

SUMMARY

Disclosed is an isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to the serine protease domain of human MASP-3 (amino acid residues 450 to 728 of SEQ ID NO:2) with high affinity (having a K_D of less than 500 pM), wherein the antibody or antigen-binding fragment thereof inhibits alternative pathway complement activation. In some embodiments, antibody or antigen-binding fragment is characterized by at least one or more of the following properties: (a) inhibits pro-Factor D maturation; (b) does not bind to human MASP-1 (SEQ ID NO:8); (c) inhibits the alternative pathway at a molar ratio of from about 1:1 to about 2.5:1 (MASP-3 target to mAb) in a mammalian subject (d) does not inhibit the classical pathway (e) inhibits of hemolysis and/or opsonization; (f) inhibits of MASP-3 serine protease substrate-specific cleavage; (g) reduces hemolysis or the reduction of C3 cleavage and C3b surface deposition; (h) reduces of Factor B and/or Bb deposition on an activating surface; (i) reduces resting levels (in circulation, and without the experimental addition of an activating surface) of active Factor D relative to pro-Factor D; (j) reduces the level of active Factor D relative to pro-Factor D in response to an activating surface; (k) reduces the production of resting and surface-induced levels of fluid-phase Ba, Bb, C3b, or C3a; and/or (l) reduces factor P deposition. In some embodiments, the isolated antibody or antigen-binding fragment thereof of paragraph 1 or 2, wherein said antibody or antigen-binding fragment thereof specifically binds to an epitope located within the serine protease domain of human MASP-3, wherein said epitope is located within at least one or more of: VLRSQRRDITVI (SEQ ID NO:9), TAAHVLRSQRRDITV (SEQ ID NO:10), DFNIQNYNHDIALLVQ (SEQ ID NO:11), PHAECKTSYESRS (SEQ ID NO:12), GNYSVTENMFC (SEQ ID NO:13), VSNYVDWVWE (SEQ ID NO:14) and/or VLRSQRRDITV (SEQ ID NO:15). In some embodiments, the antibody or antigen-binding fragment thereof binds to an epitope within at least one of: ECGQPSRSLPSLV (SEQ ID NO:16), RNAEPGLFPWQ (SEQ ID NO:17); KWFGSGALLSASWIL (SEQ ID NO:18); EHVTVYLGLH (SEQ ID NO:19); PVPLGPHVMP (SEQ ID NO:20); APHMLGL (SEQ ID NO:21); SDVLQYVKLP (SEQ ID NO:22); and/or AFVIFDDLSQRW (SEQ ID NO:23).

In one aspect, there is provided an isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to the serine protease domain of human MASP-3 (amino acid residues 450 to 728 of SEQ ID NO:2) with high affinity, wherein said antibody binds within at least one of:

(a) an epitope in human MASP-3 set forth as VLRSQRRDITV (SEQ ID NO:15), TAAHVLRSQRRDITV (SEQ ID NO:10), VLRSQRRDITVI (SEQ ID NO:9), DFNIQNYNHDIALLVQ (SEQ ID NO:11), PHAECKTSYESRS (SEQ ID NO:12), GNYSVTENMFC (SEQ ID NO:13), and/or VSNYVDWVWE (SEQ ID NO:14); or

(b) an epitope in human MASP-3 set forth as ECGQPSRSLPSLV (SEQ ID NO:16), RNAEPGLFPWQ (SEQ ID NO:17); KWFGSGALLSASWIL (SEQ ID NO:18); EHVTVYLGLH (SEQ ID NO:19); PVPLGPHVMP (SEQ ID NO:20); APHMLGL (SEQ ID NO:21); SDVLQYVKLP (SEQ ID NO:22); and/or AFVIFDDLSQRW (SEQ ID NO:23),

wherein the antibody or antigen-binding fragment thereof inhibits alternative pathway complement activation.

Disclosed is an isolated antibody, or antigen-binding fragment thereof, that binds to MASP-3 comprising: (a) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:209 (XXDIN, wherein X at position 1 is S or T and wherein X at position 2 is N or D); a HC-CDR2 set forth as SEQ ID NO:210 (WIYPRDXXXKYNXXFXD, wherein X at position 7 is G or D; X at position 8 is S, T or R;

X at position 9 is I or T; X at position 13 is E or D; X at position 14 is K or E; and X at position 16 is T or K); and a HC-CDR3 set forth as SEQ ID NO:211 (XEDXY, wherein X at position 1 is L or V, and wherein X at position 4 is T or S); and (b) a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:212 (KSSQSLLXXRTRKNYLX, wherein X at position 8 is N, I, Q or A; wherein X at position 9 is S or T; and wherein X at position 17 is A or S); a LC-CDR2 set forth as SEQ ID NO:144 (WASTRES) and a LC-CDR3 set forth as SEQ ID NO:146 (KQSYNLYT).

Disclosed is an isolated antibody, or antigen-binding fragment thereof, that binds to MASP-3 comprising: (a) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:213 (SYGXX, wherein X at position 4 is M or I and wherein X at position 5 is S or T); a HC-CDR2 set forth as SEQ ID NO:74; and a HC-CDR3 set forth as SEQ ID NO:214 (GGXAXDY, wherein X at position 3 is E or D and wherein X at position 5 is M or L); and (b) a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:215 (KSSQSLLDSXXKTYLX, wherein X at position 10 is D, E or A; wherein X at position 11 is G or A; and wherein X at position 16 is N or S); a LC-CDR2 set forth as SEQ ID NO:155; and a LC-CDR3 set forth as SEQ ID NO:216 (WQGTTHFPXT, wherein X at position 8 is W or Y).

Disclosed is an isolated antibody, or antigen-binding fragment thereof, that binds to MASP-3 comprising: (a) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:84 (GKWIE); a HC-CDR2 set forth as SEQ ID NO:86 (EILPGTGSTNYNEKFKG) or SEQ ID NO:275 (EILPGTGSTNYAQKFQG); and a HC-CDR3 set forth as SEQ ID NO:88 (SEDV); and (b) a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:142 (KSSQSLLNSRTRKNYLA), SEQ ID NO:257 (KSSQSLLQSRTRKNYLA); SEQ ID NO:258 (KSSQSLLASRTRKNYLA); or SEQ ID NO:259 (KSSQSLLNTRTRKNYLA), a LC-CDR2 set forth as SEQ ID NO:144 (WASTRES); and a LC-CDR3 set forth as SEQ ID NO:161 (KQSYNIPT).

Disclosed is an isolated antibody, or antigen-binding fragment thereof, that binds to MASP-3 comprising: (a) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:91 (GYWIE); a HC-CDR2 set forth as SEQ ID NO:93 (EMLPGSGSTHYNEKFKG), and a HC-CDR3 set forth as SEQ ID NO:95 (SIDY); and (b) a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:163 (RSSQSLVQSNGNTYLH), a LC-CDR2 set forth as SEQ ID NO:165 (KVSNRFS) and a LC-CDR3 set forth as SEQ ID NO:167 (SQSTHVPPT).

Disclosed is an isolated antibody, or antigen-binding fragment thereof, that binds to MASP-3 comprising:

(a) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:109 (RVHFAIRDTNYWMQ), a HC-CDR2 set forth as SEQ ID NO:110 (AIYPGNGDTSYNQKFKG), a HC-CDR3 set forth as SEQ ID NO:112 (GSHYFDY); and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:182 (RASQSIGTSIH), a LC-CDR2 set forth as SEQ ID NO:184 (YASESIS) and a LC-CDR3 set forth as SEQ ID NO:186 (QQSNSWPYT); or

(b) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:125 (DYVMN), a HC-CDR2 set forth as SEQ ID NO:127 (DVNPNDGTTYNQKFKG), a HC-CDR3 set forth as SEQ ID NO:129 (CPFYYLGKGTHFDY); and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:196 (RASQDISNFLN), a LC-CDR2 set forth as SEQ ID NO:198 (YTSRLHS) and a LC-CDR3 set forth as SEQ ID NO:200 (QQGFTLPWT); or

(c) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:137 a HC-CDR2 set forth as SEQ ID NO:138, a HC-CDR3 set forth as SEQ ID NO:140; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:206, a LC-CDR2 set forth as SEQ ID NO:207 and a LC-CDR3 set forth as SEQ ID NO:208; or

(d) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:98, a HC-CDR2 set forth as SEQ ID NO:99, a HC-CDR3 set forth as SEQ ID NO:101; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:169, a LC-CDR2 set forth as SEQ ID NO:171 and a LC-CDR3 set forth as SEQ ID NO:173; or

(e) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:103, a HC-CDR2 set forth as SEQ ID NO:105, a HC-CDR3 set forth as SEQ ID NO:107; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:176, a LC-CDR2 set forth as SEQ ID NO:178 and a LC-CDR3 set forth as SEQ ID NO:193; or

(f) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:114, a HC-CDR2 set forth as SEQ ID NO:116, a HC-CDR3 set forth as SEQ ID NO:118; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:188, a LC-CDR2 set forth as SEQ ID NO:178 and a LC-CDR3 set forth as SEQ ID NO:190; or

(g) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:114, a HC-CDR2 set forth as SEQ ID NO:121, a HC-CDR3 set forth as SEQ ID NO:123; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:191, a LC-CDR2 set forth as SEQ ID NO:178 and a LC-CDR3 set forth as SEQ ID NO:193.

In another aspect, there is provided an isolated DNA sequence encoding the heavy and/or light chain variable regions of an antibody or antigen-binding fragment thereof as described herein.

In another aspect, there is provided a cloning or expression vector comprising one or more DNA sequences as described herein.

In another aspect, there is provided a host cell comprising one or more cloning or expression vectors as described herein.

In another aspect, there is provided a process for producing the antibody or antigen-binding fragment as described herein comprising culturing the host cell as described herein and isolating the antibody or antigen-binding fragment thereof.

In another aspect, there is provided a composition comprising the antibody or antigen-binding fragment as described herein and a pharmaceutically acceptable excipient.

Disclosed is a method of inhibiting alternative pathway complement activation in a mammal, the method comprising administering to a mammal subject in need thereof an amount of a composition comprising a high affinity MASP-3 inhibitory antibody or antigen-binding fragment thereof sufficient to inhibit alternative pathway complement pathway activation in the mammal. In one embodiment of the method, the antibody, or antigen binding fragment thereof binds to MASP-3 with an affinity of less than 500 pM. In one embodiment of the method, as a result of administering the composition comprising the antibody or antigen-binding fragment one or more of the following is present in the mammalian subject: (a) inhibition of Factor D maturation; (b) inhibition of the alternative pathway when administered to the subject at a molar ratio of from about 1:1 to about 2.5:1 (MASP-3 target to mAb); (c) the classical pathway is not inhibited; (d) inhibition of hemolysis and/or opsonization; (e) a reduction of hemolysis or the reduction of C3 cleavage and C3b surface deposition; (f) a reduction of Factor B and Bb deposition on an activating surface; (g) a reduction of resting levels (in circulation, and without the experimental addition of an activating surface) of active Factor D relative to pro-Factor D; (h) a reduction of levels of active Factor D relative to pro-Factor D in response to an activating surface; and/or (i) a reduction of the production of resting and surface-induced levels of fluid-phase Ba, Bb, C3b, or C3a. In one embodiment of the method, the composition comprises an MASP-3 inhibitory antibody that inhibits the alternative pathway at a molar ratio of from about 1:1 to about 2.5:1 (MASP-3 target to mAb).

In another aspect, there is provided use of a composition as described herein comprising a high affinity MASP-3 inhibitory antibody or antigen-binding fragment thereof in the manufacture of a medicament for inhibiting alternative pathway complement activation in a mammal.

Disclosed is a method of inhibiting MASP-3-dependent complement activation in a subject suffering from paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), ischemia-reperfusion injury, arthritis, disseminated intravascular coagulation, thrombotic microangiopathy, asthma, dense deposit disease, pauci-immune necrotizing crescentic glomerulonephritis, traumatic brain injury, aspiration pneumonia, endophthalmitis, neuromyelitis optica or Behcet's disease. The method includes the step of administering to the subject a composition comprising an amount of a high affinity MASP-3 inhibitory agent effective to inhibit MASP-3-dependent complement activation. In some embodiments, the method further comprises administering to the subject a composition comprising a MASP-2 inhibitory agent.

Disclosed is a method of manufacturing a medicament for use in inhibiting the effects of MASP-3-dependent complement activation in living subjects in need thereof, comprising combining a therapeutically effective amount of a MASP-3 inhibitory agent in a pharmaceutical carrier. In some embodiments, the MASP-3

inhibitory agent is a high affinity MASP-3 inhibitory antibody. In some embodiments, the method in accordance with this embodiment of the disclosure comprises manufacturing a medicament for use in inhibiting the effects of MASP-3-dependent complement activation in a subject suffering from, or at risk for developing a disease or disorder selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), ischemia-reperfusion injury, arthritis, disseminated intravascular coagulation, thrombotic microangiopathy, asthma, dense deposit disease, pauci-immune necrotizing crescentic glomerulonephritis, traumatic brain injury, aspiration pneumonia, endophthalmitis, neuromyelitis optica or Behcet's disease. In some embodiments, the method further comprises combining a therapeutically effective amount of a MASP-2 inhibitory agent into or with the medicament comprising the MASP-3 inhibitor.

Disclosed is a pharmaceutical composition comprising a physiologically acceptable carrier and a high affinity MASP-3 inhibitory monoclonal antibody or antigen binding fragment thereof that binds to human MASP-3 and inhibits alternative pathway complement activation. In one embodiment, said high affinity MASP-3 antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region comprising (i) VHCDR1 comprising SEQ ID NO:84, (ii) VHCDR2 comprising SEQ ID NO:86 or SEQ ID NO:275 and (iii) VHCDR3 comprising SEQ ID NO:88; and (b) a light chain variable region comprising (i) VLCDR1 comprising SEQ ID NO:142, SEQ ID NO:257, SEQ ID NO:258, or SEQ ID NO:259 (ii) VLCDR2 comprising SEQ ID NO:144 and (iii) VLCDR3 comprising SEQ ID NO:161.

Disclosed is a method for treating a subject suffering from, or at risk for developing paroxysmal nocturnal hemoglobinuria (PNH), comprising administering to the subject a pharmaceutical composition comprising an effective amount of a high affinity monoclonal antibody or antigen binding fragment thereof that binds to human MASP-3 and inhibits alternative pathway complement activation to treat or reduce the risk of PNH in the subject. In one embodiment antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region comprising (a) a heavy chain variable region comprising (i) VHCDR1 comprising SEQ ID NO:84, (ii) VHCDR2 comprising SEQ ID NO:86 or SEQ ID NO:275 and (iii) VHCDR3 comprising SEQ ID NO:88; and (b) a light chain variable region comprising (i) VLCDR1 comprising SEQ ID NO:142, SEQ ID NO:257, SEQ ID NO:258, or SEQ ID NO:259 (ii) VLCDR2 comprising

SEQ ID NO:144 and (iii) VLCDR3 comprising SEQ ID NO:161. In some embodiments, the pharmaceutical composition increases the survival of red blood cells in the subject suffering from PNH. In some embodiments, wherein the subject suffering from or at risk for developing PNH exhibits one or more symptoms selected from the group consisting of (i) below normal levels of hemoglobin, (ii) below normal levels of platelets; (iii) above normal levels of reticulocytes, and (iv) above normal levels of bilirubin. In some embodiments, the pharmaceutical composition is administered systemically (e.g., subcutaneously, intramuscularly, intravenously, intra-arterially or as an inhalant) to a subject suffering from, or at risk for developing PNH. In some embodiments, the subject suffering from or at risk for PNH has previously undergone, or is currently undergoing treatment with a terminal complement inhibitor that inhibits cleavage of complement protein C5. In some embodiments, the method further comprises administering to the subject a terminal complement inhibitor that inhibits cleavage of complement protein C5. In some embodiments, the terminal complement inhibitor is a humanized anti-C5 antibody or antigen-binding fragment thereof. In some embodiments, the terminal complement inhibitor is eculizumab.

Disclosed is a method for treating a subject suffering from, or at risk for developing arthritis (inflammatory and non-inflammatory arthritides) comprising administering to the subject a pharmaceutical composition comprising an effective amount of a high affinity monoclonal antibody or antigen binding fragment thereof that binds to human MASP-3 and inhibits alternative pathway complement activation to treat or reduce the risk of arthritis in the subject. In one embodiment, said antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region comprising (i) VHCDR1 comprising SEQ ID NO:84, (ii) VHCDR2 comprising SEQ ID NO:86 or SEQ ID NO:275 and (iii) VHCDR3 comprising SEQ ID NO:88; and (b) a light chain variable region comprising (i) VLCDR1 comprising SEQ ID NO:142, SEQ ID NO:257, SEQ ID NO:258 or SEQ ID NO:259 (ii) VLCDR2 comprising SEQ ID NO:144 and (iii) VLCDR3 comprising SEQ ID NO:161. In some embodiments, the subject is suffering from arthritis selected from the group consisting of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, Behcet's disease, infection-related arthritis and psoriatic arthritis. In some embodiments, the pharmaceutical composition is administered systemically (i.e., subcutaneously, intramuscularly, intravenously, intra-arterially or as an

inhalant). In some embodiments, the pharmaceutical composition is administered locally to a joint.

As described herein, the various embodiments of the high affinity MASP-3 inhibitory antibodies, optionally in combination with the various embodiments of the MASP-2 inhibitory agents can be used in the pharmaceutical compositions of the disclosure.

As described herein, the pharmaceutical compositions of the disclosure can be used in accordance with the methods of the disclosure.

These and other embodiments of the herein described disclosure will be evident upon reference to the following detailed description and drawings. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference in their entirety, as if each was incorporated individually.

DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 illustrates a new understanding of the lectin and alternative pathways;

FIGURE 2 is a schematic diagram adapted from Schwaeble et al., *Immunobiol* 205:455-466 (2002), as modified by Yongqing et al., *BBA* 1824:253 (2012), illustrating the MASP-1, MASP-3 and MAp44 protein domains and the exons encoding the same;

FIGURE 3 depicts the human MASP-3 amino acid sequence (SEQ ID NO:2) with the leader sequence shown in underline;

FIGURE 4 shows an alignment of full length MASP-3 protein from multiple species;

FIGURE 5 shows an alignment of the SP domain of MASP-3 protein from multiple species;

FIGURE 6 is a Kaplan-Meyer plot graphically illustrating the percent survival of MASP-2 KO and WT mice after administration of an infective dose of 2.6×10^7 cfu of *N. meningitidis* serogroup A Z2491, demonstrating that MASP-2 deficient mice are protected from *N. meningitidis* induced mortality, as described in Example 1;

FIGURE 7 is a Kaplan-Meyer plot graphically illustrating the percent survival of MASP-2 KO and WT mice after administration of an infective dose of 6×10^6 cfu of *N.*

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. An isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to the serine protease domain of human MASP-3 (amino acid residues 450 to 728 of SEQ ID NO:2) with high affinity, wherein said antibody binds within at least one of:
 - (a) an epitope in human MASP-3 set forth as VLRSQRRDTTV (SEQ ID NO:15), TAAHVLRSQRRDTTV (SEQ ID NO:10), VLRSQRRDTTVI (SEQ ID NO:9), DFNIQNYNHDIQLVQ (SEQ ID NO:11), PHAECKTSYESRS (SEQ ID NO:12), GNYSVTENMFC (SEQ ID NO:13), and/or VSNYVDWVWE (SEQ ID NO:14); or
 - (b) an epitope in human MASP-3 set forth as ECGQPSRSLPSLV (SEQ ID NO:16), RNAEPGLFPWQ (SEQ ID NO:17); KWFGSGALLSASWIL (SEQ ID NO:18); EHVTVYLGLH (SEQ ID NO:19); PVPLGPHVMP (SEQ ID NO:20); APHMLGL (SEQ ID NO:21); SDVLQYVKLP (SEQ ID NO:22); and/or AFVIFDDLQSRW (SEQ ID NO:23),wherein the antibody or antigen-binding fragment thereof inhibits alternative pathway complement activation.
2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment is characterized by at least one or more of the following properties:
 - (a) inhibits pro-Factor D maturation;
 - (b) does not bind to human MASP-1 (SEQ ID NO:8);
 - (c) inhibits the alternative pathway at a molar ratio of from about 1:1 to about 2.5:1 (MASP-3 target to mAb) in a mammalian subject;
 - (d) does not inhibit the classical pathway.
 - (e) inhibition of hemolysis and/or opsonization;
 - (f) inhibition of MASP-3 serine protease substrate-specific cleavage;
 - (g) a reduction of hemolysis or the reduction of C3 cleavage and C3b surface deposition;
 - (h) a reduction of Factor B and Bb deposition on an activating surface;
 - (i) a reduction of resting levels (in circulation, and without the experimental addition of an activating surface) of active Factor D relative to pro-Factor D;

- (j) a reduction of levels of active Factor D relative to pro-Factor D in response to an activating surface;
- (k) a reduction of the production of resting and surface-induced levels of fluid-phase Ba, Bb, C3b, or C3a; and/or
- (l) a reduction in factor P deposition.

3. The antibody or antigen-binding fragment thereof of claim 1(a), wherein said antibody or antigen-binding fragment binds to an epitope within SEQ ID NO:15.

4. The antibody or antigen-binding fragment of claim 1(a), wherein said antibody or antigen-binding fragment binds to an epitope within SEQ ID NO:10.

5. The antibody or antigen-binding fragment of claim 1(a), wherein said antibody or antigen-binding fragment binds to an epitope within SEQ ID NO:9.

6. The antibody or antigen-binding fragment of claim 4, wherein said antibody or antigen binding fragment also binds to an epitope within SEQ ID NO:12.

7. The antibody or antigen-binding fragment of claim 5, wherein said antibody or antigen binding fragment also binds to an epitope within at least one of SEQ ID NO:11, SEQ ID NO: 13 and/or SEQ ID NO:14.

8. The isolated antibody, or antigen-binding fragment thereof, that binds to MASP-3 according to claim 1(a) comprising:

- (a) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:84 (GKWIE); a HC-CDR2 set forth as SEQ ID NO:86 (EILPGTGSTNYNEKFKG) or SEQ ID NO:275 (EILPGTGSTNYAQKFQG); and a HC-CDR3 set forth as SEQ ID NO:88 (SEDV); and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:142 (KSSQSLLNSRTRKNYLA), SEQ ID NO:257 (KSSQSLLQSRTRKNYLA); SEQ ID NO:258 (KSSQSLLASRTRKNYLA); or SEQ ID NO:259 (KSSQSLLNTRTRKNYLA), a LC-CDR2 set forth as SEQ ID NO:144 (WASTRES); and a LC-CDR3 set forth as SEQ ID NO:161 (KQSYNIPT); or
- (b) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:213 (SYGXX, wherein X at position 4 is M or I and wherein X at position 5 is S or T); a HC-CDR2 set forth as SEQ ID NO:74; and a HC-CDR3 set forth as SEQ ID NO:214 (GGXAXDY, wherein X at position 3 is E or D and wherein X

at position 5 is M or L); and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:215 (KSSQSLLDSXXKTYLX, wherein X at position 10 is D, E or A; wherein X at position 11 is G or A; and wherein X at position 16 is N or S); a LC-CDR2 set forth as SEQ ID NO:155; and a LC-CDR3 set forth as SEQ ID NO:216 (WQGTTHFPXT, wherein X at position 8 is W or Y; or

- (a) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:209 (XXDIN, wherein X at position 1 is S or T and wherein X at position 2 is N or D); a HC-CDR2 set forth as SEQ ID NO:210 (WIYPRDXXXKYNXXFXD, wherein X at position 7 is G or D; X at position 8 is S, T or R; X at position 9 is I or T; X at position 13 is E or D; X at position 14 is K or E; and X at position 16 is T or K); and a HC-CDR3 set forth as SEQ ID NO:211 (XEDXY, wherein X at position 1 is L or V, and wherein X at position 4 is T or S); and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:212 (KSSQSLLXXRTRKKNYLX, wherein X at position 8 is N, I, Q or A; wherein X at position 9 is S or T; and wherein X at position 17 is A or S); a LC-CDR2 set forth as SEQ ID NO:144 (WASTRES) and a LC-CDR3 set forth as SEQ ID NO:146 (KQSYNLYT).

9. The isolated antibody, or antigen-binding fragment thereof, that binds to MASP-3 according to claim 1(b) comprising:

- (a) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:91 (GYWIE); a HC-CDR2 set forth as SEQ ID NO:93 (EMLPGSGSTHYNEKFKG), and a HC-CDR3 set forth as SEQ ID NO:95 (SIDY); and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:163 (RSSQSLVQSNGNTYLH), a LC-CDR2 set forth as SEQ ID NO:165 (KVSNRFS) and a LC-CDR3 set forth as SEQ ID NO:167 (SQSTHVPPT); or
- (b) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:109 (RVHFAIRDTNYWMQ), a HC-CDR2 set forth as SEQ ID NO:110 (AIYPGNGDTSYNQKFKG), a HC-CDR3 set forth as SEQ ID NO:112 (GSHYFDY); and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:182 (RASQSIGTSIH), a LC-CDR2 set forth as SEQ ID NO:184 (YASESIS) and a LC-CDR3 set forth as SEQ ID NO:186 (QQSNSWPYT); or
- (c) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:125 (DYVMN), a HC-CDR2 set forth as SEQ ID NO:127 (DVNPNDGTTYNQKFKG), a HC-CDR3 set forth as SEQ ID NO:129 (CPFYYLGKGTHFDY); and a light chain

variable region comprising a LC-CDR1 set forth as SEQ ID NO:196 (RASQDISNFLN), a LC-CDR2 set forth as SEQ ID NO:198 (YTSRLHS) and a LC-CDR3 set forth as SEQ ID NO:200 (QQGFTLPWT); or

- (d) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:132, a HC-CDR2 set forth as SEQ ID NO:133, a HC-CDR3 set forth as SEQ ID NO:135; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:203, a LC-CDR2 set forth as SEQ ID NO:165 and a LC-CDR3 set forth as SEQ ID NO:204; or
- (e) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:137 a HC-CDR2 set forth as SEQ ID NO:138, a HC-CDR3 set forth as SEQ ID NO:140; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:206, a LC-CDR2 set forth as SEQ ID NO:207 and a LC-CDR3 set forth as SEQ ID NO:208; or
- (f) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:98, a HC-CDR2 set forth as SEQ ID NO:99, a HC-CDR3 set forth as SEQ ID NO:101; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:169, a LC-CDR2 set forth as SEQ ID NO:171 and a LC-CDR3 set forth as SEQ ID NO:173; or
- (g) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:103, a HC-CDR2 set forth as SEQ ID NO:105, a HC-CDR3 set forth as SEQ ID NO:107; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:176, a LC-CDR2 set forth as SEQ ID NO:178 and a LC-CDR3 set forth as SEQ ID NO:193; or
- (h) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:114, a HC-CDR2 set forth as SEQ ID NO:116, a HC-CDR3 set forth as SEQ ID NO:118; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:188, a LC-CDR2 set forth as SEQ ID NO:178 and a LC-CDR3 set forth as SEQ ID NO:190; or
- (i) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:114, a HC-CDR2 set forth as SEQ ID NO:121, a HC-CDR3 set forth as SEQ ID NO:123; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:191, a LC-CDR2 set forth as SEQ ID NO:178 and a LC-CDR3 set forth as SEQ ID NO:193.

10. The antibody or antigen binding fragment thereof of any of Claims 1, 8 or 9, wherein the antibody or antigen-binding fragment is selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a murine antibody, and an antigen-binding fragment of any of the foregoing.

11. The antibody or antigen-binding fragment thereof of any of Claims 1, 8 or 9, wherein said antibody or antigen binding fragment thereof is selected from the group

consisting of a single chain antibody, an ScFv, a Fab fragment, an Fab' fragment, an F(ab')₂ fragment, a univalent antibody lacking a hinge region and a whole antibody.

12. The antibody or antigen-binding fragment thereof of any of Claims 1, 8 or 9, further comprising an immunoglobulin constant region.

13. The antibody or antigen binding fragment thereof of any one of claims 1, 8 or 9, wherein the antibody or antigen-binding fragment is humanized.

14. The antibody or antigen-binding fragment thereof of any of Claims 1, 8 or 9, wherein said antibody binds to the serine protease domain of human MASP-3 with an affinity of less than 500 pM.

15. The antibody or antigen-binding fragment thereof of any of Claims 1, 8 or 9, wherein said antibody inhibits alternative pathway activation in mammalian blood.

16. An isolated DNA sequence encoding the heavy and/or light chain variable regions of an antibody or antigen-binding fragment thereof from any one of claims 1, 8 or 9.

17. A cloning or expression vector comprising one or more DNA sequences of Claim 16.

18. A host cell comprising one or more cloning or expression vectors of claim 17.

19. A process for producing the antibody or antigen-binding fragment of any of claims 1, 8 or 9 comprising culturing the host cell of Claim 18 and isolating the antibody or antigen-binding fragment thereof.

20. A composition comprising the antibody or antigen-binding fragment of any of Claims 1, 8 or 9 and a pharmaceutically acceptable excipient.

21. Use of a composition according to claim 20 comprising a high affinity MASP-3 inhibitory antibody or antigen-binding fragment thereof in the manufacture of a medicament for inhibiting alternative pathway complement activation in a mammal.