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Non-Patent Literature

[0019] NPL 1: Holers et al., Immunol. Rev. 223:300-316 (2008)

NPL 2: Dmytrijuk et al., The Oncologist 13(9):993-1000 (2008)

NPL 3: Yeung et al., J Immunol. 182(12): 7663-7671 (2009)

NPL 4: Datta-Mannan et al., J Biol. Chem. 282(3):1709-1717 (2007)

NPL 5: Dall'Acqua et al., J. Immunol. 169(9):5171-5180 (2002)

Summary of Invention

Technical Problem

[0020] An objective of the invention is to provide anti-CS antibodies and methods of using the same.

Solution to Problem

[0021] The invention provides anti-CS antibodies and methods of using the same.

[0022] In one aspect, the present invention refers to an anti-C5 antibody comprising: (a) a VH sequence of SEQ ID NO: 106 and a VL sequence of SEQ ID NO: 111; (b) a VH sequence of SEQ ID NO: 107 and a VL sequence of SEQ ID NO: 111; (c) a VH sequence of SEQ ID NO: 108 and a VL sequence of SEQ ID NO: 111; (d) a VH sequence of SEQ ID NO: 109 and a VL sequence of SEQ ID NO: 111; (e) a VH sequence of SEQ ID NO: 109 and a VL sequence of SEQ ID NO: 112; (f) a VH sequence of SEQ ID NO: 109 and a VL sequence of SEQ ID NO: 113; or (g) a VH sequence of SEQ ID NO: 110 and a VL sequence of SEQ ID NO: 113. In another aspect, the present invention refers to an isolated nucleic acid encoding the antibody as described herein. In another aspect, the present invention refers to a host cell comprising the nucleic acid as described herein. In another aspect, the present invention refers to method of producing an antibody comprising culturing the host cell as described herein so that the antibody is produced. In another aspect, the present invention refers to a pharmaceutical formulation comprising the antibody as described herein and a pharmaceutically acceptable carrier. In some embodiments, an isolated anti-C5 antibody of the present invention-disclosure binds to an epitope within the beta chain of C5. In some embodiments, an isolated anti-CS antibody of the present invention-disclosure binds to an epitope within the MG1-MG2 domain of the beta chain of C5. In some embodiments, an isolated anti-CS antibody of the present

~~invention-disclosure~~ binds to an epitope within a fragment consisting of amino acids 33-124 of the beta chain (SEQ ID NO: 40) of C5. In some ~~embodiments~~examples, an isolated anti-C5 antibody of the present ~~invention-disclosure~~ binds to an epitope within the beta chain (SEQ ID NO: 40) of C5 which comprises at least one fragment selected from the group consisting of amino acids 47-57, 70-76, and 107-110. In some ~~embodiments~~examples, an isolated anti-C5 antibody of the present ~~invention-disclosure~~ binds to an epitope within a fragment of the beta chain (SEQ ID NO: 40) of C5 which comprises at least one amino acid residue selected from the group consisting of Glu48, Asp51, His70, His72, Lys109, and His110 of SEQ ID NO: 40. In further ~~embodiments~~examples, the antibody binds to C5 with a higher affinity at neutral pH than at acidic pH. In further ~~embodiments~~examples, the antibody binds to C5 with a higher affinity at pH7.4 than at pH5.8. In another ~~embodiment~~example, an isolated anti-C5 antibody of the present ~~invention-disclosure~~ binds to the same epitope as an antibody described in Table 2. In further ~~embodiments~~examples, the antibody binds to the same epitope as an antibody described in Table 2 with a higher affinity at

pH7.4 than at pH5.8. In a further ~~embodiment~~example, the anti-C5 antibody of the present ~~invention~~disclosure binds to the same epitope as an antibody described in Tables 7 or 8.

In further ~~embodiment~~examples, the antibody binds to the same epitope as an antibody described in Tables 7 or 8 with a higher affinity at pH7.4 than at pH5.8.

[0023] In certain ~~embodiment~~examples, an anti-C5 antibody of the present ~~invention~~disclosure competes for binding C5 with an antibody comprising a VH and VL pair selected from: (a) a VH of SEQ ID NO:1 and a VL of SEQ ID NO:11; (b) a VH of SEQ ID NO: 5 and a VL of SEQ ID NO:15; (c) a VH of SEQ ID NO:4 and a VL of SEQ ID NO:14; (d) a VH of SEQ ID NO: 6 and a VL of SEQ ID NO: 16; (e) a VH of SEQ ID NO:2 and a VL of SEQ ID NO:12; (f) a VH of SEQ ID NO: 3 and a VL of SEQ ID NO: 13; (g) a VH of SEQ ID NO:9 and a VL of SEQ ID NO:19; (h) a VH of SEQ ID NO:7 and a VL of SEQ ID NO: 17; (i) a VH of SEQ ID NO:8 and a VL of SEQ ID NO:18; and (j) a VH of SEQ ID NO:10 and a VL of SEQ ID NO:20. In further ~~embodiment~~examples, the anti-C5 antibody binds to C5 with a higher affinity at neutral pH than at acidic pH. In further ~~embodiment~~examples, the anti-C5 antibody binds to C5 with a higher affinity at pH7.4 than at pH5.8.

[0024] In some ~~embodiment~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure has a characteristic selected from the group consisting of: (a) the antibody contacts amino acids D51 and K109 of C5 (SEQ ID NO:39); (b) the affinity of the antibody for C5 (SEQ ID NO:39) is greater than the affinity of the antibody for a C5 mutant consisting of an E48A substitution of SEQ ID NO:39; or (c) the antibody binds to a C5 protein consisting of the amino acid sequence of SEQ ID NO:39 at pH7.4, but does not bind to a C5 protein consisting of the amino acid sequence of SEQ ID NO:39 with a H72Y substitution at pH7.4. In further ~~embodiment~~examples, the antibody binds to C5 with a higher affinity at neutral pH than at acidic pH. In further ~~embodiment~~examples, the antibody binds to C5 with a higher affinity at pH7.4 than at pH5.8.

[0025] In some ~~embodiment~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure inhibits activation of C5. In some ~~embodiment~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure inhibits activation of C5 variant R885H. In some ~~embodiment~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure is a monoclonal antibody. In some ~~embodiment~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure is a human, humanized, or chimeric antibody. In some ~~embodiment~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure is an antibody fragment that binds to C5. In some ~~embodiment~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure is a full length IgG1 or IgG4 antibody.

[0026] In some ~~embodiment~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure comprises (a) a HVR-H3 comprising the amino acid sequence DX₁GYX₂X₃PTHAMX₄X₅, wherein X₁ is G or A, X₂ is V, Q or D, X₃ is T or Y, X₄ is Y or H, X₅ is L or Y

(SEQ ID NO: 128), (b) a HVR-L3 comprising the amino acid sequence $QX_1TX_2VGSSYGNX_3$, wherein X_1 is S, C, N or T, X_2 is F or K, X_3 is A, T or H (SEQ ID NO: 131), and (c) a HVR-H2 comprising the amino acid sequence $X_1IX_2TGSGAX_3YX_4AX_5WX_6KG$, wherein X_1 is C, A or G, X_2 is Y or F, X_3 is T, D or E, X_4 is Y, K or Q, X_5 is S, D or E, X_6 is A or V (SEQ ID NO: 127).

[0027] In some ~~embodiments~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure comprises (a) a HVR-H1 comprising the amino acid sequence $SSYYX_1X_2$, wherein X_1 is M or V, X_2 is C or A (SEQ ID NO: 126), (b) a HVR-H2 comprising the amino acid sequence $X_1IX_2TGSGAX_3YX_4AX_5WX_6KG$, wherein X_1 is C, A or G, X_2 is Y or F, X_3 is T, D or E, X_4 is Y, K or Q, X_5 is S, D or E, X_6 is A or V (SEQ ID NO: 127), and (c) a HVR-H3 comprising the amino acid sequence $DX_1GYX_2X_3PTHAMX_4X_5$, wherein X_1 is G or A, X_2 is V, Q or D, X_3 is T or Y, X_4 is Y or H, X_5 is L or Y (SEQ ID NO: 128). In further ~~embodiments~~examples, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence $X_1ASQX_2IX_3SX_4LA$, wherein X_1 is Q or R, X_2 is N, Q or G, X_3 is G or S, X_4 is D, K or S (SEQ ID NO: 129); (b) a HVR-L2 comprising the amino acid sequence $GASX_1X_2X_3S$, wherein X_1 is K, E or T, X_2 is L or T, X_3 is A, H, E or Q (SEQ ID NO: 130); and (c) a HVR-L3 comprising the amino acid sequence $QX_1TX_2VGSSYGNX_3$, wherein X_1 is S, C, N or T, X_2 is F or K, X_3 is A, T or H (SEQ ID NO: 131).

[0028] In some ~~embodiments~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure comprises (a) a HVR-L1 comprising the amino acid sequence $X_1ASQX_2IX_3SX_4LA$, wherein X_1 is Q or R, X_2 is N, Q or G, X_3 is G or S, X_4 is D, K or S (SEQ ID NO: 129); (b) a HVR-L2 comprising the amino acid sequence $GASX_1X_2X_3S$, wherein X_1 is K, E or T, X_2 is L or T, X_3 is A, H, E or Q (SEQ ID NO: 130); and (c) a HVR-L3 comprising the amino acid sequence $QX_1TX_2VGSSYGNX_3$, wherein X_1 is S, C, N or T, X_2 is F or K, X_3 is A, T or H (SEQ ID NO: 131).

[0029] In some ~~embodiments~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure comprises a heavy chain variable domain framework FR1 comprising the amino acid sequence of any one of SEQ ID NOs: 132-134; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 135-136; FR3 comprising the amino acid sequence of any one of SEQ ID NOs: 137-139; and FR4 comprising the amino acid sequence of any one of SEQ ID NOs: 140-141. In some ~~embodiments~~examples, an isolated anti-C5 antibody of the present ~~invention~~disclosure comprises a light chain variable domain framework FR1 comprising the amino acid sequence of any one of SEQ ID NOs: 142-143; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 144-145; FR3 comprising the amino acid sequence of any one of SEQ ID NOs: 146-147; and FR4 comprising the amino acid sequence of SEQ ID NO: 148.

[0030] In some ~~embodiments~~examples, an isolated anti-05 antibody of the present ~~invention~~disclosure

comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 10, 106-110; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 20, 111-113; or (c) a VH sequence as in (a) and a VL sequence as in (b). In further ~~embodimentsexamples~~, the antibody comprises a VH sequence of any one of SEQ ID NOs: 10, 106-110. In further ~~embodimentsexamples~~, the antibody comprises a VL sequence of any one of SEQ ID NOs: 20, 111-113.

[0031] The ~~invention-disclosure~~ provides an antibody comprising a VH sequence of any one of SEQ ID NOs: 10, 106-110 and a VL sequence of any one of SEQ ID NOs: 20, 111-113.

[0032] The ~~invention-disclosure~~ also provides isolated nucleic acids encoding an anti-C5 antibody of the present ~~invention-disclosure~~. The ~~invention-disclosure~~ also provides host cells comprising a nucleic acid of the present ~~invention-disclosure~~. The ~~invention-disclosure~~ also provides a method of producing an antibody comprising culturing a host cell of the present ~~invention-disclosure~~ so that the antibody is produced.

[0033] The ~~invention-disclosure~~ further provides a method of producing an anti-C5 antibody. In some ~~embodimentsexamples~~, the method comprises immunizing an animal against a polypeptide which comprises the MG1-MG2 domain (SEQ ID NO: 43) of the beta chain of C5. In some ~~embodimentsexamples~~, the method comprises immunizing an animal against a polypeptide which comprises the region corresponding to amino acids at positions 33 to 124 of the beta chain (SEQ ID NO: 40) of C5. In some ~~embodimentsexamples~~, the method comprises immunizing an animal against a polypeptide which comprises at least one fragment selected from amino acids 47-57, 70-76, and 107-110 of the beta chain (SEQ ID NO: 40) of C5. In some ~~embodimentsexamples~~, the method comprises immunizing an animal against a polypeptide which comprises a fragment of the beta chain (SEQ ID NO: 40) of C5, which comprises at least one amino acid selected from Glu48, Asp51, His70, His72, Lys109, and His110.

[0034] The ~~invention-disclosure~~ also provides a pharmaceutical formulation comprising an anti-C5 antibody of the present ~~invention-disclosure~~ and a pharmaceutically acceptable carrier.

[0035] Anti-C5 antibodies of the present ~~invention-disclosure~~ may be for use as a medicament. Anti-C5 antibodies of the present ~~invention-disclosure~~ may be for use in treating a complement-mediated disease or condition which involves excessive or uncontrolled activation of C5. Anti-C5 antibodies of the present ~~invention-disclosure~~ may be for use in enhancing the clearance of C5 from plasma.

[0036] Anti-CS antibodies of the present ~~invention-disclosure~~ may be used in the manufacture of a medicament. In some ~~embodimentsexamples~~, the medicament is for treatment of a complement-mediated disease or condition which involves excessive or uncontrolled activation of C5. In some ~~embodimentsexamples~~, the medicament is for enhancing the clearance of C5 from plasma.

[0037] The ~~invention-disclosure~~ also provides a method of treating an individual having a complement-mediated disease or condition which involves excessive or uncontrolled activation of C5. In some ~~embodiments~~examples, the method comprises administering to the individual an effective amount of an anti-C5 antibody of the present ~~invention-disclosure~~. The ~~invention-disclosure~~ also provides a method of enhancing the clearance of C5 from plasma in an individual. In some ~~embodiments~~examples, the method comprises administering to the individual an effective amount of an anti-C5 antibody of the present ~~invention-disclosure~~ to enhance the clearance of C5 from plasma.

Brief Description of Drawings

[0038] [fig.1] Figure 1 illustrates epitope binning of anti-05 antibodies, as described in Example 2.2. Antibodies grouped into the same epitope bin are boxed with a thick line.

[fig.2A] Figure 2A illustrates BIACORE (registered trademark) sensorgrams of anti-05 antibodies at pH7.4 (solid line) and pH5.8 (dashed line) to assess pH-dependency, as described in Example 3.2. CFA0305, CFA0307, CFA0366, CFA0501, CFA0538, and CFA0599 are antibodies grouped into epitope C, as described in Example 2.2.

[fig.2B] Figure 2B illustrates BIACORE (registered trademark) sensorgrams of anti-05 antibodies at pH7.4 (solid line) and pH5.8 (dashed line) to assess pH-dependency, as described in Example 3.2. CFA0666, CFA0672, and CFA0675 are antibodies grouped into epitope C, and CFA0330 and CFA0341 are antibodies grouped into epitope B, as described in Example 2.2. 305L05 is a humanized antibody of CFA0305, as described in Example 2.3.

[fig.3] Figure 3 illustrates Western Blot analysis against C5 beta-chain-derived fragments (amino acids 19-180, 161-340, 321-500, and 481-660 of SEQ ID NO:40) fused to GST-tag, as described in Example 4.1. CFA0305, CFA0307, CFA0366, CFA0501, CFA0538, CFA0599, CFA0666, CFA0672, and CFA0675 are antibodies grouped into epitope C. Anti-GST antibody is a positive control. The position of the GST-fused C5 fragments (46-49 kDa) is marked with an arrow.

[fig.4] Figure 4 illustrates BIACORE (registered trademark) sensorgrams of anti-05 antibodies towards MG1-MG2 domain of C5 beta-chain, as described in Example 4.3. The upper panel shows the results of CFA0305 (solid line), CFA0307 (dashed line), CFA0366 (dash-dot line), and eculizumab (dotted line). The middle panel shows the results of CFA0501 (solid line), CFA0599 (dashed line), CFA0538 (dash-dot line), and eculizumab (dotted line). The lower panel shows the results of CFA0666 (solid line), CFA0672 (dashed line), CFA0675 (dash-dot line), and eculizumab (dotted line). CFA0305, CFA0307, CFA0366, CFA0501, CFA0538, CFA0599, CFA0666, CFA0672, and CFA0675 are antibodies grouped into epitope C. Eculizumab is a control anti-05 antibody.

Claims

[Claim 1]

An anti-C5 antibody comprising:

- (a) a VH sequence of SEQ ID NO: 106 and a VL sequence of SEQ ID NO: 111;
- (b) a VH sequence of SEQ ID NO: 107 and a VL sequence of SEQ ID NO: 111;
- (c) a VH sequence of SEQ ID NO: 108 and a VL sequence of SEQ ID NO: 111;
- (d) a VH sequence of SEQ ID NO: 109 and a VL sequence of SEQ ID NO: 111;
- (e) a VH sequence of SEQ ID NO: 109 and a VL sequence of SEQ ID NO: 112;
- (f) a VH sequence of SEQ ID NO: 109 and a VL sequence of SEQ ID NO: 113; or
- (g) a VH sequence of SEQ ID NO: 110 and a VL sequence of SEQ ID NO: 113.

[Claim 2]

The antibody of claim 1, which comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 114, and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 38.

[Claim 3]

The antibody of any one of claims 1 to 2, which is a full length IgG1 or IgG4 antibody.

[Claim 4]

An isolated nucleic acid encoding the antibody of any one of claims 1 to 3.

[Claim 5]

A host cell comprising the nucleic acid of claim 4.

[Claim 6]

A method of producing an antibody comprising culturing the host cell of claim 5 so that the antibody is produced.

[Claim 7]

A pharmaceutical formulation comprising the antibody of any one of claims 1 to 3 and a pharmaceutically acceptable carrier.

Claims

- [Claim 1] An isolated antibody that binds to C5, wherein the antibody comprises (a) a HVR-H3 comprising the amino acid sequence $DX_1GYX_2X_3$ PTHAMX₄X₅, wherein X₁ is G or A, X₂ is V, Q or D, X₃ is T or Y, X₄ is Y or H, X₅ is L or Y (SEQ ID NO: 128), (b) a HVR-L3 comprising the amino acid sequence $QX_1TX_2VGSSYGNX_3$, wherein X₁ is S, C, N or T, X₂ is F or K, X₃ is A, T or H (SEQ ID NO: 131), and (c) a HVR-H2 comprising the amino acid sequence $X_1IX_2TGSGAX_3YX_4AX_5WX_6$ KG, wherein X₁ is C, A or G, X₂ is Y or F, X₃ is T, D or E, X₄ is Y, K or Q, X₅ is S, D or E, X₆ is A or V (SEQ ID NO: 127).
- [Claim 2] An isolated antibody that binds to C5, wherein the antibody comprises (a) a HVR-H1 comprising the amino acid sequence $SSYYX_1X_2$, wherein X₁ is M or V, X₂ is C or A (SEQ ID NO: 126), (b) a HVR-H2 comprising the amino acid sequence $X_1IX_2TGSGAX_3YX_4AX_5WX_6$ KG, wherein X₁ is C, A or G, X₂ is Y or F, X₃ is T, D or E, X₄ is Y, K or Q, X₅ is S, D or E, X₆ is A or V (SEQ ID NO: 127), and (c) a HVR-H3 comprising the amino acid sequence $DX_1GYX_2X_3$ PTHAMX₄X₅, wherein X₁ is G or A, X₂ is V, Q or D, X₃ is T or Y, X₄ is Y or H, X₅ is L or Y (SEQ ID NO: 128).
- [Claim 3] The antibody of claim 2, further comprising (a) a HVR-L1 comprising the amino acid sequence $X_1ASQX_2IX_3SX_4LA$, wherein X₁ is Q or R, X₂ is N, Q or G, X₃ is G or S, X₄ is D, K or S (SEQ ID NO: 129); (b) a HVR-L2 comprising the amino acid sequence $GASX_1X_2X_3S$, wherein X₁ is K, E or T, X₂ is L or T, X₃ is A, H, E or Q (SEQ ID NO: 130); and (c) a HVR-L3 comprising the amino acid sequence $QX_1TX_2VGSSYGNX_3$, wherein X₁ is S, C, N or T, X₂ is F or K, X₃ is A, T or H (SEQ ID NO: 131).
- [Claim 4] An isolated antibody that binds to C5, comprising (a) a HVR-L1 comprising the amino acid sequence $X_1ASQX_2IX_3SX_4LA$, wherein X₁ is Q or R, X₂ is N, Q or G, X₃ is G or S, X₄ is D, K or S (SEQ ID NO: 129); (b) a HVR-L2 comprising the amino acid sequence $GASX_1X_2X_3S$, wherein X₁ is K, E or T, X₂ is L or T, X₃ is A, H, E or Q (SEQ ID NO: 130); and (c) a HVR-L3 comprising the amino acid sequence $QX_1TX_2VGSSYGNX_3$, wherein X₁ is S, C, N or T, X₂ is F or K, X₃ is A, T or H (SEQ ID NO: 131).
- [Claim 5] The antibody of claim 2, further comprising a heavy chain variable domain framework FR1 comprising the amino acid sequence of any

one of SEQ ID NOs: 132-134; a FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 135-136; a FR3 comprising the amino acid sequence of any one of SEQ ID NOs: 137-139; and a FR4 comprising the amino acid sequence of any one of SEQ ID NOs: 140-141.

- [Claim 6] The antibody of claim 4, further comprising a light chain variable domain framework FR1 comprising the amino acid sequence of any one of SEQ ID NOs: 142-143; a FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 144-145; a FR3 comprising the amino acid sequence of any one of SEQ ID NOs: 146-147; and a FR4 comprising the amino acid sequence of SEQ ID NO: 148.
- [Claim 7] An isolated antibody that binds to C5, comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 10, 106-110; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 20, 111-113; or (c) a VH sequence as in (a) and a VL sequence as in (b).
- [Claim 8] The antibody of claim 7, comprising a VH sequence of any one of SEQ ID NOs: 10, 106-110.
- [Claim 9] The antibody of claim 7, comprising a VL sequence of any one of SEQ ID NOs: 20, 111-113.
- [Claim 10] An antibody comprising a VH sequence of any one of SEQ ID NOs: 10, 106-110 and a VL sequence of any one of SEQ ID NOs: 20, 111-113.
- [Claim 11] The antibody of any one of claims 1 to 10, which is a full length IgG1 or IgG4 antibody.
- [Claim 12] An isolated nucleic acid encoding the antibody of any one of claims 1 to 11.
- [Claim 13] A host cell comprising the nucleic acid of claim 12.
- [Claim 14] A method of producing an antibody comprising culturing the host cell of claim 13 so that the antibody is produced.
- [Claim 15] A pharmaceutical formulation comprising the antibody of any one of claims 1 to 11 and a pharmaceutically acceptable carrier.