In one aspect, the present disclosure provides a composition comprising the antibody or antigen-binding fragment as described herein and a pharmaceutically acceptable excipient.

In one aspect, the present disclosure provides an isolated DNA sequence encoding the heavy and light chain variable regions of an antibody or antigen-binding fragment as described herein.

In one aspect, the present disclosure provides a cloning or expression vector comprising one or more DNA sequences as described herein.

In one aspect, the present disclosure refers to a host cell comprising one or more cloning or expression vectors as described herein.

In one aspect, the present disclosure refers to a process for producing the antibody or antigen-binding fragment thereof as described herein comprising culturing the host cell as described herein and isolating the antibody or antigen-binding fragment thereof.

In another example, the present disclosure provides 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 example of the method, the antibody, or antigen binding fragment thereof binds to MASP-3 with an affinity of less than 500 pM. In one example 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 example 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 example, the present disclosure provides 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 examples, the method further comprises administering to the subject a composition comprising a MASP-2 inhibitory agent.

In another example, the present disclosure provides 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 examples, the MASP-3

inhibitory agent is a high affinity MASP-3 inhibitory antibody. In some examples, the method in accordance with this example 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 examples, 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.

In one aspect, the present disclosure provides use of a composition as described herein in the manufacture of a medicament for treating an alternative pathway disease or disorder selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD, including wet and dry AMD), ischemia-reperfusion injury, arthritis, disseminated intravascular coagulation, thrombotic microangiopathy (including hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS),thrombotic thrombocytopenic purpura (TTP) or transplant-associated TMA), asthma, dense deposit disease, pauci-immune necrotizing crescentic glomerulonephritis, traumatic brain injury, aspiration pneumonia, endophthalmitis, neuromyelitis optica, Behcet's disease, multiple sclerosis, Guillain Barre Syndrome, Alzheimer's disease, amylotrophic lateral sclerosis (ALS), lupus nephritis, systemic lupus erythematosus (SLE), diabetic retinopathy, uveitis, chronic obstructive pulmonary disease (COPD), C3 glomerulopathy, transplant rejection, graft-versus-host disease (GVHD), hemodialysis, sepsis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), ANCA vasculitis, anti-phospholipid syndrome, atherosclerosis, IgA nephropathy and myasthenia gravis, wherein the composition comprising a MASP-3 inhibitory antibody or antigen-binding fragment thereof is in an amount sufficient to inhibit alternative pathway complement activation in the mammalian subject.

In another example, the present disclosure provides 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 example, 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.

In another example, the present disclosure provides 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 example 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

CLAIMS

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

1.An isolated antibody, or antigen-binding fragment thereof, that binds to MASP-3 comprising: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).

2. The antibody or antigen binding fragment thereof of Claim 1, 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.

3. The antibody or antigen-binding fragment thereof of Claim 1, 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.

4. The antibody or antigen-binding fragment thereof of Claim 1, further comprising an immunoglobulin constant region.

5. The antibody or antigen binding fragment thereof of Claim 1, wherein the antibody or antigen-binding fragment is humanized.

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

7. The antibody or antigen-binding fragment thereof of Claim 1, wherein said antibody inhibits alternative pathway activation in mammalian blood.

8. An isolated DNA sequence encoding the heavy and light chain variable regions of an antibody or antigen-binding fragment thereof from any one of claims 1-7.

9. A cloning or expression vector comprising one or more DNA sequences of Claim 8.

10. A host cell comprising one or more cloning or expression vectors of claim 9.

11. A process for producing the antibody or antigen-binding fragment of any of claims 1-7 comprising culturing the host cell of claim 10 and isolating the antibody or antigen-binding fragment thereof.

12. A composition comprising the antibody or antigen-binding fragment of any of Claims 1-7 and a pharmaceutically acceptable excipient.

13. Use of a composition according to claim 12 in the manufacture of a medicament for treating an alternative pathway disease or disorder selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD, including wet and dry AMD), ischemia-reperfusion injury, arthritis, disseminated intravascular coagulation, thrombotic microangiopathy (including hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS),thrombotic thrombocytopenic purpura (TTP) or transplant-associated TMA), asthma, dense deposit disease, pauci-immune necrotizing crescentic glomerulonephritis, traumatic brain injury, aspiration pneumonia, endophthalmitis, neuromyelitis optica, Behcet's disease, multiple sclerosis, Guillain Barre Syndrome, Alzheimer's disease, amylotrophic lateral sclerosis (ALS), lupus nephritis, systemic lupus erythematosus (SLE), diabetic retinopathy, uveitis, chronic obstructive pulmonary disease (COPD), C3 glomerulopathy, transplant rejection, graft-versus-host disease (GVHD), hemodialysis, sepsis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), ANCA vasculitis, anti-phospholipid syndrome, atherosclerosis, IgA nephropathy and myasthenia gravis, wherein the composition comprising a MASP-3 inhibitory antibody or antigen-binding fragment thereof is in an amount sufficient to inhibit alternative pathway complement activation in the mammalian subject.

14. The isolated antibody or antigen-binding fragment thereof of Claim 1, wherein the LC-CDR1 comprises SEQ ID NO:258.

15. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR2 comprises SEQ ID NO:86.

16. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR2 comprises SEQ ID NO:275.

17. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the LC-CDR1 comprises SEQ ID NO:142.

18. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the LC-CDR1 comprises SEQ ID NO:257.

19. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the LC-CDR1 comprises SEQ ID NO:259.

20. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:84, the HC-CDR2 comprises SEQ ID NO:86, the HC-CDR3 comprises SEQ ID NO:88, the LC-CDR1 comprises SEQ ID NO:258, the LC-CDR2 comprises SEQ ID NO:144 and the LC-CDR3 comprises SEQ ID NO:161.

21. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:84, the HC-CDR2 comprises SEQ ID NO:275, the HC-CDR3 comprises SEQ ID NO:88; the LC-CDR1 comprises SEQ ID NO:258, the LC-CDR2 comprises SEQ ID NO:144 and the LC-CDR3 comprises SEQ ID NO:161.

22. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO:30.

23. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the light chain variable region comprises the amino acid sequence set forth as SEQ ID NO:45.

24. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO:30 and the light chain variable region comprises the amino acid sequence set forth as SEQID NO:45.

25. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO:254 or SEQ ID NO:255.

26. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the light chain variable region comprises the amino acid sequence set forth as SEQ ID NO:256 or SEQ ID NO:280.

27. An isolated antibody or antigen-binding fragment thereof that binds to human MASP-3, comprising a heavy chain variable region comprising SEQ ID NO:254 or SEQ ID NO:255 and a light chain variable region comprising SEQ ID NO:256 or SEQ ID NO:280.

28. The isolated antibody or antigen-binding fragment thereof of claim 27, wherein the heavy chain variable region comprises SEQ ID NO:254 and the light chain variable region comprises SEQ ID NO:256.

29. The isolated antibody or antigen-binding fragment thereof of claim 27, wherein the heavy chain variable region comprises SEQ ID NO:255 and the light chain variable region comprises SEQ ID NO:256.

30. The isolated antibody or antigen-binding fragment thereof of claim 27, wherein the heavy chain variable region comprises SEQ ID NO:254 and the light chain variable region comprises SEQ ID NO: 280.

31. The isolated antibody or antigen-binding fragment thereof of claim 27, wherein the heavy chain variable region comprises SEQ ID NO:255 and the light chain variable region comprises SEQ ID NO: 280.

32. The isolated antibody of claim 27, wherein the antibody 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.

33. The isolated antibody of claim 27, further comprising an immunoglobulin constant region.