using corticosteroids and immunosuppressive drugs. Unfortunately, these anti-inflammatory agents have had little to no clinical effect. Currently there are no effective treatments or therapeutics for fibrosis, but both animal studies and anecdotal human reports suggest that fibrotic tissue damage may be reversed (Tampe and Zeisberg, *Nat Rev Nephrol*, Vol 10:226-237, 2014).

The kidney has a limited capacity to recover from injury. Various renal pathologies result in local inflammation that causes scarring and fibrosis of renal tissue. The perpetuation of inflammatory stimuli drives tubulointerstitial inflammation and fibrosis and progressive renal functional impairment in chronic kidney disease. Its progression to end-stage renal failure is associated with significant morbidity and mortality. Since tubulointerstitial fibrosis is the common end point of multiple renal pathologies, it represents a key target for therapies aimed at preventing renal failure. Risk factors (e.g., proteinuria) independent of the primary renal disease contribute to the development of renal fibrosis and loss of renal excretory function by driving local inflammation, which in turn enhances disease progression.

In view of the role of fibrosis in many diseases and disorders, such as, for example, tubulointerstitial fibrosis leading to chronic kidney disease, there is a pressing need to develop therapeutically effective agents for treating diseases and conditions caused or exacerbated by fibrosis. In further view of the paucity of new and existing treatments targeting inflammatory pro-fibrotic pathways in renal disease, there is a need to develop therapeutically effective agents to treat, inhibit, prevent and/or reverse renal fibrosis and thereby prevent progressive chronic kidney disease.

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~~example, the ~~invention~~disclosure provides a method for treating, inhibiting, alleviating or preventing fibrosis in a mammalian subject suffering, or at risk of developing a disease or disorder caused or exacerbated by fibrosis and/or inflammation, comprising administering to the subject an amount of a MASP-2 inhibitory agent effective to inhibit fibrosis. In one ~~embodiment~~example, the MASP-2 inhibitory agent is a MASP-2 antibody or

fragment thereof. In one ~~embodiment~~example, 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. In one ~~embodiment~~example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one ~~embodiment~~example, the subject is suffering from a disease or disorder caused by or exacerbated by at least one of (i) fibrosis and/or inflammation associated with an ischemia reperfusion injury, (ii) renal fibrosis and/or renal inflammation (e.g., tubulointerstitial fibrosis, chronic kidney disease, chronic renal failure, glomerular disease (e.g., focal segmental glomerulosclerosis), an immune complex disorder (e.g., IgA nephropathy, membraneous nephropathy), lupus nephritis, nephrotic syndrome, diabetic nephropathy, tubulointerstitial damage and glomerulonepthritis (e.g., C3 glomerulopathy), (iii) pulmonary fibrosis and/or inflammation (e.g., chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis associated with scleroderma, bronchiectasis and pulmonary hypertension), (iv) hepatic fibrosis and/or inflammation (e.g., cirrhosis, nonalcoholic fatty liver disease (steatohepatitis)), liver fibrosis secondary to alcohol abuse, liver fibrosis secondary to acute or chronic hepatitis, biliary disease and toxic liver injury (e.g., hepatotoxicity due to drug-induced liver damage induced by acetaminophen or other drug), (v) cardiac fibrosis and/or inflammation (e.g., cardiac fibrosis, myocardial infarction, valvular fibrosis, atrial fibrosis, endomyocardial fibrosis arrhythmogenic right ventricular cardiomyopathy (ARVC), (vi) vascular fibrosis (e.g., vascular disease, an atherosclerotic vascular disease, vascular stenosis, restenosis, vasculitis, phlebitis, deep vein thrombosis and abdominal aortic aneurysm), (vii) fibrosis of the skin (e.g., excessive wound healing, scleroderma, systemic sclerosis, keloids, connective tissue diseases, scarring, and hypertrophic scars), (viii) fibrosis of the joints (e.g., arthrofibrosis), (ix) fibrosis of the central nervous system (e.g., stroke, traumatic brain injury and spinal cord injury), (x) fibrosis of the digestive system (e.g., Crohn's disease, pancreatic fibrosis and ulcerative colitis), (xi) ocular fibrosis (e.g., anterior subcapsular cataract, posterior capsule opacification, macular degeneration, and retinal and vitreal retinopathy), (xii) fibrosis of musculoskeletal soft-tissue structures (e.g., adhesive capsulitis, Dupuytren's contracture and myelofibrosis), (xiii) fibrosis of the reproductive organs (e.g., endometriosis and Peyronie's disease), (xiv) a chronic infectious disease that causes fibrosis and/or inflammation (e.g., alpha virus, Hepatitis A, Hepatitis B, Hepatitis C, tuberculosis, HIV and influenza), (xv) an

autoimmune disease that causes fibrosis and/or inflammation (e.g., scleroderma and systemic lupus erythematosus (SLE), (xvi) scarring associated with trauma (e.g., wherein the scarring associated with trauma is selected from the group consisting of surgical complications (e.g., surgical adhesions wherein scar tissue can form between internal organs causing contracture, pain and can cause infertility), chemotherapeutic drug-induced fibrosis, radiation-induced fibrosis and scarring associated with burns), or (xvii) organ transplant, breast fibrosis, muscle fibrosis, retroperitoneal fibrosis, thyroid fibrosis, lymph node fibrosis, bladder fibrosis and pleural fibrosis.

In another ~~aspect~~example, the present ~~invention~~disclosure provides a method for treating, inhibiting, alleviating or preventing renal fibrosis in a mammalian subject suffering, or at risk of developing a disease or disorder caused or exacerbated by renal fibrosis and/or inflammation, comprising administering to the subject an amount of a MASP-2 inhibitory agent effective to inhibit renal fibrosis. In one ~~embodiment~~example, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one ~~embodiment~~example, 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. In one ~~embodiment~~example, the MASP-2 antibody or fragment thereof specifically binds to a polypeptide comprising SEQ ID NO:6 with an affinity of at least 10 times greater than it binds to a different antigen in the complement system. In one ~~embodiment~~example, 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. In one ~~embodiment~~example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one ~~embodiment~~example, the MASP-2 inhibitory agent is administered subcutaneously, intraperitoneally, intra-muscularly, intra-arterially, intravenously, or as an inhalant. In one ~~embodiment~~example, the MASP-2 inhibitory agent is administered in an amount effective to inhibit tubulointerstitial fibrosis. In one ~~embodiment~~example, the MASP-2 inhibitory agent is administered in an amount effective to reduce, delay or eliminate the need for dialysis in the subject. In one ~~embodiment~~example, the subject is suffering from a renal disease or disorder selected from the group consisting of chronic kidney disease, chronic renal failure, glomerular disease (e.g., focal segmental glomerulosclerosis), an immune complex disorder (e.g., IgA nephropathy, membraneous nephropathy), lupus nephritis, nephrotic syndrome, diabetic nephropathy, tubulointerstitial damage and glomerulonepthritis (e.g.,

C3 glomerulopathy). In one ~~embodiment~~example, the subject is suffering from proteinuria and the MASP-2 inhibitory agent is administered in an amount effective to reduce proteinuria in the subject. In one ~~embodiment~~example, the MASP-2 inhibitory agent is administered in an amount and for a time effective to achieve at least a 20 percent reduction (e.g., at least a 30 percent reduction, or at least a 40 percent reduction, or at least a 50 percent reduction) in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion in the subject prior to treatment. In one ~~embodiment~~example, the subject is suffering from a renal disease or disorder associated with proteinuria selected from the group consisting of nephrotic syndrome, pre-eclampsia, eclampsia, toxic lesions of kidneys, amyloidosis, collagen vascular diseases (e.g., systemic lupus erythematosus), dehydration, glomerular diseases (e.g. membranous glomerulonephritis, focal segmental glomerulonephritis, C3 glomerulopathy, minimal change disease, lipoid nephrosis), strenuous exercise, stress, benign orthostatis (postural) proteinuria, focal segmental glomerulosclerosis, IgA nephropathy (i.e., Berger's disease), IgM nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, minimal change disease, sarcoidosis, Alport's syndrome, diabetes mellitus (diabetic nephropathy), drug-induced toxicity (e.g., NSAIDS, nicotine, penicillamine, lithium carbonate, gold and other heavy metals, ACE inhibitors, antibiotics (e.g., adriamycin) or opiates (e.g. heroin) or other nephrotoxins); Fabry's disease, infections (e.g., HIV, syphilis, hepatitis A, B or C, poststreptococcal infection, urinary schistosomiasis); aminoaciduria, Fanconi syndrome, hypertensive nephrosclerosis, interstitial nephritis, sickle cell disease, hemoglobinuria, multiple myeloma, myoglobinuria, organ rejection (e.g., kidney transplant rejection), ebola hemorrhagic fever, Nail patella syndrome, familial mediterranean fever, HELLP syndrome, systemic lupus erythematosus, Wegener's granulomatosis, Rheumatoid arthritis, Glycogen storage disease type 1, Goodpasture's syndrome, Henoch-Schönlein purpura, urinary tract infection which has spread to the kidneys, Sjögren's syndrome and post-infections glomerulonepthritis. In one ~~embodiment~~example, the subject is suffering from IgA nephropathy. In one ~~embodiment~~example, the subject is suffering from membranous nephropathy.

In another ~~aspect~~example, the present ~~invention~~disclosure provides a method of preventing or reducing renal damage in a subject suffering from a disease or condition associated with proteinuria comprising administering an amount of a MASP-2 inhibitory agent effective to reduce or prevent proteinurea in the subject. In one ~~embodiment~~example, the MASP-2

inhibitory agent is a MASP-2 antibody or fragment thereof. In one ~~embodiment~~example, 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. In one ~~embodiment~~example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one ~~embodiment~~example, the disease or condition associated with proteinuria is selected from the group consisting of nephrotic syndrome, pre-eclampsia, eclampsia, toxic lesions of kidneys, amyloidosis, collagen vascular diseases (e.g., systemic lupus erythematosus), dehydration, glomerular diseases (e.g. membranous glomerulonephritis, focal segmental glomerulonephritis, C3 glomerulopathy, minimal change disease, lipoid nephrosis), strenuous exercise, stress, benign orthostatis (postural) proteinuria, focal segmental glomerulosclerosis, IgA nephropathy (i.e., Berger's disease), IgM nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, minimal change disease, sarcoidosis, Alport's syndrome, diabetes mellitus (diabetic nephropathy), drug-induced toxicity (e.g., NSAIDS, nicotine, penicillamine, lithium carbonate, gold and other heavy metals, ACE inhibitors, antibiotics (e.g., adriamycin) or opiates (e.g. heroin)); Fabry's disease, infections (e.g., HIV, syphilis, hepatitis A, B or C, poststreptococcal infection, urinary schistosomiasis); aminoaciduria, Fanconi syndrome, hypertensive nephrosclerosis, interstitial nephritis, sickle cell disease, hemoglobinuria, multiple myeloma, myoglobinuria, organ rejection (e.g., kidney transplant rejection), ebola hemorrhagic fever, Nail patella syndrome, familial mediterranean fever, HELLP syndrome, systemic lupus erythematosus, Wegener's granulomatosis, Rheumatoid arthritis, Glycogen storage disease type 1, Goodpasture's syndrome, Henoch-Schönlein purpura, urinary tract infection which has spread to the kidneys, Sjögren's syndrome and post-infections glomerulonepthritis. In one ~~embodiment~~example, the MASP-2 inhibitory agent is administered in an amount and for a time effective to achieve at least a 20 percent reduction (e.g., at least a 30 percent reduction, or at least a 40 percent reduction, or at least a 50 percent reduction) in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion in the subject prior to treatment.

In one aspect, the present disclosure refers to use of a MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof in an amount effective to reduce or prevent proteinurea in a subject in the manufacture of a medicament for preventing or reducing renal damage in a subject suffering from a disease or condition

associated with proteinuria selected from the group consisting of sickle cell disease, pre-eclampsia, eclampsia, toxic lesions of kidneys, amyloidosis, focal segmental glomerulonephritis, C3 glomerulopathy, minimal change disease, lipoid nephrosis, benign orthostatis proteinuria, focal segmental glomerulosclerosis, IgM nephropathy, sarcoidosis, Alport's syndrome, Fabry's disease, infections; aminoaciduria, Fanconi syndrome, hypertensive nephrosclerosis, interstitial nephritis, hemoglobinuria, multiple myeloma, myoglobinuria, organ rejection, ebola hemorrhagic fever, Nail patella syndrome, familial mediterranean fever, HELLP syndrome, Wegener's granulomatosis, Rheumatoid arthritis, Glycogen storage disease type 1, Goodpasture's syndrome, Henoch-Schönlein purpura, urinary tract infection which has spread to the kidneys, Sjögren's syndrome and post-infections glomerulonepthritis.

In another aspect, the present disclosure refers to a MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use in reducing or preventing renal damage in a subject suffering from a disease or condition associated with proteinurea, wherein the disease or condition associated with proteinuria is selected from the group consisting of sickle cell disease, pre-eclampsia, eclampsia, toxic lesions of kidneys, amyloidosis, focal segmental glomerulonephritis, C3 glomerulopathy, minimal change disease, lipoid nephrosis, benign orthostatis proteinuria, focal segmental glomerulosclerosis, IgM nephropathy, sarcoidosis, Alport's syndrome, Fabry's disease, infections; aminoaciduria, Fanconi syndrome, hypertensive nephrosclerosis, interstitial nephritis, hemoglobinuria, multiple myeloma, myoglobinuria, organ rejection, ebola hemorrhagic fever, Nail patella syndrome, familial mediterranean fever, HELLP syndrome, Wegener's granulomatosis, Rheumatoid arthritis, Glycogen storage disease type 1, Goodpasture's syndrome, Henoch-Schönlein purpura, urinary tract infection which has spread to the kidneys, Sjögren's syndrome and post-infections glomerulonepthritis.

In another ~~aspect~~example, the present ~~invention~~disclosure provides a method of inhibiting the progression of chronic kidney disease, comprising administering an amount of a MASP-2 inhibitory agent effective to reduce or prevent renal fibrosis, e.g., tubulointerstitial fibrosis, in a subject in need thereof. In one ~~embodiment~~example, the

MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one ~~embodiment~~example, 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. In one ~~embodiment~~example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one ~~embodiment~~example, the subject in need thereof exhibits proteinuria prior to administration of the MASP-2 inhibitory agent and administration of the MASP-2 inhibitory agent decreases proteinuria in the subject. In one ~~embodiment~~example, the MASP-2 inhibitory agent is administered in an amount and for a time effective to achieve at least a 20 percent reduction (e.g., at least a 30 percent reduction, or at least a 40 percent reduction, or at least a 50 percent reduction) in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion in the subject prior to treatment. In one ~~embodiment~~example, the MASP-2 inhibitory agent is administered in an amount effective to reduce, delay or eliminate the need for dialysis in the subject.

In another ~~aspect~~example, the ~~invention~~disclosure provides a method of protecting a kidney from renal injury in a subject that has undergone, is undergoing, or will undergo treatment with one or more nephrotoxic agents, comprising administering an amount of a MASP-2 inhibitory agent effective to prevent or ameliorate drug-induced nephropathy. In one ~~embodiment~~example, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one ~~embodiment~~example, 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. In one ~~embodiment~~example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation.

In another ~~aspect~~example, the ~~invention~~disclosure provides a method of treating a human subject suffering from Immunoglobulin A Nephropathy (IgAN) 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 ~~embodiment~~example, the subject is suffering from steroid-dependent IgAN. In one ~~embodiment~~example, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one ~~embodiment~~example, 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. In one ~~embodiment~~example, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In one ~~embodiment~~example, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less. In one ~~embodiment~~example, the method further comprises identifying a human subject having steroid-dependent IgAN 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 improve renal function. In one ~~embodiment~~example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective to improve renal function. In one ~~embodiment~~example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective and for a time sufficient to achieve at least a 20 percent reduction in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion in the subject prior to treatment. In one ~~embodiment~~example, the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject. In one ~~embodiment~~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 ~~aspect~~example, the ~~invention~~disclosure provides a method of treating a human subject suffering from membranous nephropathy (MN) 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 ~~embodiment~~example, the subject is suffering from steroid-dependent MN. In one ~~embodiment~~example, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one ~~embodiment~~example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective to improve renal function. In one ~~embodiment~~example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective and for a time sufficient to achieve at least a 20

percent reduction in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion in the subject prior to treatment. In one ~~embodiment~~example, the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject. In one ~~embodiment~~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.

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

CLAIMS

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

~~1. A method for treating, inhibiting, alleviating or preventing fibrosis in a mammalian subject suffering, or at risk of developing a disease or disorder caused or exacerbated by fibrosis and/or inflammation, comprising administering to the subject an amount of a MASP-2 inhibitory agent effective to inhibit fibrosis.~~

~~2. The method of claim 1, wherein the MASP-2 inhibitory agent is a MASP-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 2, wherein the MASP-2 antibody or fragment thereof specifically binds to a polypeptide comprising SEQ ID NO:6 with an affinity of at least 10 times greater than it binds to a different antigen in the complement system.~~

~~5. The method of claim 2, 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.~~

~~6. The method of claim 1, wherein the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation.~~

~~7. The method of claim 1, wherein the MASP-2 inhibitory agent is administered subcutaneously, intraperitoneally, intra-muscularly, intra-arterially, intravenously, or as an inhalant.~~

~~8. The method of any of claims 1 to 7, wherein the disease or disorder caused or exacerbated by fibrosis and/or inflammation is associated with an ischemia reperfusion injury.~~

~~9. The method of any of claims 1 to 7, wherein the disease or disorder caused or exacerbated by fibrosis and/or inflammation is not associated with an ischemia reperfusion injury.~~

~~10. The method of any of claims 1 to 7, wherein the subject exhibits proteinuria prior to administration of the MASP-2 inhibitory agent and administration of the MASP-2 inhibitory agent decreases proteinuria in the subject.~~

~~11. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by renal fibrosis and/or inflammation.~~

~~12. The method of claim 11, wherein the MASP-2 inhibitory agent is administered in an amount effective to inhibit tubulointerstitial fibrosis.~~

~~13. The method of claim 11, wherein the MASP-2 inhibitory agent is administered in an amount effective to reduce, delay or eliminate the need for dialysis in the subject.~~

~~14. The method of claim 11, wherein the disease or disorder is selected from the group consisting of chronic kidney disease, chronic renal failure, glomerular disease (e.g., focal segmental glomerulosclerosis), an immune complex disorder (e.g., IgA nephropathy, membraneous nephropathy), lupus nephritis, nephrotic syndrome, diabetic nephropathy, tubulointerstitial damage and glomerulonepthritis (e.g., C3 glomerulopathy).~~

~~15. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by pulmonary fibrosis and/or inflammation.~~

~~16. The method of claim 15, wherein the disease or disorder is selected from the group consisting of chronic obstructive pulmonary disease, cystic fibrosis,~~

~~pulmonary fibrosis associated with scleroderma, bronchiectasis and pulmonary hypertension.~~

~~17. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by hepatic fibrosis and/or inflammation.~~

~~18. The method of claim 17, wherein the disease or disorder is selected from the group consisting of cirrhosis, nonalcoholic fatty liver disease (steatohepatitis), liver fibrosis secondary to alcohol abuse, liver fibrosis secondary to acute or chronic hepatitis, biliary disease and toxic liver injury (e.g., hepatotoxicity due to drug-induced liver damage induced by acetaminophen or other drug, such as a nephrotoxin).~~

~~19. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by cardiac fibrosis and/or inflammation.~~

~~20. The method of claim 19, wherein the disease or condition is selected from the group consisting of cardiac fibrosis, myocardial infarction, valvular fibrosis, atrial fibrosis, endomyocardial fibrosis arrhythmogenic right ventricular cardiomyopathy (ARVC).~~

~~21. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by vascular fibrosis.~~

~~22. The method of claim 21, wherein the disease or disorder is selected from the group consisting of a vascular disease, an atherosclerotic vascular disease, vascular stenosis, restenosis, vasculitis, phlebitis, deep vein thrombosis and abdominal aortic aneurysm.~~

~~23. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by fibrosis of the skin.~~

~~24. The method of claim 23, wherein the disease or disorder is selected from the group consisting of excessive wound healing, scleroderma, systemic sclerosis, keloids, connective tissue diseases, scarring, and hypertrophic scars.~~

~~25. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by fibrosis of the joints.~~

~~26. The method of claim 25, wherein the disease or disorder is arthrofibrosis.~~

~~27. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by fibrosis of the central nervous system.~~

~~28. The method of claim 27, wherein the disease or disorder is selected from the group consisting of stroke, traumatic brain injury and spinal cord injury.~~

~~29. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by fibrosis of the digestive system.~~

~~30. The method of claim 29, wherein the disease or disorder is selected from the group consisting of Crohn's disease, pancreatic fibrosis and ulcerative colitis.~~

~~31. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by ocular fibrosis.~~

~~32. The method of claim 31, wherein the disease or disorder is selected from the group consisting of anterior subcapsular cataract, posterior capsule opacification, macular degeneration, and retinal and vitreal retinopathy.~~

~~33. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by fibrosis of the musculoskeletal bone or soft-tissue structure.~~

~~34. The method of claim 33, wherein the disease or disorder is selected from the group consisting of osteoporosis and/or osteopenia associated with cystic fibrosis, myelodysplastic conditions with increased bone fibrosis, adhesive capsulitis, Dupuytren's contracture and myelofibrosis.~~

~~35. The method of any of claims 1 to 7, wherein the subject is suffering from a disease or disorder caused or exacerbated by fibrosis of the reproductive organs.~~

~~36. The method of claim 35, wherein the disease or disorder is selected from the group consisting of endometriosis and Peyronie's disease.~~

~~37. The method of any of claims 1 to 7, wherein the subject is suffering from a chronic infectious disease that causes fibrosis and/or inflammation.~~

~~38. The method of claim 37, wherein the infectious disease is selected from the group consisting of alpha virus, Hepatitis A, Hepatitis B, Hepatitis C, tuberculosis, HIV and influenza.~~

~~39. The method of any of claims 1 to 7, wherein the subject is suffering from an autoimmune disease that causes fibrosis and/or inflammation.~~

~~40. The method of claim 39, wherein the autoimmune disease is selected from the group consisting of scleroderma and systemic lupus erythematosus (SLE).~~

~~41. The method of any of claims 1 to 7, wherein the subject is suffering from scarring associated with trauma.~~

~~42. The method of claim 41, wherein the scarring associated with trauma is selected from the group consisting of surgical complications (e.g., surgical adhesions wherein scar tissue can form between internal organs causing contracture, pain and can cause infertility), chemotherapeutic drug-induced fibrosis, radiation-induced fibrosis and scarring associated with burns.~~

~~43. The method of any of claims 1 to 7, wherein the disease or disorder caused or exacerbated by fibrosis and/or inflammation is selected from the group consisting of organ transplant, breast fibrosis, muscle fibrosis, retroperitoneal fibrosis, thyroid fibrosis, lymph node fibrosis, bladder fibrosis and pleural fibrosis.~~

~~44.~~1. ~~A method of preventing or reducing renal damage in a subject suffering from a disease or condition associated with proteinuria comprising administering an amount~~Use of a MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof ~~agent~~ in an amount effective to reduce or prevent proteinurea in ~~the~~ a subject in the manufacture of a medicament for preventing or reducing renal damage in a subject suffering from a disease or condition associated with

proteinuria selected from the group consisting of sickle cell disease, pre-eclampsia, eclampsia, toxic lesions of kidneys, amyloidosis, focal segmental glomerulonephritis, C3 glomerulopathy, minimal change disease, lipoid nephrosis, benign orthostatis proteinuria, focal segmental glomerulosclerosis, IgM nephropathy, sarcoidosis, Alport's syndrome, Fabry's disease, infections; aminoaciduria, Fanconi syndrome, hypertensive nephrosclerosis, interstitial nephritis, hemoglobinuria, multiple myeloma, myoglobinuria, organ rejection, ebola hemorrhagic fever, Nail patella syndrome, familial mediterranean fever, HELLP syndrome, Wegener's granulomatosis, Rheumatoid arthritis, Glycogen storage disease type 1, Goodpasture's syndrome, Henoch-Schönlein purpura, urinary tract infection which has spread to the kidneys, Sjögren's syndrome and post-infections glomerulonepthritis.

~~45. The method of claim 44, wherein the MASP-2 inhibitory agent is a MASP-2 inhibitory antibody or fragment thereof.~~

~~46.~~2. The ~~method~~ use of claim 1~~,44 or 45,~~ wherein the medicament is for administration~~MASP-2 inhibitory agent is administered~~ in an amount and for a time effective to achieve at least a 20 percent reduction in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion prior to treatment.

3. The use of claim 1 wherein the subject is suffering from sickle cell disease.

~~47. The method of any of claims 44 to 46, wherein the disease or condition associated with proteinuria is selected from the group consisting of nephrotic syndrome, pre-eclampsia, eclampsia, toxic lesions of kidneys, amyloidosis, collagen vascular diseases (e.g., systemic lupus erythematosus), dehydration, glomerular diseases (e.g. membranous glomerulonephritis, focal segmental glomerulonephritis, C3 glomerulopathy, minimal change disease, lipoid nephrosis), strenuous exercise, stress, benign orthostatis (postural) proteinuria, focal segmental glomerulosclerosis, IgA nephropathy (i.e., Berger's disease), IgM nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, minimal change disease, sarcoidosis, Alport's syndrome, diabetes mellitus (diabetic nephropathy), drug-~~

~~induced toxicity (e.g., NSAIDS, nicotine, penicillamine, lithium carbonate, gold and other heavy metals, ACE inhibitors, antibiotics (e.g., adriamycin) or opiates (e.g. heroin) or other nephrotoxins); Fabry's disease, infections (e.g., HIV, syphilis, hepatitis A, B or C, poststreptococcal infection, urinary schistosomiasis); aminoaciduria, Fanconi syndrome, hypertensive nephrosclerosis, interstitial nephritis, sickle cell disease, hemoglobinuria, multiple myeloma, myoglobinuria, organ rejection (e.g., kidney transplant rejection), ebola hemorrhagic fever, Nail patella syndrome, familial mediterranean fever, HELLP syndrome, systemic lupus erythematosus, Wegener's granulomatosis, Rheumatoid arthritis, Glycogen storage disease type 1, Goodpasture's syndrome, Henoch-Schönlein purpura, urinary tract infection which has spread to the kidneys, Sjögren's syndrome and post-infections glomerulonepthritis.~~

~~48. The method of any of claims 44 to 46, wherein the disease or condition associated with proteinuria is IgA nepropathy (i.e., Berger's disease).~~

~~49. The method of any of claims 44 to 46, wherein the disease or condition associated with proteinuria is membranous nephropathy.~~

~~50. A method of inhibiting the progression of chronic kidney disease, comprising administering an amount of a MASP-2 inhibitory agent effective to reduce or prevent tubulointerstitial fibrosis in a subject in need thereof.~~

~~51. The method of claim 50, wherein the MASP-2 inhibitory agent is a MASP-2 inhibitory antibody, or fragment thereof.~~

~~52. The method of claim 50, wherein the subject in need thereof exhibits proteinuria prior to administration of the MASP-2 inhibitory agent and administration of the MASP-2 inhibitory agent decreases proteinuria in the subject, such that the subject has at least a 20 percent reduction in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion in the subject prior to treatment..~~

~~53. The method of claim 50, wherein the MASP-2 inhibitory agent is administered in an amount effective to reduce, delay or eliminate the need for dialysis in the subject.~~

~~54. A method of protecting a kidney from renal injury in a subject that has undergone, is undergoing, or will undergo treatment with one or more nephrotoxic agents, comprising administering an amount of a MASP-2 inhibitory agent effective to prevent or ameliorate the incidence of drug-induced nephropathy.~~

~~55. The method of claim 54, wherein the MASP-2 inhibitory agent is a MASP-2 inhibitory antibody, or fragment thereof.~~

~~56. The method of claim 54, wherein the MASP-2 inhibitory agent is administered prior to said nephrotoxic agent.~~

~~57. The method of claim 54, wherein the MASP-2 inhibitory agent is co-administered simultaneously with said nephrotoxic agent.~~

~~58. The method of claim 54, wherein the MASP-2 inhibitory agent is administered after said nephrotoxic agent to treat nephrotoxicity.~~

~~59. A method of treating a human subject suffering from Immunoglobulin A Nephropathy (IgAN) 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.~~

~~60. The method of claim 59, wherein the subject is suffering from steroid-dependent IgAN.~~

~~61. The method of claim 59 or 60, wherein the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2.~~

~~62.~~4. The ~~method~~ use of ~~any of~~ claim~~s 59 to 61~~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.

~~63.~~5. The ~~method~~ use of any one of claims 1~~59~~ to 4~~62~~, wherein the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.

~~64.~~6. The ~~method~~ use of any one of claims 1~~59~~ to 5~~63~~, wherein the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less.

~~65. The method of claim 59, wherein the method further comprises identifying a human subject having steroid-dependent IgAN 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 improve renal function.~~

~~66.~~7. The ~~method~~ use of ~~any of~~ claim~~s~~ 1~~59 to 65~~, wherein the medicament comprises ~~the~~ the MASP-2 inhibitory antibody or antigen-binding fragment thereof ~~is administered~~ in an amount effective to improve renal function.

~~67. The method of claim 66, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective and for a time sufficient to achieve at least a 20 percent reduction in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion in the subject prior to treatment.~~

~~68. The method of claim 59, wherein the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject.~~

~~69.~~8. The ~~method~~ use of any one of claims 1~~59~~ to 7~~68~~, 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:69~~70~~.

9. The use of any one of claims 1 to 8, wherein the medicament is for

administration subcutaneously, intraperitoneally, intra-muscularly, intra-arterially, intravenously, or as an inhalant.

~~70. A method of treating a human subject suffering from membranous nephropathy (MN) 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.~~

~~71. The method of claim 70, wherein the subject is suffering from steroid-dependent MN.~~

~~72. The method of claim 70 or 71, wherein the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2.~~

~~73. The method of any of claims 70 to 72, 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.~~

~~74. The method of any of claims 70 to 73, wherein the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.~~

~~75. The method of any of claims 70 to 74, wherein the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less.~~

~~76. The method of claim 70, wherein the method further comprises identifying a human subject having steroid-dependent MN 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 improve renal function.~~

~~77. The method of any of claims 70 to 76, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective to improve renal function.~~

~~78. The method of claim 77, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective and for a time~~

~~sufficient to achieve at least a 20 percent reduction in 24-hour urine protein excretion as compared to baseline 24-hour urine protein excretion in the subject prior to treatment.~~

~~79. The method of claim 70 or 71, wherein the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject.~~

~~80. The method of any of claims 70 to 79, 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.~~

10. A MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use in reducing or preventing renal damage in a subject suffering from a disease or condition associated with proteinurea, wherein the disease or condition associated with proteinuria is selected from the group consisting of sickle cell disease, pre-eclampsia, eclampsia, toxic lesions of kidneys, amyloidosis, focal segmental glomerulonephritis, C3 glomerulopathy, minimal change disease, lipoid nephrosis, benign orthostatis proteinuria, focal segmental glomerulosclerosis, IgM nephropathy, sarcoidosis, Alport's syndrome, Fabry's disease, infections; aminoaciduria, Fanconi syndrome, hypertensive nephrosclerosis, interstitial nephritis, hemoglobinuria, multiple myeloma, myoglobinuria, organ rejection, ebola hemorrhagic fever, Nail patella syndrome, familial mediterranean fever, HELLP syndrome, Wegener's granulomatosis, Rheumatoid arthritis, Glycogen storage disease type 1, Goodpasture's syndrome, Henoch-Schönlein purpura, urinary tract infection which has spread to the kidneys, Sjögren's syndrome and post-infections glomerulonepthritis.

11. The MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use of claim 10, wherein the MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof is to be administered in an amount and for a time effective to achieve at least a 20 percent reduction in 24-hour urine protein

excretion as compared to baseline 24-hour urine protein excretion prior to treatment.

12. The MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use of claim 10, wherein the subject is suffering from sickle cell disease.

13. The MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use of claim 10, wherein the MASP-2 inhibitory monoclonal 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.

14. The MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use of any one of claims 10 to 13, wherein the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.

15. The MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use of any one of claims 10 to 14, wherein the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less.

16. The MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use of claim 10, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof is to be adminstered to the subject in an amount effective to improve renal function.

17. The MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use of any one of claims 10 to 16, 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:69.

18. The MASP-2 inhibitory monoclonal antibody or antigen-binding fragment thereof for use of any one of claims 10 to 17, wherein the MASP-2 inhibitory

antibody or antigen-binding fragment thereof is to be administered subcutaneously, intraperitoneally, intra-muscularly, intra-arterially, intravenously, or as an inhalant.