

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 a disease, disorder or condition selected from the group consisting of Kawasaki disease with in-situ thrombus, atrial fibrillation and thromboembolic events associated with sickle cell disease, 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

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 a disease, disorder or condition selected from the group consisting of Kawasaki disease with in-situ thrombus, atrial fibrillation and thromboembolic events associated with sickle cell disease, wherein the MASP-2 inhibitory antibody is a MASP-2 monoclonal antibody, or fragment thereof that
10 specifically binds to 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 atrial fibrillation and the MASP-2 inhibitory antibody is to be administered in an amount sufficient to reduce the risk of stroke in said subject.
- 15 3. The use of Claim 1, wherein the subject is suffering from nonvalvular atrial fibrillation and the MASP-2 inhibitory antibody is to be administered in an amount sufficient to reduce the risk of stroke and/or embolism in said subject.
4. 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
20 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.
5. The use of Claim 1, wherein the subject is in need of anticoagulant therapy
25 and the MASP-2 inhibitory antibody is to be used as a replacement for standard anticoagulant therapy.
6. The use of Claim 5, wherein the subject has a condition that normally prohibits standard anticoagulant therapy.
7. The use of Claim 5, wherein the MASP-2 inhibitory antibody is to be
30 administered as a bridging agent perioperatively in a subject otherwise on standard anticoagulation therapy.

8. The use of Claim 1, wherein the MASP-2 antibody is a recombinant, chimeric, humanized or human antibody.
9. 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.
- 5 10. The use of Claim 1, wherein said MASP-2 inhibitory antibody is a single-chain molecule.
11. 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.
12. The use of Claim 1, wherein the MASP-2 inhibitory monoclonal antibody,
10 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
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- (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.
- 20 13. 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.