of human serum and 30% of activity remained even after 24hrs incubation of serum with the antibody.
- [0006] Antibodies are highly attractive pharmaceuticals as they are stable in plasma, highly specific for their target, and generally exhibit good pharmacokinetic profiles. However, due to their large molecular size, the dosage of therapeutic antibodies is usually high. In the case of targets that exist in high abundance, the required therapeutic dose of antibodies is even higher. As a result, methods that improve antibody pharmacokinetics, pharmacodynamics, and antigen binding properties are attractive ways to reduce the dosage and high production costs associated with therapeutic antibodies.
- [0007] It has been reported that antibodies that bind to an antigen in a pH-dependent manner (herein below also referred to as "pH-dependent antibody" or "pH-dependent-binding antibody") enables a single antibody molecule to neutralize multiple antigen molecules (NPL 9, PTL 1). The pH-dependent antibody binds strongly to its antigen at neutral pH conditions in the plasma, but dissociates from the antigen under the acidic pH condition within the endosome of a cell. Once dissociated from the antigen, the antibody is recycled back to the plasma by FcRn receptors whereas the dissociated antigens are degraded within the lysosome of the cell. The recycled antibody is then free to bind to and neutralize antigen molecules again and this process continues to be repeated as long as the antibody remains in circulation.

Citation List

Patent Literature

- [0008] [PTL 1] WO2009/125825

Non Patent Literature

- [0009] [NPL 1] Wang et. al. Mol Cell. 2016 Jul 7;63(1):135-45
 [NPL 2] Mortensen et. al. Proc Natl Acad Sci U S A. 2017 Jan 31;114(5):986-991
 [NPL 3] Gal et. al. Mol Immunol. 2009 Sep;46(14):2745-52
 [NPL 4] Almitairi et. al. Proc Natl Acad Sci U S A. 2018 Jan 23;115(4):768-773
 [NPL 5] Bally et. al. J Biol Chem. 2009 Jul 17;284(29):19340-8
 [NPL 6] Rossi et. al. 1998 J Biol Chem. 1998 Jan 9;273(2):1232-9
 [NPL 7] Lacroix et. al. J Biol Chem. 2001 Sep 28;276(39):36233-40
 [NPL 8] Tseng et. al. Mol Immunol. 1997 Jun;34(8-9):671-9
 [NPL 9] Igawa et. al. Nat Biotechnol. 2010 Nov;28(11):1203-7

Summary of Invention

Technical Problem

- [0010] The ~~invention~~disclosure provides anti-complement component antibodies such as anti-C1s an-

tibodies and anti-C1r antibodies, and methods of using the same.

Solution to Problem

[0011] In some embodiment examples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present invention disclosure is an antibody having a displacement function such that the antibody binds to C1qrs complex and promotes dissociation of C1q from C1qrs complex.

[0011a] In one aspect, the present disclosure refers to 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.
- [0012] In some embodimentexamples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present inventiondisclosure is an antibody binding to C1qrs complex on a BIAcore (registered trademark) chip and promotes dissociation of C1q from C1qrs complex. In further embodimentexamples, the antibody of the present inventiondisclosure 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 embodimentexamples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present inventiondisclosure 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 embodimentexamples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present inventiondisclosure 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 ~~embodiment~~examples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present ~~invention~~disclosure is an antibody having a neutralizing activity for human serum complement of at least 70% in an RBC assay.
- [0016] In some ~~embodiment~~examples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present ~~invention~~disclosure is an antibody that specifically binds to C1s or an antibody that specifically binds to C1r.
- [0017] In some ~~embodiment~~examples, an isolated antibody that inhibits the interaction between C1q

and C1r2s2 complex of the present inventiondisclosure is an antibody specifically binding to an epitope within a CUB1-EGF-CUB2 domain of C1s. In further embodimentexamples, the antibody of the present inventiondisclosure 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.

[0018] In some embodimentexamples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present inventiondisclosure is an antibody specifically binding to an epitope within a CUB1-EGF-CUB2 domain of C1r. In further embodimentexamples, the antibody of the present inventiondisclosure 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.

[0019] In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody having the antigen-binding activity which varies depending on an ion concentration. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody having the C1s-binding activity which varies depending on an ion concentration. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody having the C1r-binding activity which varies depending on an ion concentration.

[0020] In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to the antigen with a higher affinity at neutral pH than at acidic pH. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to C1s with a higher affinity at neutral pH than at acidic pH. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction

- between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to C1r with a higher affinity at neutral pH than at acidic pH.
- [0021] In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to the antigen with a higher affinity under a high calcium concentration condition than under a low calcium concentration condition. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to C1s with a higher affinity under a high calcium concentration condition than under a low calcium concentration condition. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to C1r with a higher affinity under a high calcium concentration condition than under a low calcium concentration condition.
- [0022] In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to the antigen with a higher affinity both at neutral pH and under a high calcium concentration condition than both at acidic pH and under a low calcium concentration. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to C1s with a higher affinity both at neutral pH and under a high calcium concentration condition than both at acidic pH and under a low calcium concentration. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody binding to C1r with a higher affinity both at neutral pH and under a high calcium concentration condition than both at acidic pH and under a low calcium concentration.
- [0023] In some [embodimentexamples](#), in an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#), the ratio of the KD value for its C1s-binding activity at acidic pH to the KD value for the C1s-binding activity at neutral pH ($KD(\text{acidic pH})/KD(\text{neutral pH})$) is 2 or more when measured at a high calcium concentration at both neutral and acidic pH. In some [embodimentexamples](#), an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#), the ratio of the KD value for its C1r-binding activity at acidic pH to the KD value for the C1r-binding activity at neutral pH ($KD(\text{acidic pH})/KD(\text{neutral pH})$) is 2 or more when measured at a high calcium concentration at both neutral and acidic pH.
- [0024] In some [embodimentexamples](#), in an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#), the ratio of the KD value for its C1s-binding activity at acidic pH to the KD value for the C1s-binding activity at neutral pH ($KD(\text{acidic pH})/KD(\text{neutral pH})$) is 2 or more when measured at a low calcium concentration at both neutral and acidic pH, wherein the anti-C1s antibody

binds to the dimeric state of C1s. In some [embodimentexamples](#), in an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#), the ratio of the KD value for its C1r-binding activity at acidic pH to the KD value for the C1r-binding activity at neutral pH (KD(acidic pH)/KD(neutral pH)) is 2 or more when measured at a low calcium concentration at both neutral and acidic pH, wherein the anti-C1s antibody binds to the dimeric state of C1r.

[0025] In some [embodimentexamples](#), in an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#), the ratio of the KD value for its C1s-binding activity at acidic pH to the KD value for the C1s-binding activity at neutral pH (KD(acidic pH)/KD(neutral pH)) is 2 or more when measured at a high calcium concentration at neutral pH and under low calcium concentration at acidic pH. In some [embodimentexamples](#), in an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#), the ratio of the KD value for its C1r-binding activity at acidic pH to the KD value for the C1r-binding activity at neutral pH (KD(acidic pH)/KD(neutral pH)) is 2 or more when measured at a high calcium concentration at neutral pH and under low calcium concentration at acidic pH.

[0026] In some [embodimentexamples](#), an anti-C1s antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) comprises a histidine residue at one or more of the following Kabat numbering system positions;
Heavy chain: H26, H27, H28, H29, H30, H31, H32, H33, H34, H35, H50, H51, H52, H52a, H53, H54, H55, H57, H58, H59, H60, H61, H62, H63, H64, H65, H93, H94, H95, H96, H97, H98, H99, H100, H100a, H101, and H102; and
Light chain: L24, L25, L26, L27, L27a, L28, L29, L30, L31, L32, L33, L50, L51, L52, L53, L54, L55, L56 L91, L92, L93, L94, L95, L95a, L96, and L97.

[0027] In some [embodimentexamples](#), an anti-C1r antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) comprises a histidine residue at one or more of the following Kabat numbering system positions;

Heavy chain: H26, H27, H28, H29, H30, H31, H32, H33, H34, H35, H50, H51, H52, H52a, H53, H54, H55, H57, H58, H59, H60, H61, H62, H63, H64, H65, H93, H94, H95, H96, H97, H98, H99, H100, H100a, H101, and H102; and
Light chain: L24, L25, L26, L27, L27a, L28, L29, L30, L31, L32, L33, L50, L51, L52, L53, L54, L55, L56 L91, L92, L93, L94, L95, L95a, L96, and L97.

[0028] In some [embodimentexamples](#), an anti-C1s antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) comprises at least one histidine which is substituted at one or more of the following Kabat numbering system positions;

Heavy chain: H26, H27, H28, H29, H30, H31, H32, H33, H34, H35, H50, H51, H52, H52a, H53, H54, H55, H57, H58, H59, H60, H61, H62, H63, H64, H65, H93, H94, H95, H96, H97, H98, H99, H100, H100a, H101, and H102; and

Light chain: L24, L25, L26, L27, L27a, L28, L29, L30, L31, L32, L33, L50, L51, L52, L53, L54, L55, L56 L91, L92, L93, L94, L95, L95a, L96, and L97.

[0029] In some embodiment examples, an anti-C1r antibody that inhibits the interaction between C1q and C1r2s2 complex of the present invention disclosure comprises at least one histidine which is substituted at one or more of the following Kabat numbering system positions;

Heavy chain: H26, H27, H28, H29, H30, H31, H32, H33, H34, H35, H50, H51, H52, H52a, H53, H54, H55, H57, H58, H59, H60, H61, H62, H63, H64, H65, H93, H94, H95, H96, H97, H98, H99, H100, H100a, H101, and H102; and
Light chain: L24, L25, L26, L27, L27a, L28, L29, L30, L31, L32, L33, L50, L51, L52, L53, L54, L55, L56 L91, L92, L93, L94, L95, L95a, L96, and L97.

[0030] In further embodiment examples, an anti-C1s antibody with pH dependency that inhibits the interaction between C1q and C1r2s2 complex of the present invention disclosure competes at neutral pH condition for binding to C1s 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.

[0031] In further embodiment examples, an anti-C1r antibody with pH dependency that inhibits the interaction between C1q and C1r2s2 complex of the present invention disclosure competes at neutral pH condition for binding to C1r 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.

[0032] In some [embodimentexamples](#), the present disclosure provides an isolated anti-C1s antibody that specifically binds to an epitope within a region encompassing the CUB1-EGF-CUB2 domain (also called interaction domain or CUB domain) consisting of CUB1, EGF, and CUB2 of complement component 1s (C1s), which is also called 'CUB1-EGF-CUB2 domain of C1s' in this description. In some [embodimentexamples](#), the antibody does not bind to the CCP1-CCP2-SP domain (also called catalytic domain, or

CCP-SP domain) of C1s. In some [embodimentexamples](#), the epitope bound by an isolated anti-C1s antibody of the present disclosure is an epitope not located in beta domain of C1s. In some [embodimentexamples](#), the epitope bound by an isolated anti-C1s antibody of the present disclosure is an epitope located in alpha domain of C1s or gamma domain of C1s. In some [embodimentexamples](#), the epitope bound by an isolated anti-C1s antibody of the present disclosure is a linear epitope. In some [embodimentexamples](#), the epitope bound by an isolated anti-C1s antibody of the present disclosure is an epitope within amino acids 16-291 of the complement C1s protein, amino acids 16-172 of the complement C1s protein, amino acids 16-210 of the complement C1s protein, amino acids 16-111 of the complement C1s protein, amino acids 112-210 of the complement C1s protein, amino acids 131-172 of the complement C1s protein or amino acids 16-130 of the complement C1s protein. In some [embodimentexamples](#), the above-described epitope of C1s is an epitope of human C1s, or preferably an epitope of human C1s and an epitope of cynomolgus C1s.

[0033] In some [embodimentexamples](#), the present disclosure provides an isolated anti-C1r antibody that specifically binds to an epitope within a region encompassing the CUB1-EGF-CUB2 domain consisting of CUB1, EGF, and CUB2 of complement component 1r (C1r), which is also called 'CUB1-EGF-CUB2 domain of C1r' in this description. In some [embodimentexamples](#), the antibody does not bind to the CCP1-CCP2-SP domain (also called catalytic domain) of C1r. In some cases, the epitope bound by an isolated anti-C1r antibody of the present disclosure is a linear epitope or conformational epitope. In some [embodimentexamples](#), the above-described epitope of C1r is an epitope of human C1r, or preferably an epitope of human C1r and an epitope of cynomolgus C1r.

[0034] In some [embodimentexamples](#), an isolated anti-C1s antibody of the present [inventiondisclosure](#) comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 32, 38, 44, 50, or 56, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33, 39, 45, 51, or 57 and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 34, 40, 46, 52, or 58, wherein the antibody comprises human-derived or primate-derived framework regions. In some [embodimentexamples](#), an isolated anti-C1s antibody of the present [inventiondisclosure](#) comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35, 41, 47, 53, or 59; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36, 42, 48, 54, or 60; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37, 43, 49, 55, or 61, wherein the antibody comprises human-derived or primate-derived framework regions.

[0035] In some [embodimentexamples](#), an isolated anti-C1r antibody of the present [inventiondisclosure](#) comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 119, 120, 121, 122, 123, 124, 125, or 126, (b) HVR-H2 comprising the amino acid sequence of

SEQ ID NO: 127, 128, 129, 130, 131, 132, 133, or 134 and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 135, 136, 137, 138, 139, 140, 141, or 142, wherein the antibody comprises human-derived or primate-derived framework regions. In some embodimentexamples, an isolated anti-C1r antibody of the present inventiondisclosure comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 143, 144, 145, 146, 147, 148, 149, or 150; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 151, 152, 153, 154, 155, 156, 157, or 158; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 159, 160, 161, 162, 163, 164, 165, or 166, wherein the antibody comprises human-derived or primate-derived framework regions.

[0036] In some embodimentexamples, anti-C1s antibody of the present inventiondisclosure comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 19, 20, 21, 23, or 24; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 26, 27, 28, 30, or 31; or (c) a VH sequence of (a) and a VL sequence of (b). In some embodimentexamples, an anti-C1s antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 19, 20, 21, 23, or 24. In some embodimentexamples, an anti-C1s antibody of the present inventiondisclosure comprises a VL sequence of SEQ ID NO: 26, 27, 28, 30, or 31. In further embodimentexamples, an anti-C1s antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 19, 20, 21, 23, or 24 and a VL sequence of SEQ ID NO: 26, 27, 28, 30, or 31. In further embodimentexamples, an anti-C1s antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 19 and a VL sequence of SEQ ID NO: 26. In further embodimentexamples, an anti-C1s antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 20 and a VL sequence of SEQ ID NO: 27. In further embodimentexamples, an anti-C1s antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 21 and a VL sequence of SEQ ID NO: 28. In further embodimentexamples, an anti-C1s antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 23 and a VL sequence of SEQ ID NO: 30. In further embodimentexamples, an anti-C1s antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 24 and a VL sequence of SEQ ID NO: 31.

[0037] In some embodimentexamples, anti-C1r antibody of the present inventiondisclosure comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 103, 104, 105, 106, 107, 108, 109, or 110; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 111, 112, 113, 114, 115, 116, 117, or 118; or (c) a VH sequence of (a) and a VL sequence of (b). In some embodimentexamples, an anti-C1r antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 103, 104, 105, 106, 107, 108, 109, or 110. In some embodimentexamples, an anti-C1r antibody of the present inventiondisclosure comprises a VL sequence of SEQ ID NO: 111, 112, 113, 114, 115, 116, 117, or 118. In further embodimentexamples, an anti-C1r antibody of the present inventiondisclosure comprises a VH sequence of SEQ ID NO: 103, 104, 105, 106,

107, 108, 109, or 110 and a VL sequence of SEQ ID NO: 111, 112, 113, 114, 115, 116, 117, or 118. In further [embodimentexamples](#), an anti-C1r antibody of the present [inventiondisclosure](#) comprises a VH sequence of SEQ ID NO: 103 and a VL sequence of SEQ ID NO: 111. In further [embodimentexamples](#), an anti-C1r antibody of the present [inventiondisclosure](#) comprises a VH sequence of SEQ ID NO: 104 and a VL sequence of SEQ ID NO: 112. In further [embodimentexamples](#), an anti-C1r antibody of the present [inventiondisclosure](#) comprises a VH sequence of SEQ ID NO: 105 and a VL sequence of SEQ ID NO: 113. In further [embodimentexamples](#), an anti-C1r antibody of the present [inventiondisclosure](#) comprises a VH sequence of SEQ ID NO: 106 and a VL sequence of SEQ ID NO: 114. In further [embodimentexamples](#), an anti-C1r antibody of the present [inventiondisclosure](#) comprises a VH sequence of SEQ ID NO: 107 and a VL sequence of SEQ ID NO: 115. In further [embodimentexamples](#), an anti-C1r antibody of the present [inventiondisclosure](#) comprises a VH sequence of SEQ ID NO: 108 and a VL sequence of SEQ ID NO: 116. In further [embodimentexamples](#), an anti-C1r antibody of the present [inventiondisclosure](#) comprises a VH sequence of SEQ ID NO: 109 and a VL sequence of SEQ ID NO: 117. In further [embodimentexamples](#), an anti-C1r antibody of the present [inventiondisclosure](#) comprises a VH sequence of SEQ ID NO: 110 and a VL sequence of SEQ ID NO: 118.

[0038] In some [embodimentexamples](#), an anti-C1s antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is a monoclonal antibody. In some [embodimentexamples](#), an anti-C1s antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is a human, humanized, or chimeric antibody. In further [embodimentexamples](#), an anti-C1s antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is a full length IgG1, IgG2, IgG3 or IgG4 antibody. In further [embodimentexamples](#), an anti-C1s antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody fragment that binds to C1s. In some specific [embodimentexamples](#), an anti-C1s antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is a human IgG1 or humanized IgG1.

[0039] In some [embodimentexamples](#), an anti-C1r antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is a monoclonal antibody. In some [embodimentexamples](#), an anti-C1r antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is a human, humanized, or chimeric antibody. In further [embodimentexamples](#), an anti-C1r antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is a full length IgG1, IgG2, IgG3 or IgG4 antibody. In further [embodimentexamples](#), an anti-C1r antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is an antibody fragment that binds to C1r. In some specific [embodimentexamples](#), an anti-C1r antibody that inhibits the interaction between C1q and C1r2s2 complex of the present [inventiondisclosure](#) is a human IgG1 or humanized IgG1.

- [0040] In some embodimentexamples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present inventiondisclosure is an antibody comprising 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/or improve pharmacokinetics of the antibody.
- [0041] In some embodimentexamples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present inventiondisclosure has 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.
- [0042] In some embodimentexamples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present inventiondisclosure binds to at least human C1s or preferably to both cynomolgus C1s and human C1s. In some embodimentexamples, an isolated antibody that inhibits the interaction between C1q and C1r2s2 complex of the present inventiondisclosure binds to at least human C1r or preferably to both cynomolgus C1r and human C1r.
- [0043] The inventiondisclosure also provides isolated nucleic acids encoding an anti-C1s antibody of the present inventiondisclosure. The inventiondisclosure also provides isolated nucleic acids encoding an anti-C1r antibody of the present inventiondisclosure. The inventiondisclosure also provides host cells comprising a nucleic acid of the present inventiondisclosure. The inventiondisclosure also provides a method of producing an antibody comprising culturing a host cell of the present inventiondisclosure so that the antibody is produced.
- [0044] In another aspect, the inventionpresent disclosure also provides a pharmaceutical formulation comprising the antibody of the present inventiondisclosure and a pharmaceutically acceptable carrier.
- [0045] Anti-C1s antibodies of the present inventiondisclosure may be for use as a medicament. Anti-C1s antibodies of the present inventiondisclosure may be for use in treating or preventing a complement-mediated disease or disorder. Anti-C1s antibodies of the present inventiondisclosure may be for use in enhancing the clearance of (or removing) C1s from plasma. Anti-C1s antibodies of the present inventiondisclosure may be for use in enhancing the clearance of (or removing) C1r2s2 from plasma. Anti-C1s antibodies of the present inventiondisclosure may be for use in enhancing the clearance of (or removing) C1r2s2 from plasma but not C1q from plasma. In some cases, the antibody inhibits a component of the classical complement pathway; in some cases, the classical complement pathway component is C1s.
- [0046] Anti-C1r antibodies of the present inventiondisclosure may be for use as a medicament. Anti-

C1r antibodies of the present invention may be for use in treating or preventing a complement-mediated disease or disorder. Anti-C1r antibodies of the present invention may be for use in enhancing the clearance of (or removing) C1r from plasma. Anti-C1r antibodies of the present invention may be for use in enhancing the clearance of (or removing) C1r2s2 from plasma. Anti-C1r antibodies of the present invention may be for use in enhancing the clearance of (or removing) C1r2s2 from plasma but not C1q from plasma. In some cases, the antibody inhibits a component of the classical complement pathway; in some cases, the classical complement pathway component is C1r.

[0047] Anti-C1s antibodies of the present invention may be used in the manufacture of a medicament. In some embodiments, the medicament is for treatment or prevention of a complement-mediated disease or disorder. In some embodiments, the medicament is for enhancing the clearance of (or removing) C1s from plasma. In some embodiments, the medicament is for enhancing the clearance of (or removing) C1r2s2 from plasma. In some embodiments, the medicament is for enhancing the clearance of (or removing) C1r2s2 from plasma but not C1q from plasma. In this context, the level of the enhancement of C1q clearance from plasma is not necessarily null (zero). That is, the level of the enhancement of C1q clearance from plasma may be zero, or may not be zero but near zero, or may be non-significant or very low enough to be technically neglected by those skilled in the art. In some cases, the medicament inhibits a component of the classical complement pathway; in some cases, the classical complement pathway component is C1s.

[0048] The enhancement of C1s/C1q clearance (CL) can be measured, for example, as follows.

The total concentrations of human C1s and C1q in mouse plasma are measured by LC/ESI-MS/MS. The calibration standards are prepared by mixing and diluting human C1s and C1q in defined amounts in mouse plasma, resulting in human C1s concentrations of 0.477, 0.954, 1.91, 3.82, 7.64, 15.3, 30.5 micrograms (micro g)/mL and human C1q concentrations of 0.977, 1.95, 3.91, 7.81, 15.6, 31.3 and 62.5 micro g/mL, respectively. A 2 micro L of the calibration standards and plasma samples is mixed with 25 micro L of 6.8 mol/L Urea, 9.1 mmol/L dithiothreitol and 0.4 micro g/mL lysozyme (chicken egg white) in 50 mmol/L ammonium bicarbonate and incubated for 45 min at 56 degrees C. Then, 2 micro L of 500 mmol/L iodoacetamide is added and incubated for 30 min at 37 degrees C in the dark. Next, 160 micro L of 0.5 micro g/mL sequencing grade modified trypsin (Promega) in 50 mmol/L ammonium bicarbonate is added and incubated at 37 degrees C overnight. Finally, 5 micro L of 10% trifluoroacetic acid is added to deactivate any residual trypsin. A 40 micro L of digestion samples are subjected to analysis by LC/ESI-MS/MS. LC/ESI-MS/MS is performed

using Xevo TQ-S triple quadrupole instrument (Waters) equipped with 2D I-class UPLC (Waters). Human C1s specific peptide LLEVPEGR and human C1q specific peptide IAFSATR are monitored by the selected reaction monitoring (SRM). SRM transition is $[M+2H]^{2+}$ (m/z 456.8) to y_6 ion (m/z 686.3) for human C1s, and $[M+2H]^{2+}$ (m/z 383.2) to y_5 ion (m/z 581.3) for human C1q. Calibration curve is constructed by the weighted ($1/x^2$) linear regression using the peak area plotted against the concentrations. The concentration in mouse plasma is calculated from the calibration curve using the analytical software Masslynx Ver.4.1 (Waters).

Pharmacokinetics for total hC1s and hC1q after administration of anti-C1s antibodies in mice is evaluated as follows.

The in vivo pharmacokinetics of hC1s, hC1q and anti-C1s antibodies is assessed after administering antigen alone (hC1q, recombinant C1r2s2, mixture of hC1q and rC1r2s2) or with anti-C1s antibody to mice (CB17/Icr-Prkdcscid/Cr1Cr1; Charles River Japan). Three mice are allocated to each dosing group.

Firstly, hC1q solution (0.84 mg/mL), rC1r2s2 (0.47 mg/mL) or a solution of mixture containing hC1q and rC1r2s2 (0.84 and 0.47 mg/mL, respectively) is injected at a dose of 10 mL/kg to mice intravenously. After dosing of antigen solution, anti-C1s antibody solution (2.5 mg/mL) is immediately administered to the same individual in the same way.

The dose setting of C1q and rC1r2s2 is designed to be physiological concentration in human plasma just after administration. Dosage of anti-C1s antibody is adjusted to be excess concentration over both antigens during the study, and thus almost all hC1s is assumed to be bound form in circulation. Blood is collected at 5, 30 minutes, 2, 7 hours, 3, 7, 14, 21 and 28 days after injection. The blood is centrifuged immediately to separate the plasma samples. Plasma concentrations of hC1s and hC1q are measured at each sampling points by LC/ESI-MS/MS. PK parameters of hC1s and hC1q are estimated by non-compartmental analysis (Phoenix WinNonlin version 8.0, Certara).

Mice are administered with an antibody with (i) an Fc containing mutations to reduce both C1q and Fc gamma receptor binding, or (ii) an Fc containing mutation to reduce C1q binding while retaining Fc gamma receptor binding. For example, in the present [inventiondisclosure](#), Fc of "SG136" contains mutations to reduce both C1q and Fc gamma receptor binding, while Fc of "SG1148" contains mutation to reduce C1q binding while retaining Fc gamma receptor binding.

The above mice PK study is conducted for a test antibody (e.g., CCP1-CCP2-SP or CUB1-EGF-CUB2 binder), and PK parameters of hC1q and hC1s are calculated. Then, C1s CL ratio (SG1148/SG136) of the binder or C1q CL ratio (SG1148/SG136) of the binder can be evaluated. In some [embodimentexamples](#), the C1q CL ratio of the antibody of the

present inventiondisclosure is 1.8 or less, 1.7 or less, 1.6 or less, 1.5 or less, 1.4 or less, 1.3 or less, 1.2 or less, 1.1 or less, 1.0 or less.

Anti-C1r antibodies of the present inventiondisclosure may be used in the manufacture of a medicament. In some embodimentexamples, the medicament is for treatment or prevention of a complement-mediated disease or disorder. In some embodimentexamples, the medicament is for enhancing the clearance of (or removing) C1r from plasma. In some embodimentexamples, the medicament is for enhancing the clearance of (or removing) C1r2s2 from plasma. In some embodimentexamples, the medicament is for enhancing the clearance of (or removing) C1r2s2 from plasma but not C1q from plasma. In some cases, the medicament inhibits a component of the classical complement pathway; in some cases, the classical complement pathway component is C1r.

[0049] The inventiondisclosure also provides a method of treating or preventing an individual having a complement-mediated disease or disorder. In some embodimentexamples, the method comprises administering to the individual an effective amount of an anti-C1s antibody of the present inventiondisclosure. The inventiondisclosure also provides a method of enhancing the clearance of (or removing) C1s from plasma in an individual. In some embodimentexamples, the method comprises administering to the individual an effective amount of an anti-C1s antibody of the present inventiondisclosure to enhance the clearance of (or remove) C1s from plasma. The inventiondisclosure also provides a method of enhancing the clearance of (or removing) C1r2s2 from plasma in an individual. The inventiondisclosure also provides a method of enhancing the clearance of (or removing) C1r2s2 from plasma not but C1q from plasma in an individual. In some embodimentexamples, the method comprises administering to the individual an effective amount of an anti-C1s antibody of the present inventiondisclosure to enhance the clearance of (or remove) C1r2s2 from plasma. In some embodimentexamples, the method comprises administering to the individual an effective amount of an anti-C1s antibody of the present inventiondisclosure to enhance the clearance of (or remove) C1r2s2 from plasma not but C1q from plasma. In some cases, the antibody inhibits a component of the classical complement pathway; in some cases, the classical complement pathway component is C1s.

[0050] The inventiondisclosure also provides a method of treating or preventing an individual having a complement-mediated disease or disorder. In some embodimentexamples, the method comprises administering to the individual an effective amount of an anti-C1r antibody of the present inventiondisclosure. The inventiondisclosure also provides a method of enhancing the clearance of (or removing) C1r from plasma in an individual. In some embodimentexamples, the method comprises administering to the individual an effective amount of an anti-C1r antibody of the present inventiondisclosure to enhance the clearance of (or remove) C1r from plasma. The inventiondisclosure also provides a method of enhancing the clearance of (or removing) C1r2s2 from plasma in an individual. The inventiondisclosure also provides a method

of enhancing the clearance of (or removing) C1r2s2 from plasma not but C1q from plasma in an individual. In some ~~embodiment~~examples, the method comprises administering to the individual an effective amount of an anti-C1r antibody of the present ~~invention~~disclosure to enhance the clearance of (or remove) C1r2s2 from plasma. In some ~~embodiment~~examples, the method comprises administering to the individual an effective amount of an anti-C1r antibody of the present ~~invention~~disclosure to enhance the clearance of (or remove) C1r2s2 from plasma not but C1q from plasma. In some cases, the antibody inhibits a component of the classical complement pathway; in some cases, the classical complement pathway component is C1r.

[0051] More specifically, the present ~~invention~~disclosure provides the following:

[1] An isolated antibody that inhibits the interaction between C1q and C1r2s2 complex, wherein the antibody has a displacement function such that the antibody binds to C1qrs complex and promotes dissociation of C1q from C1qrs complex.

[2] The antibody of [1], wherein the antibody binds to C1qrs complex on a Biacore chip 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 Biacore assay when a sufficient time passed.

[3] The antibody of [2], wherein the time point of crossover in the Biacore assay is within 60s, 100s, 150s, 200s, 500s, 700s, or 1000s after the time point of the start of antibody injection as determined by the Biacore 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.

[4] The antibody of [2], wherein almost all of C1q are dissociated from C1qrs complex within 100s, 300s, 500s, 700s, 1000s, 1500s or 2000s after the time point of the start of antibody injection as determined by the Biacore 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.

[5] An isolated antibody that inhibits the interaction between C1q and C1r2s2 complex, wherein the antibody has a neutralizing activity for human serum complement of at least 70% in an RBC assay.

[6] The antibody of any one of [1] to [5], wherein the antibody is an antibody that specifically binds to C1s or an antibody that specifically binds to C1r.

[7] 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

Claims

~~[Claim 1] An isolated antibody that inhibits the interaction between C1q and C1r2s2 complex, wherein the antibody has a displacement function such that the antibody binds to C1qrs complex and promotes dissociation of C1q from C1qrs complex.~~

[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.

- [Claim 2] The antibody of claim 1, wherein the antibody binds to C1qrs complex on a BIACORE (registered trademark)-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 BIACORE (registered trademark)-surface plasmon resonance assay ~~when a sufficient time passed.~~
- [Claim 3] The antibody of claim 2, wherein the time point of crossover in the surface plasmon resonance BIACORE (registered trademark) assay is within 1000s after the time point of the start of antibody injection as determined by the surface plasmon resonance 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/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 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/min.
- [Claim 5] ~~An isolated antibody that inhibits the interaction between C1q and C1r2s2 complex~~ 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 ~~an~~ RBCa red blood cell assay.
- ~~[Claim 6] The antibody of any one of claims 1 to 5, wherein the antibody is an antibody that specifically binds to C1s or an antibody that specifically binds to C1r.~~

[Claim 7] 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.

- [Claim ~~86~~] An isolated antibody that inhibits the interaction between C1q and C1r2s2 complex. The antibody of any one of claims 1 to 5, wherein the antigen-binding activity of the antibody is lower at pH 5.8 than at pH 7.4.
- [Claim 9] The antibody of any one of claims 1 to 8, wherein the antibody specifically binds to an epitope within a CUB1-EGF-CUB2 domain of C1s or C1r, wherein the antigen-binding activity of the antibody is lower at pH 5.8 than at pH 7.4.
- [Claim ~~107~~] The antibody of claim ~~96~~, 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(acidic pH)/KD(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(acidic pH)/KD(neutral pH)) is 2 or more.
- [Claim ~~118~~] The antibody of ~~any one of claims 8 to 10~~ claim 6 or 7, 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/or improve pharmacokinetics of the antibody.
- [Claim ~~129~~] The antibody of claim ~~118~~, wherein the antibody enhances the reduction of plasma antigen concentration, 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 ~~1310~~] The antibody of any one of claims 1 to ~~129~~, wherein the antibody binds to both cynomolgus C1s and human C1s, or to both cynomolgus C1r and human C1r.

[Claim ~~14~~11] A pharmaceutical formulation comprising the antibody of any one of claims 1 to ~~13~~10 and a pharmaceutically acceptable carrier.

~~[Claim 15] A method of treating an individual having a complement-mediated disease or disorder comprising administering to the individual an effective amount of the antibody of any one of claims 1 to 13.~~