

(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), DFNIQNYNHDIALVQ (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 AFVIFDDLSQLRW (SEQ ID NO:23),

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

In one aspect, the present disclosure refers to 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:56, a HC-CDR2 set forth as SEQ ID NO:58, and a HC-CDR3 set forth as SEQ ID NO:60; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:142, SEQ ID NO:257, SEQ ID NO:258 or SEQ ID NO:259, a LC-CDR2 set forth as SEQ ID NO:144, and a LC-CDR3 set forth as SEQ ID NO:146; or

(b) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:62, a HC-CDR2 set forth as SEQ ID NO:63, SEQ ID NO:67 or SEQ ID NO:69, and a HC-CDR3 set forth as SEQ ID NO:65; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:149, a LC-CDR2 set forth as SEQ ID NO:144, and a LC-CDR3 set forth as SEQ ID NO:146.

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;

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

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

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

In another aspect, the present disclosure refers to 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, the present disclosure refers to 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 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 aspect, the present disclosure refers to use of a composition as described herein the manufacture of a medicament for inhibiting alternative pathway complement activation in a subject suffering from an alternative pathway-related disease or condition 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, Amyotrophic 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, Antiphospholipid syndrome, Atherosclerosis, IgA Nephropathy and Myasthenia Gravis.

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 examples, 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 examples, the MASP-3

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) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:56, a HC-CDR2 set forth as SEQ ID NO:58, and a HC-CDR3 set forth as SEQ ID NO:60; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:142, SEQ ID NO:257, SEQ ID NO:258 or SEQ ID NO:259, a LC-CDR2 set forth as SEQ ID NO:144, and a LC-CDR3 set forth as SEQ ID NO:146; or

(b) a heavy chain variable region comprising a HC-CDR1 set forth as SEQ ID NO:62, a HC-CDR2 set forth as SEQ ID NO:63, SEQ ID NO:67 or SEQ ID NO:69, and a HC-CDR3 set forth as SEQ ID NO:65; and a light chain variable region comprising a LC-CDR1 set forth as SEQ ID NO:149, a LC-CDR2 set forth as SEQ ID NO:144, and a LC-CDR3 set forth as SEQ ID NO:146.

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 claim 1.

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 claim 1 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 claim 1 and a pharmaceutically acceptable excipient.

13. Use of a composition according to claim 12 in the manufacture of a medicament for inhibiting alternative pathway complement activation in a subject suffering from an alternative pathway-related disease or condition 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, Amyotrophic 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, Antiphospholipid syndrome, Atherosclerosis, IgA Nephropathy and Myasthenia Gravis.

14. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:56, the HC-CDR2 comprises SEQ ID NO:58, the HC-CDR3 comprises SEQ ID NO:60 and wherein the LC-CDR1 comprises SEQ ID NO:142, SEQ ID NO:257, SEQ ID NO:258 or SEQ ID NO:259; wherein the LC-CDR2 comprises SEQ ID NO:144 and wherein the LC-CDR3 comprises SEQ ID NO:146.

15. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:62, the HC-CDR2 comprises SEQ ID NO:63, SEQ ID NO:67 or SEQ ID NO:69, the HC-CDR3 comprises SEQ ID NO:65 and wherein the LC-CDR1 comprises SEQ ID NO:149, the LC-CDR2 comprises SEQ ID NO:144 and the LC-CDR3 comprises SEQ ID NO:146.

16. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:56, the HC-CDR2 comprises SEQ ID NO:58, the HC-CDR3 comprises SEQ ID NO:60, the LC-CDR1 comprises SEQ ID NO:142, the LC-CDR2 comprises SEQ ID NO:144, and the LC-CDR3 comprises SEQ ID NO:146.

17. The isolated antibody or antigen-binding fragment thereof of claim 16, wherein the heavy chain variable region comprises SEQ ID NO: 24 and the light chain variable region comprises SEQ ID NO:40.

18. The isolated antibody or antigen-binding fragment thereof of claim 16, wherein the heavy chain variable region comprises SEQ ID NO: 248 and the light chain variable region comprises SEQ ID NO:250.

19. The isolated antibody or antigen-binding fragment thereof of claim 16, wherein the heavy chain variable region comprises SEQ ID NO: 249 and the light chain variable region comprises SEQ ID NO:250.

20. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:56, the HC-CDR2 comprises SEQ ID NO:58, the HC-

CDR3 comprises SEQ ID NO:60, the LC-CDR1 comprises SEQ ID NO:258, the LC-CDR2 comprises SEQ ID NO:144, and the LC-CDR3 comprises SEQ ID NO:146.

21. The isolated antibody or antigen-binding fragment thereof of claim 20, wherein the heavy chain variable region comprises SEQ ID NO: 248 and the light chain variable region comprises SEQ ID NO:278.

22. The isolated antibody or antigen-binding fragment thereof of claim 20, wherein the heavy chain variable region comprises SEQ ID NO: 249 and the light chain variable region comprises SEQ ID NO:278.

23. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:62, the HC-CDR2 comprises SEQ ID NO:63, the HC-CDR3 comprises SEQ ID NO:65, the LC-CDR1 comprises SEQ ID NO:149, the LC-CDR2 comprises SEQ ID NO:144, and the LC-CDR3 comprises SEQ ID NO:146.

24. The isolated antibody or antigen-binding fragment thereof of claim 23, wherein the heavy chain variable region comprises SEQ ID NO:25 and the light chain variable region comprises SEQ ID NO:41.

25. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:62, the HC-CDR2 comprises SEQ ID NO:67, the HC-CDR3 comprises SEQ ID NO:65, the LC-CDR1 comprises SEQ ID NO:149, the LC-CDR2 comprises SEQ ID NO:144, and the LC-CDR3 comprises SEQ ID NO:146.

26. The isolated antibody or antigen-binding fragment thereof of claim 25, wherein the heavy chain variable region comprises SEQ ID NO:26 and the light chain variable region comprises SEQ ID NO:42.

27. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the HC-CDR1 comprises SEQ ID NO:62, the HC-CDR2 comprises SEQ ID NO:69, the HC-CDR3 comprises SEQ ID NO:65, the LC-CDR1 comprises SEQ ID NO:149, the LC-CDR2 comprises SEQ ID NO:144, and the LC-CDR3 comprises SEQ ID NO:146.

28. The isolated antibody or antigen-binding fragment thereof of claim 27, wherein the heavy chain variable region comprises SEQ ID NO:27 and the light chain variable region comprises SEQ ID NO:42.

29. The use according to claim 13, wherein the alternative pathway-related disease or condition is paroxysmal nocturnal hemoglobinuria (PNH).

30. The use according to claim 13, wherein the alternative pathway-related disease or condition is age-related macular degeneration (AMD, including wet and dry AMD), arthritis, 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, neuromyelitis optica, Amyotrophic lateral sclerosis (ALS), lupus nephritis, systemic lupus erythematosus (SLE), Uveitis, Chronic obstructive pulmonary disease (COPD), C3 glomerulopathy, ANCA vasculitis, IgA Nephropathy or Myasthenia Gravis.