

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 example, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one 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 example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one example, 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 example, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one example, the MASP-2 inhibitory agent is a MASP-2 monoclonal antibody, or
10 fragment thereof that specifically binds to a portion of SEQ ID NO:6. In one 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 example, the antibody or fragment thereof is selected from the group consisting of a recombinant antibody, an antibody having
15 reduced effector function, a chimeric antibody, a humanized antibody and a human antibody. In one example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one example, the MASP-2 inhibitory agent is administered subcutaneously, intraperitoneally, intra-muscularly, intra-arterially, intravenously, or as
20 an inhalant. In one example, the MASP-2 inhibitory agent is administered in an amount effective to inhibit tubulointerstitial fibrosis. In one 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 example, the subject is suffering from a renal disease or disorder selected from the group consisting of chronic kidney disease, chronic renal
25 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 example, the subject is suffering from proteinuria and the MASP-2 inhibitory agent is administered in an amount effective
30 to reduce proteinuria in the subject. In one 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 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 glomerulonephritis. In one example, the subject is suffering from IgA nephropathy. In one example, 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 example, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one 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 example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one 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
5 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.,
10 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,
15 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
20 glomerulonephritis. In one 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.

25 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 example, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one example, the MASP-2 inhibitory agent is a MASP-2 monoclonal antibody, or fragment
30 thereof that specifically binds to a portion of SEQ ID NO:6. In one example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one 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 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
5 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 example, 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
10 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 example, the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof. In one example, the MASP-2 inhibitory agent is a MASP-2 monoclonal antibody or fragment thereof that specifically binds to a
15 portion of SEQ ID NO:6. In one example, 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
20 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 is suffering from steroid-dependent IgAN. 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 antibody or fragment thereof is selected from the
25 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 method further
30 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 example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective to improve renal function. In one 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 example, the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject. 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:69.

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 example, the subject is suffering from steroid-dependent MN. 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 antigen-binding fragment thereof is administered in an amount effective to improve renal function. In one 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 example, the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject. 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:69.

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 example, the subject is suffering
5 from steroid-dependent LN. 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 antigen-binding fragment thereof is administered in an amount effective to improve renal function. In one example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an
10 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 example, the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject. In one example, the MASP-2 inhibitory antibody or antigen-binding fragment
15 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.

Disclosed is a method of reducing proteinuria in a human subject suffering from
20 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:69 according to a dosage regimen as follows:

- 25 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
30 intravenously for a treatment period of at least 12 weeks,
- wherein the method reduces proteinuria in said human subject.

In one aspect, the present disclosure refers to 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 steroid-
5 dependent lupus nephritis (LN), wherein the composition is to be administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject and 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
10 comprising CDR-L1, CDR-L2 and CDR-L3 of the amino acid sequence set forth as SEQ ID NO:69.

In another aspect, the present disclosure refers to 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
15 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, in the manufacture of a medicament for reducing proteinuria in a human subject suffering from steroid-dependent Immunoglobulin A Nephropathy (IgAN), wherein the medicament is to be administered according to a dosage regimen as follows:
20 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; wherein the medicament reduces proteinuria in said human subject.

SEQ ID NO:48 is 9 aa peptide bond

EXPRESSION VECTOR:

SEQ ID NO:49 is the MASP-2 minigene insert

SEQ ID NO: 50 is the murine MASP-2 cDNA

5 SEQ ID NO: 51 is the murine MASP-2 protein (w/leader)

SEQ ID NO: 52 is the mature murine MASP-2 protein

SEQ ID NO: 53 the rat MASP-2 cDNA

SEQ ID NO: 54 is the rat MASP-2 protein (w/ leader)

SEQ ID NO: 55 is the mature rat MASP-2 protein

10 SEQ ID NO: 56-59 are the oligonucleotides for site-directed mutagenesis
of human MASP-2 used to generate human MASP-2A

SEQ ID NO: 60-63 are the oligonucleotides for site-directed mutagenesis
of murine MASP-2 used to generate murine MASP-2A

15 SEQ ID NO: 64-65 are the oligonucleotides for site-directed mutagenesis
of rat MASP-2 used to generate rat MASP-2A

SEQ ID NO: 66 DNA encoding 17D20_dc35VH21N11VL (OMS646)
heavy chain variable region (VH) (without signal peptide)

SEQ ID NO: 67 17D20_dc35VH21N11VL (OMS646) heavy chain
variable region (VH) polypeptide

20 SEQ ID NO: 68 17N16mc heavy chain variable region (VH) polypeptide

SEQ ID NO: 70 DNA encoding 17D20_dc35VH21N11VL (OMS646)
light chain variable region (VL)

SEQ ID NO: 69 17D20_dc35VH21N11VL (OMS646) light chain variable
region (VL) polypeptide

25 SEQ ID NO: 71 17N16_dc17N9 light chain variable region (VL)
polypeptide

SEQ ID NO:72: SGMI-2L(full-length)

SEQ ID NO: 73: SGMI-2M (medium truncated version)

SEQ ID NO:74: SGMI-2S (short truncated version)

30 SEQ ID NO:75: mature polypeptide comprising the VH-M2ab6-SGMI-2-
N and the human IgG4 constant region with hinge mutation

SEQ ID NO:76: mature polypeptide comprising the VH-M2ab6-SGMI-2-
C and the human IgG4 constant region with hinge mutation

complement activation system. The anti-MASP-2 antibodies useful in this aspect of the invention include polyclonal, monoclonal or recombinant antibodies derived from any antibody producing mammal and may be multispecific, chimeric, humanized, anti-idiotypic, and antibody fragments. Antibody fragments include Fab, Fab', F(ab)₂,
5 F(ab')₂, Fv fragments, scFv fragments and single-chain antibodies as further described herein.

MAASP-2 antibodies can be screened for the ability to inhibit MASP-2-dependent complement activation system and for antifibrotic activity and/or the ability to inhibit renal damage associated with proteinuria or Adriamycin-induced nephropathy using the
10 assays described herein. Several MASP-2 antibodies have been described in the literature and some have been newly generated, some of which are listed below in TABLE 1. For example, as described in Examples 10 and 11 herein, anti-MASP-2 Fab₂ antibodies have been identified that block MASP-2-dependent complement activation. As described in Example 12, and also described in WO2012/151481, which is hereby incorporated herein
15 by reference, fully human MASP-2 scFv antibodies (e.g., OMS646) have been identified that block MASP-2-dependent complement activation. As described in Example 13, and also described in WO2014/144542, which is hereby incorporated herein by reference, SGMI-2 peptide-bearing MASP-2 antibodies and fragments thereof with MASP-2 inhibitory activity were generated by fusing the SGMI-2 peptide amino acid sequence
20 (SEQ ID NO:72, 73 or 74) onto the amino or carboxy termini of the heavy and/or light chains of a human MASP-2 antibody (e.g., OMS646-SGMI-2).

Accordingly, in one embodiment, the MASP-2 inhibitory agent for use in the methods of the invention comprises a human antibody such as, for example OMS646. Accordingly, in one embodiment, a MASP-2 inhibitory agent for use in the compositions
25 and methods of the claimed invention comprises a human antibody that binds a polypeptide consisting of human MASP-2 (SEQ ID NO:6), wherein the antibody comprises: (I) (a) a heavy-chain variable region comprising: i) a heavy-chain CDR-H1 comprising the amino acid sequence from 31-35 of SEQ ID NO:67; and ii) a heavy-chain CDR-H2 comprising the amino acid sequence from 50-65 of SEQ ID NO:67; and iii) a
30 heavy-chain CDR-H3 comprising the amino acid sequence from 95-107 of SEQ ID NO:67 and b) a light-chain variable region comprising: i) a light-chain CDR-L1 comprising the amino acid sequence from 24-34 of SEQ ID NO:69; and ii) a light-chain CDR-L2 comprising the amino acid sequence from 50-56 of SEQ ID NO:69; and iii) a

light-chain CDR-L3 comprising the amino acid sequence from 89-97 of SEQ ID NO:69, or (II) a variant thereof comprising a heavy-chain variable region with at least 90% identity to SEQ ID NO:67 (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to SEQ ID NO:67) and a light-chain variable region with at least 90% identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to SEQ ID NO:69.

In some embodiments, the method comprises administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen binding fragment thereof, comprising a heavy-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:67 and a light-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:69.

In some embodiments, the method comprises administering to the subject a composition comprising a MASP-2 inhibitory antibody, or antigen binding fragment thereof, that specifically recognizes at least part of an epitope on human MASP-2 recognized by reference antibody OMS646 comprising a heavy-chain variable region as set forth in SEQ ID NO:67 and a light-chain variable region as set forth in SEQ ID NO:69. In one embodiment, the MASP-2 inhibitory agent for use in the methods of the invention comprises the human antibody OMS646.

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Presented below are the light-chain variable region (VL) sequences for the mother clones and daughter clones shown above in TABLE 8.

The Kabat CDRs (24-34 (L1); 50-56 (L2); and 89-97 (L3) are bolded; and the Chothia CDRs (24-34 (L1); 50-56 (L2) and 89-97 (L3) are underlined. These regions are the same whether numbered by the Kabat or Chothia system.

17D20m d3521N11 light chain variable region (VL) (SEQ ID NO:69, encoded by SEQ ID NO:70)

QPVLTQPPSLSVSPGQTASITCS**GEKLGDKYAYWY**QQKPGQSPVLVMYQ
DKQRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQ**AWDSSTAVE**GGGTKL
 TVL

17N16m d17N9 light chain variable region (VL) (SEQ ID NO:71)

SYELIQPPSVSVAPGQTATITCA**GDNLGKKRVHWY**QQRPGQAPVLVIYD
DSDRPSGIPDRFSASNSGNTATLTITRGEAGDEADYYCQ**VWDIATDHV**VFGGGT
 KLTVLAAAGSEQKLISE

The MASP-2 antibodies OMS100 and MoAb_d3521N11VL, (comprising a heavy chain variable region set forth as SEQ ID NO:67 and a light chain variable region set forth as SEQ ID NO:69, also referred to as “OMS646” and “mAb6”), which have both been demonstrated to bind to human MASP-2 with high affinity and have the ability to block functional complement activity, were analyzed with regard to epitope binding by dot blot analysis. The results show that OMS646 and OMS100 antibodies are highly specific for MASP-2 and do not bind to MASP-1/3. Neither antibody bound to MAP19 nor to MASP-2 fragments that did not contain the CCP1 domain of MASP-2, leading to the conclusion that the binding sites encompass CCP1.

The MASP-2 antibody OMS646 was determined to avidly bind to recombinant MASP-2 (Kd 60-250pM) with >5000 fold selectivity when compared to C1s, C1r or MASP-1 (see TABLE 9 below):

TABLE 9: Affinity and Specificity of OMS646 MASP-2 antibody-MASP-2 interaction as assessed by solid phase ELISA studies

Antigen	K _D (pM)
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as steroid-dependent MN) either intravenously, intramuscularly, or subcutaneously. Treatment may be chronic and administered daily to monthly, but preferably at least every two weeks, or at least once a week, such as twice a week or three times a week.

In one embodiment, the method comprises treating a subject suffering from IgAN (such as steroid-dependent IgAN) or MN (such as steroid-dependent MN) comprising administering to the subject a composition comprising an amount of 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:69. In some embodiments, the composition comprises a MASP-2 inhibitory antibody comprising (a) a heavy-chain variable region comprising: i) a heavy-chain CDR-H1 comprising the amino acid sequence from 31-35 of SEQ ID NO:67; and ii) a heavy-chain CDR-H2 comprising the amino acid sequence from 50-65 of SEQ ID NO:67; and iii) a heavy-chain CDR-H3 comprising the amino acid sequence from 95-107 of SEQ ID NO:67 and b) a light-chain variable region comprising: i) a light-chain CDR-L1 comprising the amino acid sequence from 24-34 of SEQ ID NO:69; and ii) a light-chain CDR-L2 comprising the amino acid sequence from 50-56 of SEQ ID NO:69; and iii) a light-chain CDR-L3 comprising the amino acid sequence from 89-97 of SEQ ID NO:69, or (II) a variant thereof comprising a heavy-chain variable region with at least 90% identity to SEQ ID NO:67 (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to SEQ ID NO:67) and a light-chain variable region with at least 90% identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to SEQ ID NO:69).

In some embodiments, the method comprises administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen binding fragment thereof, comprising a heavy-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:67 and a light-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:69.

In some embodiments, the method comprises administering to the subject a composition comprising a MASP-2 inhibitory antibody, or antigen binding fragment thereof, that specifically recognizes at least part of an epitope on human MASP-2 recognized by reference antibody OMS646 comprising a heavy-chain variable region as

set forth in SEQ ID NO:67 and a light-chain variable region as set forth in SEQ ID NO:69.

In some embodiments, the method comprises administering to a subject suffering from, or at risk for developing IgAN (such as steroid-dependent IgAN) or MN (such as steroid-dependent MN), a composition comprising a MASP-2 inhibitory antibody, or antigen binding fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:67 and a light-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:69 in a dosage from 1 mg/kg to 10 mg/kg (i.e., 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg or 10 mg/kg) at least once weekly (such as at least twice weekly or at least three times weekly) for a period of at least 3 weeks, or for at least 4 weeks, or for at least 5 weeks, or for at least 6 weeks, or for at least 7 weeks, or for at least 8 weeks, or for at least 9 weeks, or for at least 10 weeks, or for at least 11 weeks, or for at least 12 weeks.

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EXAMPLE 20

This Example describes the initial results of an ongoing Phase 2 clinical trial to evaluate the safety and clinical efficacy of a fully human monoclonal MASP-2 inhibitory antibody in adults with steroid-dependent lupus nephritis (LN).

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Background:

Chronic kidney diseases affect more than 20 million people in the United States (Drawz P. et al., *Ann Intern Med* 162(11); ITC1-16, 2015). Glomerulonephropathies (GNs), including IgAN, MN and LN are kidney diseases in which the glomeruli are damaged and frequently lead to end-stage renal disease and dialysis. Many of these patients have persistent renal inflammation and progressive deterioration. Often these patients are treated with corticosteroids or immunosuppressive agents, which have many serious long-term adverse consequences. Many patients continue to deteriorate even on these treatments.

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Lupus Nephritis

A main complication of systemic lupus erythematosus (SLE) is nephritis, also known as lupus nephritis, which is classified as a secondary form of glomerulonephritis. Up to 60% of adults with SLE have some form of kidney involvement later in the course

to result in at least a partial remission in proteinuria (i.e., greater than 50 percent reduction in 24-hour urine protein excretion as compared to baseline).

In some embodiments, the method comprises administering a MASP-2 inhibitory antibody to a subject suffering from LN (such as steroid-dependent LN), via a catheter
5 (e.g., intravenously) for a first time period (e.g., at least one day to a week or two weeks or three weeks or four weeks or longer) followed by administering a MASP-2 inhibitory antibody to the subject subcutaneously for a second time period (e.g., a chronic phase of at least two weeks or longer).

In some embodiments, the method comprises administering a MASP-2 inhibitory
10 antibody to a subject suffering from LN (such as steroid-dependent LN) either intravenously, intramuscularly, or subcutaneously. Treatment may be chronic and administered daily to monthly, but preferably at least every two weeks, or at least once a week, such as twice a week or three times a week.

In one embodiment, the method comprises treating a subject suffering from LN
15 (such as steroid-dependent LN) comprising administering to the subject a composition comprising an amount of 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
20 set forth as SEQ ID NO:69. In some embodiments, the composition comprises a MASP-2 inhibitory antibody comprising (a) a heavy-chain variable region comprising: i) a heavy-chain CDR-H1 comprising the amino acid sequence from 31-35 of SEQ ID NO:67; and ii) a heavy-chain CDR-H2 comprising the amino acid sequence from 50-65 of SEQ ID NO:67; and iii) a heavy-chain CDR-H3 comprising the amino acid sequence
25 from 95-107 of SEQ ID NO:67 and b) a light-chain variable region comprising: i) a light-chain CDR-L1 comprising the amino acid sequence from 24-34 of SEQ ID NO:69; and ii) a light-chain CDR-L2 comprising the amino acid sequence from 50-56 of SEQ ID NO:69; and iii) a light-chain CDR-L3 comprising the amino acid sequence from 89-97 of SEQ ID NO:69, or (II) a variant thereof comprising a heavy-chain variable region with at
30 least 90% identity to SEQ ID NO:67 (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to SEQ ID NO:67) and a light-chain variable region with at least 90% identity (e.g., at least

91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to SEQ ID NO:69.

5 In some embodiments, the method comprises administering to the subject suffering from LN (such as steroid-dependent LN) a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen binding fragment thereof, comprising a heavy-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:67 and a light-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:69.

10 In some embodiments, the method comprises administering to the subject suffering from LN (such as steroid-dependent LN) a composition comprising a MASP-2 inhibitory antibody, or antigen binding fragment thereof, that specifically recognizes at least part of an epitope on human MASP-2 recognized by reference antibody OMS646 comprising a heavy-chain variable region as set forth in SEQ ID NO:67 and a light-chain variable region as set forth in SEQ ID NO:69.

15 In some embodiments, the method comprises administering to a subject suffering from, or at risk for developing LN (such as steroid-dependent LN) a composition comprising a MASP-2 inhibitory antibody, or antigen binding fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence set forth as SEQ ID NO:67 and a light-chain variable region comprising the amino acid sequence set
20 forth as SEQ ID NO:69 in a dosage from 1 mg/kg to 10 mg/kg (i.e., 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg or 10 mg/kg) at least once weekly (such as at least twice weekly or at least three times weekly) for a period of at least 3 weeks, or for at least 4 weeks, or for at least 5 weeks, or for at least 6 weeks, or for at least 7 weeks, or for at least 8 weeks, or for at least 9 weeks, or for at least 10 weeks, or
25 for at least 11 weeks, or for at least 12 weeks.

EXAMPLE 21

This Example describes additional results obtained in the ongoing Phase 2 Clinical Trial to evaluate the safety and clinical efficacy of a fully human monoclonal
30 MASP-2 inhibitory antibody, OMS646, on reducing proteinuria in adult patients with glomerulopathies, including IgAN as described in Example 19.

Methods:

showing an exciting response of 50 percent improvement. The improvements observed in eGFRs indicate that OMS646 could provide further benefit to patients by potentially precluding or substantially extending the time to the need for dialysis and reducing the risk of complications associated with progression of chronic kidney disease.

5 In accordance with the foregoing, in one embodiment, the invention provides 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
10 variable region comprising CDR-L1, CDR-L2 and CDR-L3 of the amino acid sequence set forth as SEQ ID NO:69 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
 - 15 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 embodiment, the dosage of the MASP-2 inhibitory antibody is about 4
20 mg/kg (i.e., from 3.6 mg/kg to 4.4 mg/kg), such as about 3.6 mg/kg, about 3.7 mg/kg, about 3.8 mg/kg, about 3.9 mg/kg, about 4.0 mg/kg, about 4.1 mg/kg, about 4.2 mg/kg, about 4.3 mg/kg or about 4.4 mg/kg.

In one embodiment, dosage of the MASP-2 inhibitory antibody is a fixed dose from about 180 mg to about 725 mg (i.e., from 160 mg to 800 mg, or from about 300 mg
25 to 500 mg, such as from about 300 mg to about 400 mg), such as about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about
30 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about

- 10E. The method according to paragraph 1E, wherein the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject.
- 11E. The method according to any of paragraphs 1E to 10E, wherein the MASP-2
5 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.
- 1F. A method of treating a human subject suffering from membranous nephropathy
10 (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.
- 2F. The method according to paragraph 1F, wherein the subject is suffering from steroid-dependent MN.
- 3F. The method according to paragraph 1F or 2F, wherein the MASP-2 inhibitory
15 antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2.
- 4F. The method according to any of paragraphs 1F to 3F, wherein the antibody or
20 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.
- 5F. The method according to any of paragraphs 1F to 4F, wherein the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.
- 6F. The method according to any of paragraphs 1F to 5F, wherein the MASP-2
25 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less.
- 7F. The method according to paragraph 1F, 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.

8F. The method according to any of paragraphs 1F to 7F, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount
5 effective to improve renal function.

9F. The method according to paragraph 8F, 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.

10 10F. The method according to paragraph 1F or 2F, wherein the composition is administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject.

11F. The method according to any of paragraphs 1F to 10F, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof comprises a heavy chain variable
15 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.

1G. 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-
20 2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation.

2G. The method according to paragraph 1G, wherein the subject is suffering from steroid-dependent LN.

3G. The method according to paragraph 1G or 2G, wherein the MASP-2 inhibitory
25 antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2.

4G. The method according to any of paragraphs 1G to 3G, 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.

5G. The method according to any of paragraphs 1G to 4G, wherein the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway.

5 6G. The method according to any of paragraphs 1G to 5G, wherein the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less.

7G. The method according to paragraph 1G, wherein the method further comprises identifying a human subject having steroid-dependent LN prior to the step of
10 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.

8G. The method according to any of paragraphs 1G to 7g, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof is administered in an amount effective to improve renal function.

15 9G. The method according to paragraph 8G, 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.

10G. The method according to paragraph 1G or 2G, wherein the composition is
20 administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject.

11G. The method according to any of paragraphs 1G to 10G, 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
25 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.

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 steroid-dependent lupus nephritis (LN), wherein the composition is to be administered in an amount sufficient to improve renal function and decrease the corticosteroid dosage in said subject and 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.
2. The use according to claim 1, wherein the antibody or antigen-binding fragment thereof is selected from the group consisting of a recombinant antibody, an antibody having reduced effector function, a chimeric antibody, a humanized antibody, and a human antibody.
3. The use according to claim 1, wherein the MASP-2 inhibitory antibody does not inhibit the classical pathway.
4. The use according to claim 1, wherein the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC₅₀ of 30 nM or less.
5. 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.
6. 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.

7. 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:69, in the manufacture of a medicament for reducing proteinuria in a human subject suffering from steroid-dependent Immunoglobulin A Nephropathy (IgAN), wherein the medicament is to be administered according to a dosage regimen as follows:

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; wherein the medicament reduces proteinuria in said human subject.
8. The use of claim 7, 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.
9. The use of claim 7, 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 by at least 30%.
10. The use of claim 7, wherein the urinary protein levels in the subject are periodically monitored during the treatment period and/or rest period.
11. The use of claim 7, 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.
12. The use of Claim 7, 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:69.