

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.

Disclosed is 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, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one embodiment, 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, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one embodiment, the subject is suffering from a disease or

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.

Disclosed is a method for treating, inhibiting, alleviating or preventing renal
5 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, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment
thereof. In one embodiment, the MASP-2 inhibitory agent is a MASP-2 monoclonal
10 antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In one
embodiment, 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, the antibody
or fragment thereof is selected from the group consisting of a recombinant antibody, an
15 antibody having reduced effector function, a chimeric antibody, a humanized antibody
and a human antibody. In one embodiment, the MASP-2 inhibitory agent selectively
inhibits lectin pathway complement activation without substantially inhibiting C1q-
dependent complement activation. In one embodiment, the MASP-2 inhibitory agent is
administered subcutaneously, intraperitoneally, intra-muscularly, intra-arterially,
20 intravenously, or as an inhalant. In one embodiment, the MASP-2 inhibitory agent is
administered in an amount effective to inhibit tubulointerstitial fibrosis. In one
embodiment, 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, the
subject is suffering from a renal disease or disorder selected from the group consisting of
25 chronic kidney disease, chronic renal failure, glomerular disease (e.g., focal segmental
glomerulosclerosis), an immune complex disorder (e.g., IgA nephropathy, membranous
nephropathy), lupus nephritis, nephrotic syndrome, diabetic nephropathy,
tubulointerstitial damage and glomerulonephritis (e.g., C3 glomerulopathy). In one
embodiment, the subject is suffering from proteinuria and the MASP-2 inhibitory agent is
30 administered in an amount effective to reduce proteinuria in the subject. In one
embodiment, 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, 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 glomerulonephritis. In one embodiment, the subject is suffering from IgA nephropathy. In one embodiment, the subject is suffering from membranous nephropathy.

Disclosed is 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, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one embodiment, 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, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one embodiment, 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 orthostasis (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 glomerulonephritis. In one embodiment, 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.

Disclosed is 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, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one embodiment, 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, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one embodiment, 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, 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, the MASP-2 inhibitory agent is administered in an amount effective to reduce, delay or eliminate the need for dialysis in the subject.

Disclosed is 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, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one embodiment, 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, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation.

Disclosed is 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, the subject is suffering from steroid-dependent IgAN. In one embodiment, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one embodiment, 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, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In one embodiment, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC₅₀ of 30 nM or less. In one embodiment, 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, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective to improve renal function. In one embodiment, 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, the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject. In one embodiment, 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.

Disclosed is 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, the subject is suffering from steroid-dependent MN. In one embodiment, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one embodiment, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective to improve renal function. In one embodiment, 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, the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject. In one embodiment, 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.

Disclosed is a method of treating a human subject suffering from Lupus Nephritis (LN) 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, the subject is suffering from steroid-dependent LN. In one embodiment, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one embodiment, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective to improve renal function. In one embodiment, 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, the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject. In one embodiment, 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.

Disclosed is a method of reducing proteinuria in a human subject suffering from IgAN comprising administering to the subject a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, comprising 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 according to a dosage regimen as follows:

- a. administering about 4 mg/kg (i.e., from 3.6 mg/kg to 4.4 mg/kg) of said antibody to a subject suffering from IgAN once weekly intravenously for a treatment period of at least 12 weeks; or
 - b. administering from about 180 mg to about 725 mg (i.e., from 162 mg to 797 mg) of said antibody to a subject suffering from IgAN once weekly intravenously for a treatment period of at least 12 weeks,
- wherein the method reduces proteinuria in said human subject.

In one aspect, there is provided use of a composition comprising a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof that specifically binds to human MASP-2 and inhibits MASP-2-dependent complement activation in the manufacture of a medicament for treating a human subject suffering from lupus nephritis (LN).

In another aspect, there is provided use of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, comprising 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 the manufacture of a medicament for reducing proteinuria in a human subject suffering from IgAN, wherein the medicament is to be administered according to a dosage regimen as follows:

- a. about 4 mg/kg (i.e., from 3.6 mg/kg to 4.4 mg/kg) of said antibody is to be administered to a subject suffering from IgAN once weekly intravenously for a treatment period of at least 12 weeks; or
- b. from about 180 mg to about 725 mg (i.e., from 162 mg to 797 mg) of said antibody is to be administered to a subject suffering from IgAN once weekly intravenously for a treatment period of at least 12 weeks,

wherein the medicament reduces proteinuria in said human subject.

Claims

1. Use of a composition comprising a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof that specifically binds to human MASP-2 and inhibits MASP-2-dependent complement activation in the manufacture of a medicament for treating a human subject suffering from lupus nephritis (LN).
2. The use according to claim 1, wherein the subject is suffering from steroid-dependent LN.
3. The use according to 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.
4. The use according to claim 1, wherein the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.
5. The use according to claim 1, wherein the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less.
6. The use according to claim 1, wherein the human subject has been identified as having steroid-dependent LN prior to a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to improve renal function is to be administered to the subject.
7. The use according to claim 1, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof is to be 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.
8. The use according to claim 1, wherein the composition is to be administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject.

9. The use according to 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.
10. Use of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, comprising 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 the manufacture of a medicament for reducing proteinuria in a human subject suffering from IgAN, wherein the medicament is to be administered according to a dosage regimen as follows:
 - a. about 4 mg/kg (i.e., from 3.6 mg/kg to 4.4 mg/kg) of said antibody is to be administered to a subject suffering from IgAN once weekly intravenously for a treatment period of at least 12 weeks; or
 - b. from about 180 mg to about 725 mg (i.e., from 162 mg to 797 mg) of said antibody is to be administered to a subject suffering from IgAN once weekly intravenously for a treatment period of at least 12 weeks,wherein the medicament reduces proteinuria in said human subject.
11. The use of claim 10, wherein the treatment period is followed by a rest period (i.e., no administration of a MASP-2 inhibitor) of at least 2 months to at least 6 months.
12. The use of claim 10, wherein proteinuria in the subject is reduced by at least 20% from baseline (prior to treatment) to at least 50% from baseline at the end of the treatment period and/or at the end of the rest period (i.e., a decrease in uACR and/or a decrease in 24-hour urine protein concentration); and/or wherein the estimated glomerular filtration rate (eGFR) increases in the subject, such as wherein the subject suffering from IgAN has proteinuria of greater than 1 gram protein/24 hour urine protein excretion prior to treatment and the medicament is effective to reduce proteinuria in the subject in the subject by at least 30%.

13. The use of claim 10, wherein the urinary protein levels in the subject are periodically monitored during the treatment period and/or rest period.
14. The use of claim 10, wherein the subject has discontinued or substantially reduced corticosteroid dosage at the end of the treatment period and/or at the end of the rest period as compared to corticosteroid dosage taken prior to the start of treatment with the MASP-2 inhibitory antibody.
15. The use of Claim 10, wherein the MASP-2 inhibitory antibody or fragment thereof comprises a heavy-chain variable region comprising an amino acid sequence forth as SEQ ID NO:67 and comprises a light-chain variable region set forth as SEQ ID NO:70.