

alternative pathway. The classical pathway is usually triggered by a complex composed of host antibodies bound to a foreign particle (*i.e.*, an antigen) and thus requires prior exposure to an antigen for the generation of a specific antibody response. Since activation of the classical pathway depends on a prior adaptive immune response by the host, the classical pathway is part of the acquired immune system. In contrast, both the lectin and alternative pathways are independent of adaptive immunity and are part of the innate immune system.

The lectin pathway is widely thought to have a major role in host defense against infection in the naïve host. Strong evidence for the involvement of MBL in host defense comes from analysis of patients with decreased serum levels of functional MBL (Kilpatrick, *Biochim. Biophys. Acta* 1572:401-413, (2002)). Such patients display susceptibility to recurrent bacterial and fungal infections. These symptoms are usually evident early in life, during an apparent window of vulnerability as maternally derived antibody titer wanes, but before a full repertoire of antibody responses develops. This syndrome often results from mutations at several sites in the collagenous portion of MBL, which interfere with proper formation of MBL oligomers. However, since MBL can function as an opsonin independent of complement, it is not known to what extent the increased susceptibility to infection is due to impaired complement activation.

In addition to its essential role in immune defense, the complement system contributes to tissue damage in many clinical conditions. Thus, there is a pressing need to develop therapeutically effective complement inhibitors to prevent these adverse effects.

SUMMARY

In one aspect, the present disclosure refers to use of a MASP-2 inhibitory antibody in the manufacture of a medicament for treating a subject suffering from, or at risk of developing, a disease, disorder or condition associated with complement-related inflammation, excessive coagulation or contact system activation initiated by fibrin or activated platelets, wherein the MASP-2 inhibitory antibody is a MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:5, wherein said MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.

In one example, the present disclosure provides a method of preventing, reducing and/or treating a disease, disorder or condition associated with fibrin-induced activation of the complement system and the associated activation of the coagulation and/or contact systems comprising administering a therapeutic amount of a MASP-2 inhibitory antibody to a subject in need thereof. In some examples, the methods of the disclosure provide anticoagulation and/or antithrombosis and/or antithrombogenesis without affecting hemostasis. In one example of the disclosure, the methods are useful for

treating a subject is suffering from, or at risk of developing, a disease, disorder or condition associated with complement-related inflammation, excessive coagulation or contact system activation initiated by fibrin or activated platelets. In one example, the methods of the disclosure are useful for treating a subject suffering from a disease, disorder or condition selected from the group consisting of arterial thrombosis, venous thrombosis, deep vein thrombosis, post-surgical thrombosis, restenosis following coronary artery bypass graft and/or an interventional cardiovascular procedure (e.g., angioplasty or stent placement), atherosclerosis, plaque rupture, plaque instability, restenosis, hypotension, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), disseminated intravascular coagulation (DIC), veno-occlusive disease (VOD), sickle cell disease, thrombotic microangiopathy, lupus nephritis, superficial thrombophlebitis, Factor V Leiden mutation, ischemic/reperfusion injury, human immunodeficiency virus (HIV) infection, undergoing hormone-replacement therapy (HRT), Alzheimer's disease and/or suffering from a hypercoagulable state, such as wherein the subject is suffering from, or at risk for developing an acquired hypercoagulable state due to at least one or more of the following: undergoing therapy with a drug selected from the group consisting of 5-FU, GM-CSF, cisplatin, heparin, COX-2 inhibitor, contrast media, corticosteroids and antipsychotics, venous stasis (due to immobilization, surgery, etc.), antiphospholipid syndrome, cancer (promyelocytic leukemia, lung, breast, prostate, pancreas, stomach and colon tumors), tissue injury due to trauma or surgery, presence of a catheter in a central vein, acquired deficiency of a protein involved in clot formation (e.g., protein C), paroxysmal nocturnal hemoglobinuria (PNH), elevated levels of homocysteine, heart failure, presence of a mechanical valve, pulmonary hypertension with in-situ thrombosis, atrial fibrillation, heparin-induced thrombocytopenia (HIT), heparin-induced thrombocytopenia and thrombosis (HITT), Kawasaki disease with in-situ thrombus, Takayasu arteritis with in-situ thrombus, thrombophilia of metastatic cancer, elevated Factor VIII levels, pregnancy and inflammatory bowel disease (IBD).

In one example, the methods of the disclosure are useful for treating a subject suffering from, or at risk for developing, a disease, disorder or condition that is amenable to treatment with a kallikrein inhibitor, such as, for example, wherein the disease or disorder amenable to treatment with a kallikrein inhibitor is selected from the group consisting of hereditary angioedema, diabetic macular edema, and bleeding during cardiopulmonary bypass. In one example, the methods of the disclosure are useful for treating a subject suffering from, or at risk for developing, a disease, disorder or condition that is amenable to treatment with a thrombin inhibitor, such as, for example, wherein the disease or disorder amenable to treatment with a thrombin inhibitor is selected from the group consisting of arterial thrombosis, venous thrombosis, pulmonary embolism, atrial fibrillation, heparin-induced thrombocytopenia, conversion from one anticoagulant to another, and off-label use for extracorporeal circuit patency of continuous renal replacement therapy (CRRT) in critically ill patients with HIT (maintenance). In one example, the method comprises identifying a subject that has previously experienced, is currently suffering from, or is at risk for developing atrial fibrillation and administering a MASP-2 inhibitory antibody in an amount sufficient to reduce the risk of stroke in said subject.

In one example, the methods of the disclosure are useful for treating a subject suffering from, or at risk for developing, a disease, disorder or condition that is amenable to treatment with a factor XII inhibitor, such as, for example, wherein the disease or disorder amenable to treatment with a factor XII inhibitor is selected from the group consisting of deep vein thrombosis (both primary prophylaxis and extended therapy), pulmonary embolism, nonvalvular atrial fibrillation, prevention of recurrent ischemia after acute coronary syndrome in subjects with or without atrial fibrillation, end-stage renal disease, cerebral ischemia, angina, reduce or prevent clotting associated with implanted medical devices (e.g., valves, small caliber grafts, etc) and/or extracorporeal circuits. In one example, the method comprises identifying a subject that has previously experienced, is currently suffering from, or is at risk for developing

nonvalvular atrial fibrillation and administering a MASP-2 inhibitory antibody in an amount sufficient to reduce the risk of stroke and/or embolism in said subject.

In one example, the methods of the disclosure are useful for treating a subject determined to have a genetic defect that causes or increases the risk of developing a hypercoagulable state, such as, for example, wherein the genetic defect is selected from the group consisting of a Prothrombin 20210 gene mutation, an MTHFR mutation, a deficiency of protein C, a deficiency of protein S, a deficiency of protein A, a deficiency of protein Z, an antithrombin deficiency and a genetic disorder producing thrombophilia.

In one example, the methods of the disclosure are useful for treating a subject that has an acquired disease, disorder or condition that increases the propensity for thromboembolism, such as, for example, wherein the acquired disease or disorder that increases the propensity for thromboembolism is selected from the group consisting of atherosclerosis, antiphospholipid antibodies, cancer (e.g., promyelocytic leukemia, lung, breast, prostate, pancreatic, stomach or colon cancer), hyperhomocysteinemia, infection, tissue injury, venous stasis (such as due to surgery, orthopedic or paralytic immobilization, heart failure, pregnancy, or obesity) and a subject taking oral contraceptives that contain estrogen.

In one example, the methods of the disclosure are useful for providing a replacement for standard anticoagulant therapy, such as Warfarin, in a subject in need of anticoagulant therapy, such as wherein the subject has a condition that normally prohibits standard anticoagulant therapy (e.g., CNS amyloid angiopathy), or wherein the MASP-2 inhibitory antibody is administered as a bridging agent perioperatively in a subject otherwise on standard anticoagulation therapy.

In accordance with any of the examples of the methods of the disclosure described herein, the MASP-2 inhibitory antibody is preferably a MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:5. In some examples, the MASP-2 antibody is a chimeric, humanized or human antibody. In some examples, the MASP-2 inhibitory antibody is an antibody fragment selected from the group consisting of Fv, Fab, Fab', F(ab)₂ and F(ab')₂. In some examples, the

5 MASP-2 inhibitory antibody is a single-chain molecule. In some examples, the MASP-2
inhibitory antibody is selected from the group consisting of an IgG1 molecule, an IgG2
and an IgG4 molecule. In some examples, the MASP-2 inhibitory antibody is an IgG4
molecule comprising a S228P mutation. In some examples, the MASP-2 inhibitory
antibody does not substantially inhibit the classical pathway. In some examples, the
10 MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof,
comprises: (a) a heavy-chain variable region comprising: i) a heavy chain CDR-H1
comprising the amino acid sequence from 31-35 of SEQ ID NO:6; and ii) a heavy-chain
CDR-H2 comprising the amino acid sequence from 50-65 of SEQ ID NO:6; and iii) a
heavy-chain CDR-H3 comprising the amino acid sequence from 95-107 of SEQ ID NO:6
15 and (b) a light-chain variable region comprising: i) a light-chain CDR-L1 comprising the
amino acid sequence from 24-34 of SEQ ID NO:7; and ii) a light-chain CDR-L2
comprising the amino acid sequence from 50-56 of SEQ ID NO:7; and iii) a light-chain
CDR-L3 comprising the amino acid sequence from 89-97 of SEQ ID NO:7. In some
examples, the MASP-2 inhibitory monoclonal antibody comprises a heavy-chain variable
region set forth as SEQ ID NO:6 and a light-chain variable region set forth as SEQ ID
NO:7. In some examples, the MASP-2 inhibitory antibody or antigen binding-fragment
thereof specifically recognizes at least part of an epitope recognized by a reference
antibody comprising a heavy chain variable region as set forth in SEQ ID NO:6 and a
20 light-chain variable region as set forth in SEQ ID NO:7.

These and other aspects and examples 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
25 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 disclosure will
30 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:

CLAIMS

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

- 5 1. Use of a MASP-2 inhibitory antibody in the manufacture of a medicament for treating a subject suffering from, or at risk of developing, a disease, disorder or condition associated with complement-related inflammation, excessive coagulation or contact system activation initiated by fibrin or activated platelets, wherein the MASP-2 inhibitory antibody is a MASP-2 monoclonal antibody, or fragment thereof that specifically binds to
10 a portion of SEQ ID NO:5, wherein said MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.
2. The use of Claim 1, wherein the subject is suffering from an acquired hypercoagulable state.
3. The use of Claim 2, wherein the acquired hypercoagulable state is due to a
15 disease or condition selected from the group consisting of Kawasaki disease with in-situ thrombus, pulmonary hypertension with in-situ thrombosis, Takayasu arteritis with in-situ thrombus, atrial fibrillation, undergoing therapy with a drug selected from the group consisting of 5-FU, GM-CSF, cisplatin, heparin, COX-2 inhibitor, contrast media, corticosteroids and antipsychotics; venous stasis from immobilization and/or surgery,
20 acquired deficiency of a protein involved in clot formation (e.g., protein C), elevated levels of homocysteine, heart failure, presence of a mechanical valve, heparin-induced thrombocytopenia (HIT), heparin-induced thrombocytopenia and thrombosis (HITT), , thrombophilia of metastatic cancer, elevated Factor VIII levels, pregnancy, suffering from antiphospholipid syndrome, cancer (promyelocytic leukemia, lung, breast, prostate, pancreas, stomach and colon tumors); tissue injury due to trauma or surgery, presence of
25 a catheter in a central vein, paroxysmal nocturnal hemoglobinuria (PNH), or inflammatory bowel disease (IBD).
4. The use of Claim 1, wherein the subject has an acquired disease, disorder or condition that increases the propensity for thromboembolism.
- 30 5. The use of Claim 4, wherein the acquired disease, disorder or condition that increases the propensity for thromboembolism is selected from the group consisting of infection, tissue injury, atherosclerosis, antiphospholipid antibodies, cancer,

hyperhomocysteinemia, venous stasis (such as due to surgery, orthopedic or paralytic immobilization, heart failure, pregnancy, or obesity) and a subject taking oral contraceptives that contain estrogen.

5 6. The use of Claim 1, wherein the subject is suffering from a disease or disorder selected from the group consisting of sickle cell disease, arterial thrombosis, venous thrombosis, deep vein thrombosis, post-surgical thrombosis, atherosclerotic, plaque rupture, and/or plaque instability, hypotension, superficial thrombophlebitis, Factor V Leiden mutation, and undergoing hormone-replacement therapy (HRT), following coronary artery bypass graft and/or an interventional cardiovascular procedure such as
10 angioplasty or stent replacement; atherosclerosis, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), disseminated intravascular coagulation (DIC), veno-occlusive disease (VOD), thrombotic microangiopathy, lupus nephritis, ischemic/reperfusion injury, human immunodeficiency virus (HIV) infection, Alzheimer's disease, hereditary angioedema, diabetic macular edema and bleeding during
15 cardiopulmonary bypass.

7. The use of Claim 1, wherein the subject is suffering from, or at risk for developing, a disease or disorder that is amenable to treatment with a thrombin inhibitor such as wherein the disease or disorder amenable to treatment with a thrombin inhibitor is selected from the group consisting of, pulmonary embolism, conversion from one
20 anticoagulant to another, and off-label use for extracorporeal circuit patency of continuous renal replacement therapy (CRRT) in critically ill patients with HIT (maintenance).

8. The use of Claim 1, wherein the subject has previously experienced, is currently suffering from, or is at risk for developing atrial fibrillation and the MASP-2
25 inhibitory antibody is to be administered in an amount sufficient to reduce the risk of stroke in said subject.

9. The use of Claim 1, wherein the subject is suffering from, or at risk for developing, a disease or disorder that is amenable to treatment with a factor XII inhibitor, such as wherein the disease or disorder amenable to treatment with a factor XII inhibitor
30 is selected from the group consisting of deep vein thrombosis (both primary prophylaxis and extended therapy), nonvalvular atrial fibrillation, prevention of recurrent ischemia after acute coronary syndrome in subjects with or without atrial fibrillation, end-stage

renal disease, cerebral ischemia, angina, reduce or prevent clotting associated with medical devices (e.g., valves, small caliber grafts) and/or extracorporeal circuits.

10. The use of Claim 1, wherein the subject has previously experienced, is currently suffering from, or is at risk for developing nonvalvular atrial fibrillation and the
5 MASP-2 inhibitory antibody is to be administered in an amount sufficient to reduce the risk of stroke and/or embolism in said subject.

11. The use of Claim 1, wherein the subject has a genetic defect that causes or increases the risk of developing, a hypercoagulable state, wherein the genetic defect is selected from the group consisting of a Prothrombin 20210 gene mutation, an MTHFR
10 mutation, a deficiency of protein C, a deficiency of protein S, a deficiency of protein A, a deficiency of protein Z, an antithrombin deficiency and a genetic disorder producing thrombophilia.

12. The use of Claim 1, wherein the subject is in need of anticoagulant therapy and the MASP-2 inhibitory antibody is to be used as a replacement for standard
15 anticoagulant therapy such as Warfarin.

13. The use of Claim 12, wherein the subject has a condition that normally prohibits standard anticoagulant therapy, such as CNS amyloid angiopathy.

14. The use of Claim 12, wherein the MASP-2 inhibitory antibody is to be administered as a bridging agent perioperatively in a subject otherwise on standard
20 anticoagulation therapy.

15. The use of Claim 1, wherein the MASP-2 antibody is a recombinant, chimeric, humanized or human antibody.

16. The use of Claim 1, wherein said MASP-2 inhibitory antibody is an antibody fragment selected from the group consisting of Fv, Fab, Fab', F(ab)₂ and F(ab')₂.

25 17. The use of Claim 1, wherein said MASP-2 inhibitory antibody is a single-chain molecule.

18. The use of Claim 1, wherein said MASP-2 inhibitory antibody is selected from the group consisting of an IgG1 molecule, an IgG2 and an IgG4 molecule.

19. The use of Claim 1, wherein the MASP-2 inhibitory monoclonal antibody,
30 or antigen-binding fragment thereof, comprises:

(a) a heavy-chain variable region comprising: i) a heavy chain CDR-H1 comprising the amino acid sequence from 31-35 of SEQ ID NO:6; and ii) a heavy-chain CDR-H2 comprising the amino acid sequence from 50-65 of SEQ ID NO:6; and iii) a

heavy-chain CDR-H3 comprising the amino acid sequence from 95-107 of SEQ ID NO:6
and

- (b) a light-chain variable region comprising: i) a light-chain CDR-L1 comprising
the amino acid sequence from 24-34 of SEQ ID NO:7; and ii) a light-chain CDR-L2
5 comprising the amino acid sequence from 50-56 of SEQ ID NO:7; and iii) a light-chain
CDR-L3 comprising the amino acid sequence from 89-97 of SEQ ID NO:7.

20. The use of Claim 1, wherein the MASP-2 inhibitory monoclonal antibody
comprises a heavy-chain variable region set forth as SEQ ID NO:6 and a light-chain
variable region set forth as SEQ ID NO:7.

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