In another example, the present disclosure provides a method of treating a human subject suffering from, or at risk for developing graft-versus-host disease (GVHD) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation. In one example, the subject has previously undergone, or is currently undergoing, or will undergo a hematopoietic stem cell transplant. In one example, the method further comprises identifying a human subject suffering from, or at risk for developing graft-versus-host disease prior to the step of administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation. In one example, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one example, the MASP-2 inhibitory 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. In one example, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In one example, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less. In one example, the MASP-2 inhibitory antibody is delivered to the subject systemically. In one example, the subject is suffering from acute GVHD. In one example, the subject is suffering from steroid-resistant GVHD. In one example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof, comprises a heavy chain variable region comprising CDR-H1, CDR-H2 and CDR-H3 of the amino acid sequence set forth as SEQ ID NO:67 and a light chain variable region comprising CDR-L1, CDR-L2 and CDR-L3 of the amino acid sequence set forth as SEQ ID NO:70.

In one aspect, the present disclosure refers to use of a composition comprising an amount of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent lectin pathway complement activation, in the manufacture of a medicament for treating a human subject suffering from graft-versus-host disease (GVHD).

In another example, the present disclosure provides a method of treating, preventing or amelioriating one or more neurological symptoms associated with graft-versus-host disease or TMA comprising administering to a subject in need thereof a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation. In one example, the one or more neurological symptoms associated with graft-versus-host disease or TMA is selected from the group consisting of asthenia, paresthesias,

developing diffuse alveolar hemorrhage (DAH) prior to the step of administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation. In one example, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one example, the MASP-2 inhibitory 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. In one example, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In one example, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less. In one example, the MASP-2 inhibitory antibody is delivered to the subject systemically. In one example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof, comprises a heavy chain variable region comprising CDR-H1, CDR-H2 and CDR-H3 of the amino acid sequence set forth as SEQ ID NO:67 and a light chain variable region comprising CDR-L1, CDR-L2 and CDR-L3 of the amino acid sequence set forth as SEQ ID NO:70.In another example, the present disclosure provides compositions for inhibiting the adverse effects of MASP-2-dependent complement activation, comprising a therapeutically effective amount of a MASP-2 inhibitory agent, such as a MASP-2 inhibitory antibody and a pharmaceutically acceptable carrier. Methods are also provided for manufacturing a medicament for use in inhibiting the adverse effects of MASP-2-dependent complement activation in living subjects in need thereof, comprising a therapeutically effective amount of a MASP-2 inhibitory agent in a pharmaceutical carrier. Methods are also provided for manufacturing medicaments for use in inhibiting MASP-2-dependent complement activation for treatment of each of the conditions, diseases and disorders described herein below.

In another example, the present disclosure refers to use of a composition comprising an amount of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation, in the manufacture of a medicament for treating a human subject suffering from, or at risk for developing diffuse alveolar hemorrhage, wherein the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.

In another example, the present disclosure provides a method of treating a human subject suffering from, or at risk for developing veno-occulsive disease (VOD) associated with hematopoietic stem cell transplant comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation. In one example, the subject has previously undergone, or is currently undergoing, or will undergo a hematopoietic stem cell transplant. In one example, the method further

cell transplant diffuse alveolar hemorrhage and/or a subject suffering from, or at risk for developing veno-occlusive disease (VOD) as further described herein.

In another example, the present disclosure refers to use of a composition comprising an amount of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation, in the manufacture of a medicament for treating a human subject suffering from, or at risk for developing veno-occlusive disease, wherein the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.

DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will 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:

FIGURE 1 is a diagram illustrating the genomic structure of human MASP-2;

FIGURE 2A is a schematic diagram illustrating the domain structure of human MASP-2 protein;

FIGURE 2B is a schematic diagram illustrating the domain structure of human MAp19 protein;

FIGURE 3 is a diagram illustrating the murine MASP-2 knockout strategy;

FIGURE 4 is a diagram illustrating the human MASP-2 minigene construct;

FIGURE 5A presents results demonstrating that MASP-2-deficiency leads to the loss of lectin-pathway-mediated C4 activation as measured by lack of C4b deposition on mannan, as described in Example 2;

FIGURE 5B presents results demonstrating that MASP-2-deficiency leads to the loss of lectin-pathway-mediated C4 activation as measured by lack of C4b deposition on zymosan, as described in Example 2;

FIGURE 5C presents results demonstrating the relative C4 activation levels of serum samples obtained from MASP-2+/-; MASP-2-/- and wild-type strains as measure by C4b deposition on mannan and on zymosan, as described in Example 2;

FIGURE 6 presents results demonstrating that the addition of murine recombinant MASP-2 to MASP-2-/- serum samples recovers lectin-pathway-mediated C4 activation in a protein concentration dependant manner, as measured by C4b deposition on mannan, as described in Example 2;

FIGURE 7 presents results demonstrating that the classical pathway is functional in the MASP-2-/- strain, as described in Example 8;

FIGURE 8A presents results demonstrating that anti-MASP-2 Fab2 antibody #11 inhibits C3 convertase formation, as described in Example 10;

CLAIMS

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

1. Use of a composition comprising an amount of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent lectin pathway complement activation, in the manufacture of a medicament for treating a human subject suffering from graft-versus-host disease (GVHD).

2. The use of Claim 1, wherein a human subject suffering from graft-versus-host disease is identified prior to the administration to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation.

3. The use of Claim 1, wherein the subject has previously undergone a hematopoietic stem cell transplant.

4. The use of claim 1, wherein the subject is suffering from acute GVHD.

5. The use of claim 1, wherein the subject is suffering from chronic GVHD.

6. The use of claim 1, wherein the subject is suffering from steroid-resistant GVHD.

7. The use of Claim 1, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof, comprises a heavy chain variable region comprising CDR-H1, CDR-H2 and CDR-H3 of the amino acid sequence set forth as SEQ ID NO:67 and a light chain variable region comprising CDR-L1, CDR-L2 and CDR-L3 of the amino acid sequence set forth as SEQ ID NO:70.

8. The use of any of claims 1-7, wherein a composition comprising said MASP-2 inhibitory antibody is to be administered to the subject in a dosage of from 1 mg/kg to 10 mg/kg at least once weekly.

9. The use of claim 1, wherein the subject is suffering from one or more neurological symptoms associated with graft-versus-host disease and a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, is to be administered to the subject after receiving a hematopoietic stem cell transplant, effective to treat, prevent or ameliorate one or more neurological symptoms associated with graft-versus-host disease.

10. The use of claim 9, wherein the one or more neurological symptoms associated with graft-versus-host-disease is selected from the group consisting of asthenia, paresthesias, tetraplegia, sensorimotor deficit, dysautonomic polyneuropathy, and/or neurogenic bladder.