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 [PTL8] WO 2002/30985
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 [PTL10] WO 2010/015608
 [PTL11] WO 2009/125825
 [PTL12] WO 2011/122011
 [PTL13] WO 2011/111007

Non Patent Literature

[0019]
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 [NPL2] Dmytrijuk et al., The Oncologist 13(9):993-1000 (2008)
 [NPL3] Yeung et al., J Immunol. 182(12): 7663-7671 (2009)
 [NPL4] Datta-Mannan et al., J Biol. Chem. 282(3):1709-1717 (2007)
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Summary

[0020]

The disclosure provides anti-C5 antibodies and methods of using the same. In one aspect, there is provided an isolated monoclonal antibody that binds to C5, wherein the antibody binds to an epitope within a fragment consisting of amino acids 33-124 of the beta chain (SEQ ID NO: 40) of C5 with a higher affinity at pH7.4 than at pH5.8, and wherein the epitope comprises at least one fragment selected from the group consisting of amino acids 47-57, 70-76, and 107-110.. In another aspect, there is provided a pharmaceutical formulation comprising the antibody of the present invention a pharmaceutically acceptable carrier.

[0021]

In some examples, an isolated anti-C5 antibody 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.

[0022]

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) 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 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.

[0023]

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.

[0024]

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.

[0025]

In some examples, an isolated anti-C5 antibody of the present 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 QX₁TX₂VGSSYGNX₃, 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 X₁IX₂TGSGAX₃YX₄AX₅

WX₆KG, 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).

[0026]

In some examples, an isolated anti-C5 antibody of the present disclosure comprises (a) a HVR-H1 comprising the amino acid sequence SSYYX₁X₂, wherein X₁ is M or V, X₂ is C or A (SEQ ID NO: 126), (b) a HVR-H2 comprising the amino acid sequence X₁IX₂TGSGAX₃YX₄AX₅WX₆KG, 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 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). In further examples, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence X₁ASQX₂IX₃SX₄LA, 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 GASX₁X₂X₃S, 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 QX₁TX₂VGSSYGNX₃, wherein X₁ is S, C, N or T, X₂ is F or K, X₃ is A, T or H (SEQ ID NO: 131).

[0027]

In some examples, an isolated anti-C5 antibody of the present disclosure comprises (a) a HVR-L1 comprising the amino acid sequence X₁ASQX₂IX₃SX₄LA, 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 GASX₁X₂X₃S, 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 QX₁TX₂VGSSYGNX₃, wherein X₁ is S, C, N or T, X₂ is F or K, X₃ is A, T or H (SEQ ID NO: 131).

[0028]

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.

[0029]

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.

[0030]

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.

[0031]

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.

[0032]

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.

[0033]

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

[0034]

Specifically, the present disclosure provides the following examples:

[1] An isolated antibody that binds to C5, wherein the antibody binds to an epitope within the beta chain of C5 with a higher affinity at neutral pH than at acidic pH.

[2] The antibody of [1], wherein the antibody 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; and

(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.

[3] The antibody of [1], wherein the antibody competes for binding C5 with an

Claims

1. An isolated monoclonal antibody that binds to C5, wherein the antibody binds to an epitope within a fragment consisting of amino acids 33-124 of the beta chain (SEQ ID NO: 40) of C5 with a higher affinity at pH7.4 than at pH5.8, and wherein the epitope comprises at least one fragment selected from the group consisting of amino acids 47-57, 70-76, and 107-110.
2. The antibody of claim 1, wherein the antibody binds to an epitope within a fragment of the beta chain (SEQ ID NO: 40) of C5 which comprises at least one amino acid selected from the group consisting of Glu48, Asp51, His70, His72, Lys109, and His110.
3. The antibody of any one of claims 1 to 2, which inhibits activation of C5.
4. The antibody of any one of claims 1 to 3, which inhibits activation of C5 variant R885H.
5. The antibody of any one of claims 1 to 4, which is a human, humanized, or chimeric antibody.
6. The antibody of any one of claims 1 to 5, which is an antibody fragment that binds to C5.
7. The antibody of any one of claims 1 to 5, which is a full length IgG1 or IgG4 antibody.
8. A pharmaceutical formulation comprising the antibody of any one of claims 1 to 7 and a pharmaceutically acceptable carrier.