the most potent anaphylatoxin, inducing alterations in smooth muscle and vascular tone, as well as vascular permeability. It is also a powerful chemotaxin and activator of both neutrophils and monocytes. C5a-mediated cellular activation can significantly amplify inflammatory responses by inducing the release of multiple additional inflammatory mediators, including cytokines, hydrolytic enzymes, arachidonic acid metabolites, and reactive oxygen species. C5 cleavage leads to the formation of C5b-9, also known as the membrane attack complex (MAC). There is now strong evidence that sublytic MAC deposition may play an important role in inflammation in addition to its role as a lytic pore-forming complex.

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

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

In one aspect, the present invention refers to the use of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof comprising a heavy chain variable region set forth as SEQ ID NO:67 and a light chain variable region set forth as SEQ ID NO:70, in the manufacture of a medicament for treating a human subject suffering from persistent thrombotic microangiopathy (TMA) associated with hematopoietic stem cell transplant (HSCT-TMA), wherein the medicament is to be administered at least weekly for a period of at least three weeks, at a dose of at least 4mg/kg, wherein said subject has TMA that persists despite a reduction or discontinuation of an immunosuppressive agent, or wherein said subject has TMA that persists at least 30 days after transplant, wherein said medicament improves at least one or more of the following clinical parameters associated with persistent TMA associated with hematopoietic stem cell transplant: (i) an increase in platelet count; (ii) an increase in haptoglobin; (iii) a decrease in lactate dehydrogenase (LDH); and/or (iv) a decrease in creatinine. Also described herein is a method of inhibiting microvascular endothelial cell injury and/or thrombus formation in a subject suffering from a thrombotic microangiopathy (TMA) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody effective to inhibit MASP-2-dependent complement activation. In some examples, the subject is suffering from, or at risk for developing a TMA selected from the group consisting of hemolytic uremic syndrome (aHUS), thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (HUS). In some examples, prior to administration of the composition the subject is determined to exhibit one or more symptoms selected from the group consisting of (i) anemia, (ii) thrombocytopenia (iii) renal insufficiency and (iv) rising creatinine, and the composition is administered in an effective amount and for a sufficient time period to improve said one or more symptoms. In some examples, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof. In some examples, the MASP-2 inhibitory agent is an anti-MASP-2 monoclonal antibody, or

fragment thereof that specifically binds to a portion of SEQ ID NO:6. In some examples, the MASP-2 inhibitory agent inhibits microvascular endothelial cell injury.

In another example, the disclosure provides a method of inhibiting MASP-2-dependent complement activation in a subject suffering from or at risk for developing atypical hemolytic uremic syndrome (aHUS), comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation. In one example, prior to administration of the composition the subject is determined to exhibit one or more symptoms selected from the group consisting of (i) anemia, (ii) thrombocytopenia (iii) renal insufficiency and (iv) rising creatinine, and the composition is administered in an effective amount and for a sufficient time period to improve said one or more symptoms. In one example, the subject is suffering from or at risk for developing non-Factor H-dependent aHUS. In one example, the subject is suffering from aHUS associated with factor I, factor B, or membrane cofactor CD46. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In one example, the MASP-2 inhibitory agent inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

In another example, the disclosure provides a method for reducing the likelihood that a subject at risk for developing atypical hemolytic uremic syndrome (aHUS) will suffer clinical symptoms associated with aHUS. The method according to this embodiment of the disclosure comprises (a) determining the presence of a genetic marker in the subject known to be associated with aHUS; (b) periodically monitoring the subject to determine the presence or absence of at least one symptom selected from the group consisting of anemia, thrombocytopenia, renal insufficiency and rising creatinine; and (c) administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation upon the determination of the presence of at least one of anemia, thrombocytopenia, renal insufficiency or rising creatinine, wherein the composition is administered in an effective amount and for a sufficient time period to improve said one or more symptoms. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In one example of the method, step

(a) comprises performing a genetic screening test on a sample obtained from the subject and identifying the presence of at least one genetic marker associated with aHUS in a gene selected from the group consisting of complement factor H (CFH), factor I (CFI), factor B (CFB), membrane cofactor CD46, C3, complement factor H-related protein (CFHR1), anticoagulant protein thrombodulin (THBD), complement factor H-related protein 3 (CFHR3) and complement factor H-related protein 4 (CFHR4). In one example, the method further comprises monitoring the subject for the occurrence of an event known to be associated with triggering aHUS clinical symptoms and administering to the subject the composition comprising the MASP-2 inhibitory agent prior to, during, or after the occurrence of the triggering event. In one example, the event associated with triggering aHUS clinical symptoms is selected from the group consisting of drug exposure, infection, malignancy, injury, organ or tissue transplant and pregnancy. In one example, the infection is a bacterial infection. In one example, the composition is administered subcutaneously. In one example, the MASP-2 inhibitory agent inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

Disclosed is a method of inhibiting MASP-2-dependent complement activation in a subject suffering from, or at risk for developing, atypical hemolytic uremic syndrome (aHUS) secondary to an infection, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 complement activation. In one example, the subject is suffering from, or at risk for developing non-enteric aHUS associated with an *S. pneumonia* infection. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In one example, the MASP-2 inhibitory agent inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

In another example, the disclosure provides a method of treating a subject suffering from atypical hemolytic uremic syndrome (aHUS) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation, wherein the administration of the MASP-2 inhibitory agent is administered via an intravenous catheter or other catheter delivery method. In one example, the method further comprises treating the patient

CLAIMS

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

1. Use of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof comprising a heavy chain variable region set forth as SEQ ID NO:67 and a light chain variable region set forth as SEQ ID NO:70, in the manufacture of a medicament for treating a human subject suffering from persistent thrombotic microangiopathy (TMA) associated with hematopoietic stem cell transplant (HSCT-TMA), wherein the medicament is to be administered at least weekly for a period of at least three weeks, at a dose of at least 4mg/kg, wherein said subject has TMA that persists despite a reduction or discontinuation of an immunosuppressive agent, or wherein said subject has TMA that persists at least 30 days after transplant, wherein said medicament improves at least one or more of the following clinical parameters associated with persistent TMA associated with hematopoietic stem cell transplant: (i) an increase in platelet count; (ii) an increase in haptoglobin; (iii) a decrease in lactate dehydrogenase (LDH); and/or (iv) a decrease in creatinine.

2. The use of Claim 1, wherein the antibody or fragment thereof is selected from the group consisting of a recombinant antibody, an antibody having reduced effector function, a chimeric antibody, a humanized antibody, and a human antibody.

3. The use of Claim 1, wherein the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less.

4. The use of Claim 1, wherein the MASP-2 inhibitory antibody is to be delivered to the subject systemically.

5. The use of Claim 1, wherein the subject has previously undergone, or is currently undergoing, treatment with a humanized anti-C5 antibody or antigen-binding fragment thereof.

6. The use of Claim 1, wherein the increase in platelet count is at least double the platelet count prior to treatment.

7. The use of Claim 1, wherein the subject has TMA that persists for at least two weeks after the reduction or discontinuation of an immunosuppression agent.

8. The use of Claim 1, wherein the subject has TMA that persists for at least 30 days after transplant.

9. The use of Claim 1, wherein the immunosuppression agent is a calcineurin inhibitor.