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PTL 8: WO 02/30985
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PTL 11: WO 2009/125825
PTL 12: WO 2011/122011
PTL 13: WO 2011/111007

Non-Patent Literature

[0019]
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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)
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Summary of Invention

Technical Problem

[0020] An objective of the invention is to provide anti-C5 antibodies and methods of using the same.

Solution to Problem

[0021] The invention provides anti-C5 antibodies and methods of using the same.
[0022] In one aspect, the present disclosure refers to an anti-C5 antibody comprising: (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 117; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 118-120; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 123 or 124; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 125. In another aspect, the present disclosure refers to an isolated nucleic acid encoding the antibody as described herein. In another aspect, the present disclosure refers to a host cell comprising the nucleic acid as described herein. In another aspect, the present disclosure 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 disclosure refers to a pharmaceutical formulation comprising the antibody as described herein and a pharmaceutically acceptable carrier.

[0022a] In some examples, an isolated anti-C5 antibody of the present disclosure binds to an epitope within the beta chain of C5. In some examples, an isolated anti-C5 antibody of the present disclosure binds to an epitope within the MG1-MG2 domain of the beta chain of C5. In some examples, an isolated anti-C5 antibody of the present 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 examples, an isolated anti-C5 antibody of the present 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 examples, an isolated anti-C5 antibody of the present 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 examples, the antibody binds to C5 with a higher affinity at neutral pH than at acidic pH. In further examples, the antibody binds to C5 with a higher affinity at pH7.4 than at pH5.8. In another example, an isolated anti-C5 antibody of the present disclosure binds to the same epitope as an antibody described in Table 2. In further 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 example, the anti-C5 antibody of the present disclosure binds to the same epitope as an antibody described in Tables 7 or 8. In further 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 examples, an anti-C5 antibody of the present 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) aVH 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 examples, the anti-C5 antibody binds to C5 with a higher affinity at neutral pH than at acidic pH. In further examples, the anti-C5 antibody binds to C5 with a higher affinity at pH7.4 than at pH5.8.

[0024] In some examples, an isolated anti-C5 antibody of the present 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 examples, the antibody binds to C5 with a higher affinity at neutral pH than at acidic pH. In further examples, the antibody binds to C5 with a higher affinity at pH7.4 than at pH5.8.

[0025] In some examples, an isolated anti-C5 antibody of the present disclosure inhibits activation of C5. In some examples, an isolated anti-C5 antibody of the present disclosure inhibits activation of C5 variant R885H. In some examples, an isolated anti-C5 antibody of the present disclosure is a monoclonal antibody. In some examples, an isolated anti-C5 antibody of the present disclosure is a human, humanized, or chimeric

antibody. In some examples, an isolated anti-C5 antibody of the present disclosure is an antibody fragment that binds to C5. In some examples, an isolated anti-C5 antibody of the present disclosure is a full length IgG1 or IgG4 antibody.

[0026] In some examples, an isolated anti-C5 antibody of the present disclosure comprises (a) 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), (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 examples, an isolated anti-C5 antibody of the present 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 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 examples, an isolated anti-C5 antibody of the present 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 examples, an isolated anti-C5 antibody of the present 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 examples, an isolated anti-C5 antibody of the present 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 examples, an isolated anti-C5 antibody of the present 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 examples,

the antibody comprises a VH sequence of any one of SEQ ID NOs: 10, 106-110. In further examples, the antibody comprises a VL sequence of any one of SEQ ID NOs: 20, 111-113.
[0031] The 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 disclosure also provides isolated nucleic acids encoding an anti-C5 antibody of the present disclosure. The disclosure also provides host cells comprising a nucleic acid of the present disclosure. The disclosure also provides a method of producing an antibody comprising culturing a host cell of the present disclosure so that the antibody is produced.
[0033] The disclosure further provides a method of producing an anti-C5 antibody. In some examples, 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 examples, 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 examples, 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 examples, 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 disclosure also provides a pharmaceutical formulation comprising an anti-C5 antibody of the present disclosure and a pharmaceutically acceptable carrier.
[0035] Anti-C5 antibodies of the present disclosure may be for use as a medicament. Anti-C5 antibodies of the present 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 disclosure may be for use in enhancing the clearance of C5 from plasma.
[0036] Anti-C5 antibodies of the present disclosure may be used in the manufacture of a medicament. In some examples, the medicament is for treatment of a complement-mediated disease or condition which involves excessive or uncontrolled activation of C5. In some examples, the medicament is for enhancing the clearance of C5 from plasma.
[0037] The 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 examples, the method comprises administering to the individual an effective amount of an anti-C5 antibody of the present disclosure. The disclosure also provides a method of enhancing the clearance of C5 from plasma in an individual. In some examples, the method comprises administering to the individual an effective amount of an anti-C5 antibody of the present disclosure to enhance the clearance of C5 from plasma.
[Brief Description of Drawings]
[0038] [Fig. 1]Figure 1 illustrates epitope binning of anti-C5 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-C5 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-C5 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. 305LO5 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-C5 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-C5 antibody.

Claims

[Claim 1]
An anti-C5 antibody, comprising
(a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 117; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 118-120; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 123 or 124; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 125.

[Claim 2]
The antibody of claim 1, comprising
(i) (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 117; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 118; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 123; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 125;
(ii) (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 117; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 119; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 123; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 125;
(iii) (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 117; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 118; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 124; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 125; or
(iv) (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 117; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 120; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 124; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 125.

[Claim 3]
The antibody of claim 1 or 2, further comprising
[I] a heavy chain constant region comprising the amino acid sequence of any one of SEQ ID NOs: 33, 34, 35, 114, 115, and 116; and
[II] a light chain constant region comprising the amino acid sequence of any one of SEQ ID NOs: 36, 37, and 38.

[Claim 4]
The antibody of claim 3, comprising 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 5]
The antibody of any one of claims 1 to 4, wherein the antibody inhibits activation of C5.

[Claim 6]
The antibody of any one of claims 1 to 5, wherein the antibody inhibits activation of C5 variant R885H.

[Claim 7]
The antibody of any one of claims 1 to 6, wherein the antibody binds to C5 with a higher affinity at pH7.4 than at pH5.8.

[Claim 8]
The antibody of any one of claims 1 to 7, which is a full length IgG1 or IgG4 antibody.

[Claim 9]
An isolated nucleic acid encoding the antibody of any one of claims 1 to 8.

[Claim 10]
A host cell comprising the nucleic acid of claim 9.

[Claim 11]
A method of producing an antibody comprising culturing the host cell of claim 10 so that the antibody is produced.

[Claim 12]
A pharmaceutical formulation comprising the antibody of any one of claims 1 to 8 and a pharmaceutically acceptable carrier.