

to the alternative pathway C3 convertase leads to the formation of the alternative pathway C5 convertase.

All three pathways (i.e., the classical, lectin and alternative) have been thought to converge at C5, which is cleaved to form products with multiple proinflammatory effects.

5 The converged pathway has been referred to as the terminal complement pathway. C5a is 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
10 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.

15 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.

20 It is well established that angiogenesis is implicated in the pathogenesis of a variety of disorders including solid tumors and metastases, and ocular neovascular diseases such as age-related macular degeneration (AMD), proliferative diabetic retinopathy and neovascular glaucoma.

In view of the role of angiogenesis in many diseases and disorders, there is also a pressing need to develop therapeutically effective angiogenesis inhibitors.

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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
30 used as an aid in determining the scope of the claimed subject matter.

In one aspectexample, the present inventiondisclosure provides methods for preventing, treating, reverting and/or delaying angiogenesis in a mammalian subject suffering from, or at risk for developing, an angiogenesis-dependent disease or condition, comprising

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administering to the subject an amount of a MASP-2 inhibitory agent effective to inhibit angiogenesis. In some ~~embodiments of these aspects~~examples of the ~~invention~~disclosure, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In further ~~embodiment~~examples, the MASP-2 antibody has reduced effector function. In some ~~embodiment~~examples, the MASP-2 inhibitory agent is a MASP-2 inhibitory peptide or a non-peptide MASP-2 inhibitor.

In another ~~aspect~~example, the present ~~invention~~disclosure provides compositions for inhibiting the adverse effects of angiogenesis, comprising a therapeutically effective amount of a MASP-2 inhibitory agent and a pharmaceutically acceptable carrier. Methods are also provided for manufacturing a medicament for use in inhibiting the adverse effects of angiogenesis 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 angiogenesis for treatment of each of the conditions, diseases and disorders described herein below.

The methods, compositions and medicaments of the ~~invention~~disclosure are useful for inhibiting the adverse effects of angiogenesis *in vivo* in mammalian subjects, including humans suffering from an acute or chronic pathological condition or injury as further described herein.

In another ~~aspect~~example of the ~~invention~~disclosure, methods are provided for inhibiting angiogenesis in a mammalian subject suffering from an angiogenesis-dependent disease or condition comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit angiogenesis. In some ~~embodiment~~examples, the angiogenesis-dependent disease or condition is an angiogenesis-dependent cancer, such as, for example, an angiogenesis-dependent cancer selected from the group consisting of solid tumor(s), blood borne tumors, high-risk carcinoid tumors, and tumor metastases. In some ~~embodiment~~examples, the angiogenesis-dependent disease or condition is an angiogenesis-dependent benign tumor, such as, for example, an angiogenesis-dependent benign tumor selected from the group consisting of hemangiomas, acoustic neuromas, neurofibromas, trachomas, carcinoid tumors, and pyogenic granulomas. In some ~~embodiment~~examples, the angiogenesis-dependent disease or condition is an ocular angiogenic disease or condition, such as, for example, an ocular angiogenic disease or condition selected from the group consisting of age-related macular degeneration (AMD), uveitis, ocular melanoma, corneal neovascularization, primary pterygium, HSV stromal keratitis,

HSV-1-induced corneal lymphangiogenesis, proliferative diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, corneal graft rejection, neovascular glaucoma, and rubeosis.

In one aspect, the present disclosure refers to use of a MASP-2 inhibitory monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6 in the manufacture of a medicament for preventing, treating, reverting and/or delaying angiogenesis in a mammalian subject suffering from an ocular angiogenic disease or condition selected from the group consisting of uveitis, ocular melanoma, corneal neovascularization, primary pterygium, HSV stromal keratitis, HSV-1-induced corneal lymphangiogenesis, proliferative diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, corneal graft rejection, neovascular glaucoma, and rubeosis.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject suffering from an ocular angiogenic disease or condition selected from the group consisting of AMD, uveitis, ocular melanoma, corneal neovascularization, primary pterygium, HSV stromal keratitis, HSV-1-induced corneal lymphangiogenesis, proliferative diabetic retinopathy, diabetic macular edema, retinopathy of prematurity, retinal vein occlusion, corneal graft rejection, neovascular glaucoma, vitreous hemorrhage secondary to proliferative diabetic retinopathy, neuromyelitis optica and rubeosis, comprising administering to the subject an amount of a MASP-2 inhibitory agent effective to inhibit angiogenesis.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of inhibiting tumor angiogenesis comprising administering to a subject with cancer an amount of a MASP-2 inhibitory agent effective to inhibit angiogenesis.

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;

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 fragment thereof
5 that specifically binds to a portion of SEQ ID NO:6 in the manufacture of a medicament
~~A method~~ for preventing, treating, reverting and/or delaying angiogenesis in a
mammalian subject suffering from an ocular angiogenic disease or condition selected
from the group consisting of uveitis, ocular melanoma, corneal neovascularization,
10 primary pterygium, HSV stromal keratitis, HSV-1-induced corneal lymphangiogenesis,
proliferative diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion,
corneal graft rejection, neovascular glaucoma, and rubeosis~~angiogenesis dependent~~
~~disease or condition comprising administering to the subject an amount of a MASP 2~~
~~inhibitory agent effective to inhibit angiogenesis.~~
2. ~~The method of Claim 1, wherein the MASP 2 inhibitory agent is a MASP-~~
15 ~~2 antibody or fragment thereof.~~
3. ~~The method of Claim 2, wherein the MASP-2 inhibitory agent is a MASP-~~
~~2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID~~
~~NO:6.~~
4. ~~The method of Claim 1, wherein the angiogenesis dependent disease or~~
20 ~~condition is an angiogenesis dependent cancer.~~
5. ~~The method of Claim 1, wherein the angiogenesis dependent disease or~~
~~condition is a benign tumor.~~
6. ~~The method of Claim 1, wherein the angiogenesis dependent disease or~~
~~condition is an ocular angiogenic disease or condition.~~
7. ~~The method of Claim 4, wherein the subject is suffering from an~~
25 ~~angiogenesis dependent cancer selected from the group consisting of: solid tumor(s),~~
~~blood borne tumors, high risk carcinoid tumors, and tumor metastases.~~

8. ~~The method of Claim 7, wherein the subject is suffering from one or more solid tumors and the method comprises administering an amount of MASP 2 inhibitor effective to inhibit tumor angiogenesis.~~

9. ~~The method of Claim 8, wherein the subject is suffering from or at risk for tumor metastases and the method comprises administering an amount of MASP 2 inhibitor effective to inhibit tumor metastases.~~

10. ~~The method of Claim 5, wherein the subject is suffering from an angiogenesis dependent benign tumor(s) selected from the group consisting of hemangiomas, acoustic neuromas, neurofibromas, trachomas, carcinoid tumors, and pyogenic granulomas.~~

11. ~~The method of Claim 6, wherein the ocular angiogenic disease or condition is not AMD.~~

12. ~~The method of Claim 6, wherein the ocular angiogenic disease or condition is selected from the group consisting of uveitis, ocular melanoma, corneal neovascularization, primary pterygium, HSV stromal keratitis, HSV 1 induced corneal lymphangiogenesis, proliferative diabetic retinopathy, diabetic macular edema, retinopathy of prematurity, retinal vein occlusion, corneal graft rejection, neovascular glaucoma, vitreous hemorrhage secondary to proliferative diabetic retinopathy, neuromyelitis optica and rubeosis.~~

132. The ~~method-use~~ of Claim 21, 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.

143. The ~~method-use~~ of Claim 1, wherein the ~~composition-medicament~~ is ~~administered-formulated for delivery~~ subcutaneously, intraperitoneally, intra-muscularly, intra-arterially, intravenously, or as an inhalant.

4. The use of Claim 1, wherein the wherein the MASP-2 monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising SEQ ID NO:67 and a light chain variable region comprising SEQ ID NO:69.

15. ~~A method of treating a subject suffering from an ocular angiogenic disease or condition selected from the group consisting of AMD, uveitis, ocular melanoma, corneal neovascularization, primary pterygium, HSV stromal keratitis, HSV 1 induced corneal lymphangiogenesis, proliferative diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, corneal graft rejection, neovascular glaucoma, and rubeosis, comprising administering to the subject an amount of a MASP 2 inhibitory agent effective to inhibit angiogenesis.~~

16. ~~The method of Claim 15, wherein the MASP 2 inhibitory agent is a MASP 2 antibody or fragment thereof.~~

17. ~~The method of Claim 16, wherein the MASP 2 inhibitory agent is a MASP 2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6.~~

18. ~~The method of Claim 16, 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.~~

19. ~~A method of inhibiting tumor angiogenesis comprising administering to a subject with cancer an amount of a MASP 2 inhibitory agent effective to inhibit angiogenesis.~~

20. ~~The method of Claim 19, wherein the MASP 2 inhibitory agent is a MASP 2 antibody or fragment thereof.~~

21. ~~The method of Claim 20, wherein the MASP 2 inhibitory agent is a MASP 2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6.~~

22. ~~The method of Claim 20, 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.~~