CLAIMS:

1. Use of a modified MT-SP1 protease, or a catalytically active portion thereof, for formulation of a medicament for treatment of an inflammatory disease or disorder, wherein:

the MT-SP1 protease, or a catalytically active portion thereof, comprises modifications in one or more amino acid residues of a scaffold MT-SP1 protease, or a catalytically active portion of a scaffold MT-SP1 protease, wherein:

the modification(s) is/are selected from among modifications corresponding to one or both of I41D and Q175L, based on chymotrypsin numbering;

the modified amino acid residue(s) increases one or both of specificity for a target substrate and activity towards a target substrate compared to the MT-SP1 not containing the modified amino acid residue(s), wherein the target substrate is a complement protein;

the target substrate is C2 or C3;

the unmodified MT-SP1 comprises the sequence of amino acids set forth in SEQ ID NO:2 or 10 or a variant having at least 95% sequence identity to the sequence of amino acids set forth in SEQ ID NO: 2 or 10; and

the MT-SP1 protease, or catalytically active portion thereof, cleaves any one or more target substrates of a complement pathway such that complement activation in a pathway comprising the target substrate is inhibited, whereby inhibition of complement activation leads to a reduction of inflammatory symptoms associated with the disease or disorder, thereby treating the disease or disorder.

2. The use of claim 1, wherein the modification corresponds to the amino acid replacement I41D.

3. The use of claim 1, wherein the modification corresponds to the amino acid replacement Q175L.

4. The use of claim 1, wherein the modification corresponds to the amino acid replacements I41D and Q175L.

5. The use of any of claims 1-4, wherein the modified MT-SP1 comprises 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid replacements compared to the unmodified MT-SP1 set forth in SEQ ID NO:2 or 10.

6. The use of any of claims 1-5, wherein the inflammatory disorder is selected from among an immune-mediated inflammatory disorder, a neurodegenerative disorder and a cardiovascular disorder.

7. The use of any of claims 1-6, wherein the inflammatory disorder is selected from among sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), Multiple Sclerosis (MS), Myasthenia gravis (MG), asthma, inflammatory bowel disease, immune

complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), Ischemia-reperfusion injury and Guillain-Barré syndrome.

8. The use of claim 7, wherein the inflammatory disorder is ischemia-reperfusion injury, and the ischemia-reperfusion injury is caused by an event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis.

9. The use of any of claims 1-8, wherein the complement pathway is one or more of the classical, alternative and lectin pathways.

10. The use of any of claims 1-9, wherein the target substrate is C2.

11. The use of any of claims 1-10, wherein the target substrate comprises the sequence of amino acids set forth in SEQ ID NO: 311 or 312, or comprises a fragment thereof that exhibits a complement activity.

12. The use of any of claims 1-11, wherein the modification(s) in an MT-SP1 protease or catalytically active portion thereof further comprises a modification at position 151, based on chymotrypsin numbering.

13. The use of claims 1-12, wherein the modified MT-SP1 protease, or a catalytically active portion thereof, cleaves a substrate recognition site of the target substrate.

14. The use of claim 13, wherein the target substrate is C2 and the substrate recognition site includes the sequence of amino acids SLGR (SEQ ID NO:392).

15. The use of any one of claims 1-14, wherein the modified MT-SP1 protease or a catalytically active portion thereof is formulated for administration in combination with a second agent for treating a complement-mediated disorder.

16. The use of claim 15, wherein the second agent is an anti-inflammatory agent or an anticoagulant.

17. The use of claim 16, wherein the second agent is selected from among any one or more of a NSAID, antimetabolite, corticosteroid, analgesic, cytotoxic agent, pro-inflammatory cytokine inhibitor, anti-inflammatory cytokines, B cell targeting agents, compounds targeting T antigens, adhesion molecule blockers, chemokines receptor antagonists, kinase inhibitors, PPAR-□ ligands, complement inhibitors, heparin, warfarin, acenocoumarol, phenindione, EDTA, citrate, oxalate, argatroban, lepirudin, bivalirudin, and ximelagatran.

18. A pharmaceutical composition comprising a modified MT-SP1 protease, or a catalytically active portion thereof, for use in inhibiting complement activation to thereby treat an inflammatory condition or disorder, wherein:

the MT-SP1 protease, or a catalytically active portion thereof, comprises modifications in any one or more amino acid residues of a scaffold MT-SP1 protease, or a catalytically active portion of a scaffold MT-SP1 protease, wherein:

the modification(s) are selected from among modifications corresponding to one or both of I41D and Q175L, based on chymotrypsin numbering;

the unmodified MT-SP1 comprises the sequence of amino acids set forth in SEQ ID NO:2 or 10 or a variant having at least 95% sequence identity to the sequence of amino acids set forth in SEQ ID NO: 2 or 10;

the modified amino acid residue(s) increases one or both of specificity for a target substrate and activity towards a target substrate compared to the MP-SP1 not containing the modified amino acid residue(s), wherein the target substrate is a complement protein;

the target substrate is C2 or C3; and

the MT-SP1 protease, or catalytically active portion thereof, cleaves any one or more target substrates of a complement pathway such that complement activation in a pathway comprising the target substrate is inhibited, whereby inhibition of complement activation leads to a reduction of inflammatory symptoms associated with the disease or disorder, thereby treating the disease or disorder.

19. The pharmaceutical composition of claim 18, wherein the modification corresponds to the amino acid replacement I41D.

20. The pharmaceutical composition of claim 18, wherein the modification corresponds to the amino acid replacement Q175L.

21. The pharmaceutical composition of claim 18 , wherein the modification corresponds to the amino acid replacements I41D and Q175L.

22. The pharmaceutical composition of any of claims 18-21, wherein the modified MT-SP1 comprises 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid replacements compared to the unmodified MT-SP1 set forth in SEQ ID NO:2 or 10.

23. The pharmaceutical composition of any of claims 18-22, wherein the inhibition of complement activation leads to a reduction of inflammatory symptoms associated with a complement-mediated disorder selected from among an inflammatory disorder, a neurodegenerative disorder and a cardiovascular disorder.

24. The pharmaceutical composition of claim 23, wherein the complement-mediated disorder is selected from among sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), Multiple Sclerosis (MS), Myasthenia gravis (MG), asthma, inflammatory bowel disease, immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), Ischemia-reperfusion injury and Guillain-Barré syndrome.

25. The pharmaceutical composition of claim 24, wherein the complement-mediated disorder is ischemia-reperfusion injury, and the ischemia-reperfusion injury is caused by an event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis.

26. The pharmaceutical composition of any of claims 18-25, wherein the modification(s) in an MT-SP1 protease or catalytically active portion thereof further comprises a modification at position 151, based on chymotrypsin numbering.

27. The pharmaceutical composition of any of claims 18-26, wherein the modified MT-SP1 protease, or a catalytically active portion thereof, cleaves a substrate recognition site of the target substrate.

28. The pharmaceutical composition of any of claims 18-27, wherein the target substrate is C2.

29. The pharmaceutical composition of any of claims 18-27, wherein the target substrate is C3.

30. The pharmaceutical composition of claim 28 or claim 29, wherein the target substrate comprises the sequence of amino acids set forth in SEQ ID NO: 311 or 312, or comprises a fragment thereof that exhibits a complement activity.

31. The pharmaceutical composition of claim 28, wherein the target substrate is C2 and the substrate recognition site includes the sequence of amino acids SLGR (SEQ ID NO:392).

32. The pharmaceutical composition of any one of claims 18-31, wherein the MT-SP1 protease or a catalytically active portion thereof is formulated for administration in combination with a second agent for treating a complement-mediated disorder.

33. The pharmaceutical composition of claim 32, wherein the second agent is an anti-inflammatory agent or an anticoagulant.

34. The pharmaceutical composition of claim 33, wherein the second agent is selected from among any one or more of a NSAID, antimetabolite, corticosteroid, analgesic, cytotoxic agent, pro-inflammatory cytokine inhibitor, anti-inflammatory cytokines, B cell targeting agents, compounds targeting T antigens, adhesion molecule blockers, chemokines receptor antagonists, kinase inhibitors, PPAR-□ ligands, complement inhibitors, heparin, warfarin, acenocoumarol, phenindione, EDTA, citrate, oxalate, argatroban, lepirudin, bivalirudin, and ximelagatran.

35. A modified MT-SP1 protease or a catalytically active portion thereof, wherein:

the modified MT-SP1 protease comprises modifications in any one or more amino acids of a scaffold MT-SP1 protease, wherein:

the modified amino acid residue(s) increases one or both of specificity for a target substrate or selectivity towards a complement protein target substrate;

the target substrate is C2 or C3;

the modification(s) are selected from among modifications corresponding to one or both of I41D and Q175L, based on chymotrypsin numbering; and

the unmodified MT-SP1 comprises the sequence of amino acids set forth in SEQ ID NO:2 or 10 or a variant having at least 95% sequence identity to the sequence of amino acids set forth in SEQ ID NO: 2 or 10.

36. The modified non-complement protease, or a catalytically active portion thereof, of claim 35, wherein the modification(s) in the MT-SP1 protease or a catalytically active portion thereof corresponds to the amino acid replacement I41D.

37. The modified non-complement protease, or a catalytically active portion thereof, of claim 35, wherein the modification(s) in the MT-SP1 protease or a catalytically active portion thereof corresponds to the amino acid replacement Q175L.

38. The modified non-complement protease, or a catalytically active portion thereof, of claim 35, wherein the modification(s) in the MT-SP1 protease or a catalytically active portion thereof corresponds to the amino acid replacements I41D and Q175L.

39. The modified non-complement protease, or catalytically active portion thereof of any of claims 35-38, wherein the modified MT-SP1 comprises 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid replacements compared to the unmodified MT-SP1 set forth in SEQ ID NO:2 or 10.

40. The modified MT-SP1 protease, or a catalytically active portion thereof, of any of claims 35-39, further comprising a modification at position 151, based on chymotrypsin numbering.

41. The modified MT-SP1 protease, or a catalytically active portion thereof, of claim any of claims 35-40, wherein the MT-SP1 protease, or a catalytically active portion thereof, is modified to cleave a substrate recognition site of the target substrate.

42. The modified MT-SP1 protease, or a catalytically active portion thereof, of any of claims 35-41, wherein the target substrate is C2.

43. The modified MT-SP1 protease of any of claims 35-41, wherein the target substrate is C3.

44. The modified MT-SP1 protease of claim 42 or claim 43, wherein the target substrate comprises the sequence of amino acids set forth in SEQ ID NO: 311 or 312, or comprises a fragment thereof that exhibits a complement activity.

45. The modified MT-SP1 protease, or a catalytically active portion thereof, of claim 42, wherein the target substrate is C2 and the substrate recognition site includes the sequence of amino acids of SLGR (SEQ ID NO: 392).

46. A pharmaceutical composition, comprising a modified MT-SP1 protease, or a catalytically active portion thereof, of any of claims 35-45.

47. The pharmaceutical composition of claim 46, further comprising a pharmaceutically acceptable excipient.

48. The pharmaceutical composition of claim 46 or claim 47, wherein the pharmaceutical composition is formulated for systemic, oral, nasal, pulmonary, local, or topical administration.

49. A nucleic acid molecule, comprising a sequence of nucleotides that encodes any one of the modified MT-SP1 proteases, or a catalytically active portion thereof, of claims 35-45.

50. A vector, comprising the nucleic acid molecule of claim 49.

51. A cell, comprising the vector of claim 50.

CLAIMS:

1. Use of a modified non-complement protease, or a catalytically active portion thereof, in the manufacture of a medicament for treatment of an inflammatory disease or disorder, wherein:

the non-complement protease, or a catalytically active portion thereof, comprises modifications in any one or more amino acid residues of a scaffold protease, or a catalytically active portion of a scaffold protease, wherein

the scaffold protease is a non-complement protease that is an MT-SP1 protease, or a catalytically active portion thereof

the modified amino acid residue(s) increases one or both of specificity for a target substrate and activity towards a target substrate compared to the scaffold protease not containing the modified amino acid residue(s), wherein the target substrate is a complement protein; and

the non-complement protease, or catalytically active portion thereof, cleaves any one or more target substrates of a complement pathway such that complement activation in a pathway comprising the target substrate is inhibited, whereby inhibition of complement activation leads to a reduction of inflammatory symptoms associated with the disease or disorder, thereby treating the disease or disorder.

2. The use of claim 1 , wherein the inflammatory disorder is selected from among an immune-mediated inflammatory disorder, a neurodegenerative disorder and a cardiovascular disorder.

3. The use of claim 1 or claim 2, wherein the inflammatory disorder disorder is selected from among sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), Multiple Sclerosis (MS), Myasthenia gravis (MG), asthma, inflammatory bowel disease, immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), Ischemia-reperfusion injury and Guillan-Barre syndrome.

4. The use of claim 3, wherein the inflammatory disorder is ischemia-reperfusion injury, and the ischemia-reperfusion injury is caused by an event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis.

5. The use of any of claims 1-4 , wherein the complement pathway is one or more of the classical, alternative and lectin pathways.

6. The use of any of claims 1-5 , wherein the target substrate is any one or more of C1q, C2, C3, iC3, C4, iC4, C5, C6, C7, C8, C9, MBL, Factor B, Factor D, Factor P, MASP-1, MASP-2, C1r, C1s, C4b, C4a, C2b, C2a, C3b, C3a, Ba, Bb and ficolin.

7. The use of any of claims 1-6 , wherein the target substrate comprises a sequence of amino acids set forth in any one of SEQ ID NOS: 298, 299, 300, 302, 304, 305, 306, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 326, 328, 330, 332, 334, 335, 338, 340, and 344, or comprises a fragment thereof that exhibits a complement activity.

8. The use of claim 1, wherein the MT-SP1 scaffold protease or catalytically active portion thereof comprises the sequence of amino acids set forth in SEQ ID NO: 2 or 10, or is an allelic or species variant thereof.

9. The use of claim 1, wherein the modification(s) in an MT-SPl scaffold protease or catalytically active portion thereof correspond to the modification(s) in a modified MT-SPl polypeptide comprises the sequence of amino acids as set forth in SEQ ID NO:596 or 650.

10. The use of claim 8 or 9, wherein the target substrate is C2 or C3.

11. The use of any of claims 1-10 , wherein the modification(s) in an MT-SPl protease or catalytically active portion thereof comprises a modification in a position selected from among 41, 97, 146, 151, 192 and 224, based on chymotrypsin numbering.

12. The use of any of claims 1-10 , wherein the modification(s) in an MT- SPl protease or catalytically active portion thereof are in any one or more amino acids that contribute to extended substrate specificity or secondary sites of interaction.

13. The use of any of claims 1-12 , wherein the modification(s) in an MT-SP1 protease or catalytically active portion thereof are selected from any one or more of R60cD, R60cW,D96A, D96V, D96F, D96F, D96S, D96T, F97D, F97E, F97A, F97W, F99S, F99G, F99Y, F99V, F99W, F99A, Y146N, Y146D, Y146E, Y146F, Y146A, Y146W, Y146R, L172N,Q174H, Q174A, Q174V, Q174F, Q174R, Q174K, Q174L, Q174Y, Q175D, Q175E, M180E, Q192F, Q192L, Q192I, Q192E, Q192K, Q192Y, Q192R, Q192V, W215F, W215Y, D217A, D217V, D217Q, D217N, D217H, Q221aD, K224A and K224F.

14. The use of any of claims 1-13 , wherein the modification(s) in an MT-SPl protease or catalytically active portion thereof are Y146D/K224F or Y146E.

15. The use of any of claims 1-14 , wherein the modification(s) in an MT-SP1 protease or catalytically active portion thereof are selected from among Y146D/K224F, D96A, Y146E/K224N, I41T/Y146E/Q175D/K224R, I41T/Y146D/K224F, I41T/Y146E/Q175D/K224N, I41T/Y146E/G151L/Q175D/K224L, Y146E/ Q221aE/K224F, I41T/ Y146E/ G151L/Q175D/K224R, I41T/Y146E/G151L/Q175D/K224N, Q221aD, Y146E/K224R, Y146E/ Q175D/ K224N, Y146D/K224R, I41T/Y146E/G151L/Q175D/K224F, Y146E/Q175D/K224R, Y146E/L224L, G147E, Y146D/Q175D/K224R, Y146D/Q175L/K224L, Y146D/Q175W/K224L, Y146D/K224L, Y146E/Q221aE/K224R, Y146E/ K224A, Y146D/Q175H/K224L, Y146D/Q175Y/K224L, Y146E/K224Y, Y146D/Q175F/K224L, Y146D/Q221aL/K224S, I41E/Y146D/K224L, Y146D/D217F/K224L, H143V/Y146D/K224F, Y146E/K224F, Y146A/K224F, Y146E/K224T, I41T/Y146E/K224L, I41F/Y146D/K224F, I41L/Y146D/K224F, I41T/Y146D/G151L/K224F, I41A/Y146D/K224F, I41E/Y146D/K224F, I41D/Y146D/K224L, I41D/Y146D/K224F, Y146N/K224F, I41T/Y146D/Q175D/K224F, Q192F/K224F, Y146D/Q192A/K224F, Q192V/K224F, I41T/Y146D/Q175D/K224L, I41T/Y146D/Q175D/K224R, I41T/Y146D/Q175D/K224N, I41T/Y146D/G151L/Q175D/K224F, I41T/Y146D/G151L/Q175D/K224L, I41T/Y146D/G151L/Q175D/K224R, I41T/Y146D/G151L/Q175D/K224N, I41T/Y146E/Q175D/K224F, I41T/Y146E/Q175D/K224L, I41T/Y146D/G151L/K224N, Y146D/Q175D/K224N, Y146D/Q175D/K224N, Y146D/G151L/K224N, Y146D/Q175R/K224N, Y146D/Q175K/K224N, Y146D/Q175H/K224N, I41T/Y146D/G151L/Q175K/K224F, I41T/Y146D/G151L/Q175R/K224F, I41T/Y146D/G151L/Q175H/K224F, I41T/Y146D/G151L/Q175Y/K224F, I41T/Y146D/G151L/Q175K/K224N, I41T/Y146D/G151L/Q175R/K224N, I41T/Y146D/G151L/Q175H/K224N, and I41T/Y146D/G151L/Q175Y/K224N, Y146F, L172N, Q175D, Q175E, R60cD, R60cW, I41T/Y146D/K224N and I41T/Y146D/K224L based on chymotrypsin numbering.

16. The use of any of claims 1-15 , wherein the modified MT-SPl polypeptide has the sequence of amino acids as set forth in any of SEQ ID NOS: 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40-69, 404-418, 419-447, 524-533, 552-659, and 663-710.

17. The use of claims 1-16 , wherein the modified MT-SP1 protease, or a catalytically active portion thereof, cleaves a substrate recognition site of the target substrate.

18. The use of claim 17, wherein the target substrate is C2 or C3.

19. The use of claim 18, wherein the target substrate is C2 and the substrate recognition site includes a sequence of amino acids of SLGR (SEQ ID NO:392).

20. The use of any of claims 1-19 , wherein the non-complement protease, or catalytically active portion thereof, cleaves a substrate recognition site of the target substrate.

21. The use of claim 20, wherein the non-complement protease, or a catalytically active portion thereof, cleaves a Factor I substrate recognition site.

22. The use of any one of claims 1-21 , wherein the non-complement protease or a catalytically active portion thereof is formulated for administration in combination with a second agent for treating a complement-mediated disorder.

23. The use of claim 22, wherein the second agent is an anti-inflammatory agent or an anticoagulant.

24. The use of claim 23, wherein the second agent is selected from among any one or more of a NSAID, antimetabolite, corticosteroid, analgesic, cytotoxic agent, pro-inflammatory cytokine inhibitor, anti-inflammatory cytokines, B cell targeting agents, compounds targeting T antigens, adhesion molecule blockers, chemokines receptor antagonists, kinase inhibitors, PPAR-γ ligands, complement inhibitors, heparin, warfarin, acenocoumarol, phenindione, EDTA, citrate, oxalate, argatroban, lepirudin, bivalirudin, and ximelagatran.

25. A pharmaceutical composition comprising a modified non-complement protease, or a catalytically active portion thereof, for use in modulating complement activation, wherein:

the non-complement protease, or a catalytically active portion thereof, comprises modifications in any one or more amino acid residues of a scaffold protease, or a catalytically active portion of a scaffold protease, wherein:

the scaffold protease is a non-complement protease that is an MT-SP1 protease or a catalytically active portion thereof; and

the modified amino acid residue(s) increases one or both of specificity for a target substrate and activity towards a target substrate compared to the scaffold protease not containing the modified amino acid residue(s), wherein the target substrate is a complement protein; and

the non-complement protease, or catalytically active portion thereof, cleaves any one or more target substrates of a complement pathway such that complement activation in a pathway comprising the target substrate is altered.

26. The pharmaceutical composition of claim 25, wherein complement activation is inhibited.

27. The pharmaceutical composition of claim 25 or claim 26, wherein modulation of complement activation effects treatment of a subject with a complement-mediated disorder.

28. The pharmaceutical composition of claim 26 or claim 27, wherein the inhibition of complement activation leads to a reduction of inflammatory symptoms associated with a complement-mediated disorder selected from among an inflammatory disorder, a neurodegenerative disorder and a cardiovascular disorder.

29. The pharmaceutical composition of claim 28, wherein the complement-mediated disorder is selected from among sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), Multiple Sclerosis (MS), Myasthenia gravis (MG), asthma, inflammatory bowel disease, immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), Ischemia-reperfusion injury and Guillan-Barre syndrome.

30. The pharmaceutical composition of claim 29, wherein the complement-mediated disorder is ischemia-reperfusion injury, and the ischemia-reperfusion injury is caused by an event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis.

31. The pharmaceutical composition of any of claims 25-30 , wherein the complement pathway is one or more of the classical, alternative and lectin pathways.

32. The pharmaceutical composition of any of claims 25-31 , wherein the target substrate is any one or more of C1q, C2, C3, iC3, C4, iC4, C5, C6, C7, C8, C9, MBL, Factor B, Factor D, Factor P, MASP-1, MASP-2, C1r, C1s, C4b, C4a, C2b, C2a, C3b, C3a, Ba, Bb and ficolin.

33. The pharmaceutical composition of any of claims 25-32 , wherein the target substrate comprises a sequence of amino acids set forth in any one of SEQ ID NOS: 298, 299, 300, 302, 304, 305, 306, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 326, 328, 330, 332, 334, 335, 338, 340, and 344, or comprises a fragment thereof that exhibits a complement activity.

34. The pharmaceutical composition of any of claims 25-33 , wherein the MT-SP1 protease or catalytically active portion thereof comprises the sequence of amino acids set forth in SEQ ID NO: 2 or 10, or is an allelic or species variant thereof.

35. The pharmaceutical composition of any of claims 25-33, wherein the modification(s) in an MT-SPl protease or catalytically active portion thereof correspond to the modification(s) in a modified MT-SPl polypeptide comprises the sequence of amino acids as set forth in SEQ ID NO:596 or 650.

36. The pharmaceutical composition of any of claims 25-35, wherein the target substrate is C2 or C3.

37. The pharmaceutical composition of any of claims 25-36, wherein the modification(s) in an MT-SPl protease or catalytically active portion thereof comprises a modification in a position selected from among 41, 97, 146, 151, 192 and 224, based on chymotrypsin numbering.

38. The pharmaceutical composition of claims 25-36, wherein the modification(s) in an MT- SPl protease or catalytically active portion thereof are in any one or more amino acids that contribute to extended substrate specificity or secondary sites of interaction.

39. The pharmaceutical composition of any of claims 25-38, wherein the modification(s) in an MT-SP1 protease or catalytically active portion thereof are selected from any one or more of R60cD, R60cW,D96A, D96V, D96F, D96F, D96S, D96T, F97D, F97E, F97A, F97W, F99S, F99G, F99Y, F99V, F99W, F99A, Y146N, Y146D, Y146E, Y146F, Y146A, Y146W, Y146R, L172N,Q174H, Q174A, Q174V, Q174F, Q174R, Q174K, Q174L, Q174Y, Q175D, Q175E, M180E, Q192F, Q192L, Q192I, Q192E, Q192K, Q192Y, Q192R, Q192V, W215F, W215Y, D217A, D217V, D217Q, D217N, D217H, Q221aD, K224A and K224F.

40. The pharmaceutical composition of any of claims 25-39, wherein the modification(s) in an MT-SPl protease or catalytically active portion thereof are Y146D/K224F or Y146E.

41. The pharmaceutical composition of any of claims 25-40, wherein the modification(s) in an MT-SP1 protease or catalytically active portion thereof are selected from among Y146D/K224F, D96A, Y146E/K224N, I41T/Y146E/Q175D/K224R, I41T/Y146D/K224F, I41T/Y146E/Q175D/K224N, I41T/Y146E/G151L/Q175D/K224L, Y146E/ Q221aE/K224F, I41T/ Y146E/ G151L/Q175D/K224R, I41T/Y146E/G151L/Q175D/K224N, Q221aD, Y146E/K224R, Y146E/ Q175D/ K224N, Y146D/K224R, I41T/Y146E/G151L/Q175D/K224F, Y146E/Q175D/K224R, Y146E/L224L, G147E, Y146D/Q175D/K224R, Y146D/Q175L/K224L, Y146D/Q175W/K224L, Y146D/K224L, Y146E/Q221aE/K224R, Y146E/ K224A, Y146D/Q175H/K224L, Y146D/Q175Y/K224L, Y146E/K224Y, Y146D/Q175F/K224L, Y146D/Q221aL/K224S, I41E/Y146D/K224L, Y146D/D217F/K224L, H143V/Y146D/K224F, Y146E/K224F, Y146A/K224F, Y146E/K224T, I41T/Y146E/K224L, I41F/Y146D/K224F, I41L/Y146D/K224F, I41T/Y146D/G151L/K224F, I41A/Y146D/K224F, I41E/Y146D/K224F, I41D/Y146D/K224L, I41D/Y146D/K224F, Y146N/K224F, I41T/Y146D/Q175D/K224F, Q192F/K224F, Y146D/Q192A/K224F, Q192V/K224F, I41T/Y146D/Q175D/K224L, I41T/Y146D/Q175D/K224R, I41T/Y146D/Q175D/K224N, I41T/Y146D/G151L/Q175D/K224F, I41T/Y146D/G151L/Q175D/K224L, I41T/Y146D/G151L/Q175D/K224R, I41T/Y146D/G151L/Q175D/K224N, I41T/Y146E/Q175D/K224F, I41T/Y146E/Q175D/K224L, I41T/Y146D/G151L/K224N, Y146D/Q175D/K224N, Y146D/Q175D/K224N, Y146D/G151L/K224N, Y146D/Q175R/K224N, Y146D/Q175K/K224N, Y146D/Q175H/K224N, I41T/Y146D/G151L/Q175K/K224F, I41T/Y146D/G151L/Q175R/K224F, I41T/Y146D/G151L/Q175H/K224F, I41T/Y146D/G151L/Q175Y/K224F, I41T/Y146D/G151L/Q175K/K224N, I41T/Y146D/G151L/Q175R/K224N, I41T/Y146D/G151L/Q175H/K224N, and I41T/Y146D/G151L/Q175Y/K224N, Y146F, L172N, Q175D, Q175E, R60cD, R60cW, I41T/Y146D/K224N and I41T/Y146D/K224L based on chymotrypsin numbering.

42. The pharmaceutical composition of any of claims 25-41, wherein the modified MT-SPl polypeptide comprises the sequence of amino acids as set forth in any of SEQ ID NOS: 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40-69, 404-418, 419-447, 524-533, 552-659, and 663-710.

43. The pharmaceutical composition of any of claims 25-42, wherein the modified MT-SP1 protease, or a catalytically active portion thereof, cleaves a substrate recognition site of the target substrate.

44. The pharmaceutical composition of claim 43, wherein the target substrate is C2 or C3.

45. The pharmaceutical composition of claim 44, wherein the target substrate is C2 and the substrate recognition site includes a sequence of amino acids of SLGR (SEQ ID NO:392).

46. The pharmaceutical composition of any of claims 25-45, wherein the non-complement protease, or catalytically active portion thereof, cleaves a substrate recognition site of the target substrate.

47. The pharmaceutical composition of claim 46, wherein the non-complement protease, or a catalytically active portion thereof, cleaves a Factor I substrate recognition site.

48. The pharmaceutical composition of any one of claims 25-47, wherein the non-complement protease or a catalytically active portion thereof is formulated for administration in combination with a second agent for treating a complement-mediated disorder.

49. The pharmaceutical composition of claim 48, wherein the second agent is an anti-inflammatory agent or an anticoagulant.

50. The pharmaceutical composition of claim 49, wherein the second agent is selected from among any one or more of a NSAID, antimetabolite, corticosteroid, analgesic, cytotoxic agent, pro-inflammatory cytokine inhibitor, anti-inflammatory cytokines, B cell targeting agents, compounds targeting T antigens, adhesion molecule blockers, chemokines receptor antagonists, kinase inhibitors, PPAR-γ ligands, complement inhibitors, heparin, warfarin, acenocoumarol, phenindione, EDTA, citrate, oxalate, argatroban, lepirudin, bivalirudin, and ximelagatran.

51. A modified non-complement protease, or a catalytically active portion thereof, comprising modifications in any one or more amino acids of a scaffold protease, or a catalytically active portion of a scaffold protease, wherein:

the scaffold protease is a non-complement protease that is an MT-SP1 protease, or a catalytically active portion thereof;

the modified amino acid residue(s) increases one or both of specificity for a target substrate and activity towards a target substrate, wherein the target substrate is a complement protein; and

the scaffold protease comprises at least two or more modifications, wherein:

one modification is at position 146 and the second modification is at position 224, based on chymotrypsin numbering, provided that:

(i) where the protease includes only two modifications, the protease does not include Y146D and K224F as the two modifications; and

(ii) where the protease contains three modifications, the protease does not include F99V or I or L or T with Y146D and K224F.

52. The modified non-complement protease, or a catalytically active portion thereof, of claim 51, comprising a modification at position 151, based on chymotrypsin numbering.

53. The modified non-complement protease, or a catalytically active portion thereof, of claim 51, comprising a modification at position 41, based on chymotrypsin numbering.

54. The modified non-complement protease, or a catalytically active portion thereof, of any of claims 51-53, wherein:

the modification(s) in the MT-SP1 protease or a catalytically active portion thereof are selected from among Y146E/K224N, I41T/Y146E/Q175D/K224R, I41T/Y146D/K224F, I41T/Y146E/Q175D/K224N, I41T/Y146E/G151L/Q175D/K224L, Y146E/ Q221aE/K224F, I41T/ Y146E/ G151L/Q175D/K224R, I41T/Y146E/G151L/Q175D/K224N, Y146E/K224R, Y146E/ Q175D/ K224N, Y146D/K224R, I41T/Y146E/G151L/Q175D/K224F, Y146E/Q175D/K224R, Y146E/K224L, Y146D/Q175D/K224R, Y146D/Q175L/K224L, Y146D/Q175W/K224L, Y146D/K224L, Y146E/Q221aE/K224R, Y146E/ K224A, Y146D/Q175H/K224L, Y146D/Q175Y/K224L, Y146E/K224Y, Y146D/Q175F/K224L, Y146D/Q221aL/K224S, I41E/Y146D/K224L, Y146D/D217F/K224L, H143V/Y146D/K224F, Y146E/K224F, Y146A/K224F, Y146E/K224T, I41T/Y146E/K224L, I41F/Y146D/K224F, I41L/Y146D/K224F, I41T/Y146D/G151L/K224F, I41A/Y146D/K224F, I41E/Y146D/K224F, I41D/Y146D/K224L, I41D/Y146D/K224F, Y146N/K224F, I41T/Y146D/Q175D/K224F, Y146D/Q192A/K224F, I41T/Y146D/Q175D/K224L, I41T/Y146D/Q175D/K224R, I41T/Y146D/Q175D/K224N, I41T/Y146D/G151L/Q175D/K224F, I41T/Y146D/G151L/Q175D/K224L, I41T/Y146D/G151L/Q175D/K224R, I41T/Y146D/G151L/Q175D/K224N, I41T/Y146E/Q175D/K224F, I41T/Y146E/Q175D/K224L, , I41T/Y146D/G151L/K224N, Y146D/Q175D/K224N, Y146D/G151L/K224N, Y146D/Q175R/K224N, Y146D/Q175K/K224N, Y146D/Q175H/K224N, I41T/Y146D/G151L/Q175K/K224F, I41T/Y146D/G151L/Q175R/K224F, I41T/Y146D/G151L/Q175H/K224F, I41T/Y146D/G151L/Q175Y/K224F, I41T/Y146D/G151L/Q175K/K224N, I41T/Y146D/G151L/Q175R/K224N, I41T/Y146D/G151L/Q175H/K224N, I41T/Y146D/G151L/Q175Y/K224N, I41T/Y146D/K224L and I41T/Y146D/K224N, based on chymotrypsin numbering.

55. The modified non-complement protease, or a catalytically active portion thereof, of any of claims 51-53 , wherein modification(s) in the MT-SP1, or catalytically active portion are selected from among I41T/Y146D/G151L/K224F, I41T/Y146D/G151L/Q175D/K224F, I41T/Y146D/G151L/Q175D/K224L, I41T/Y146D/G151L/Q175D/K224R, I41T/Y146D/G151L/Q175D/K224N, I41T/Y146D/G151L/K224N, Y146D/G151L/K224N, I41T/Y146D/G151L/Q175K/K224F, I41T/Y146D/G151L/Q175R/K224F, I41T/Y146D/G151L/Q175H/K224F, I41T/Y146D/G151L/Q175Y/K224F, I41T/Y146D/G151L/Q175K/K224N, I41T/Y146D/G151L/Q175R/K224N, I41T/Y146D/G151L/Q175H/K224N, I41T/Y146D/G151L/Q175Y/K224N, I41T/Y146E/G151L/Q175D/K224L, I41T/ Y146E/ G151L/Q175D/K224R, I41T/Y146E/G151L/Q175D/K224N, and I41T/Y146E/G151L/Q175D/K224F,

based on chymotrypsin numbering.

56. The modified non-complement protease, or a catalytically active portion thereof, of claim 55, wherein modification(s) in the MT-SPl or catalytically active portion correspond to modification of I41T/Y146D/G151L/K224F, based on chymotrypsin numbering.

57. The modified non-complement protease of any of claims 51-56 , wherein the modified non-complement protease has the sequence of amino acids set forth in any one of SEQ ID NOS: 552-559, 561-566, 570-580, 583-591, 594-602, 604, 606-613, 615-620, 624-634, 637-645, 648-656, 658, or 663-710.

58. A modified non-complement protease, or a catalytically active portion thereof, comprising modifications in any one or more amino acids of a scaffold protease, or a catalytically active portion of a scaffold protease, wherein:

the scaffold protease is a non-complement protease that is an MT-SP1 protease, or a catalytically active portion thereof;

the modified amino acid residue(s) increases one or both of specificity for a target substrate and activity towards a target substrate, wherein the target substrate is a complement protein; and

the modification(s) in the MT-SP1 protease or catalytically active portion thereof are selected from any one or more of D96A, D96V, D96F, D96S, D96T, F99S, F99G, Q174H, Q174A, Q174V, Q174F, Q174R, Q174K, Q174L, Q174Y, Q192L, Q192I, Q192E, Q192K, Q192Y, D217Q, D217N, and D217H, based on chymotrypsin numbering.

59. A modified non-complement protease, wherein:

the modified non-complement protease comprises modifications in any one or more amino acids of a scaffold protease, wherein:

the modified amino acid residue(s) increases one or both of specificity for a target substrate or selectivity towards a complement protein target substrate;

the scaffold protease is an MT-SP1 protease or a catalytically active portion thereof; and

the modifications are selected from among I41T, I41A, I41L, I41F, I41D, I41E, G147E, G151L, Q221aD, Q221$_a$L. Q221$_a$E, Q175H, Q175L, Q175W, Q175Y, Q175K, K224L, K224R, K224N, K224T, K224Y and K224S, based on chymotrypsin numbering.

60. The modified non-complement protease, or a catalytically active portion thereof, of claim 58 or 59, wherein the modification(s) in the MT-SP1 protease or a catalytically active portion thereof correspond to a modified MT-SP1 polypeptide comprising the sequence of amino acids as set forth in any one of SEQ ID NOS: 41-51, 56, 57, 60-64, 67, 419-429, 434, 435, 438-442, 445, 524, 525, 527-530, 532, 533, 560, 568, 614 or 622.

61. The modified non-complement protease, or a catalytically active portion thereof, of any of claims 51-60 , wherein the scaffold protease that is an MT-SP1 protease or a catalytically active portion thereof comprises a sequence of amino acids set forth in SEQ ID NO: 2 or 10.

62. The modified non-complement protease, or catalytically active portion thereof, of any of claims 51-60 , wherein the modification(s) in the MT-SP1 protease or a catalytically active portion thereof correspond to a modified MT-SP1 polypeptide comprising the sequence of amino acids as set forth in SEQ ID NO: 596 or 650.

63. The modified non-complement protease, or a catalytically active portion thereof, of claim any of claims 51-62, wherein the MT-SP1 protease, or a catalytically active portion thereof, is modified to cleave a substrate recognition site of the target substrate.

64. The modified non-complement protease, or a catalytically active portion thereof, of any of claims 51-63, wherein the target substrate is C2 or C3.

65. The modified non-complement protease, or a catalytically active portion thereof, of claim 64, wherein the target substrate is C2 and the substrate recognition site includes a sequence of amino acids of SLGR (SEQ ID NO: 392).

66. A pharmaceutical composition, comprising a modified non-complement protease, or a catalytically active portion thereof, of any of claims 51-65.

67. The pharmaceutical composition of claim 66, further comprising a pharmaceutically acceptable excipient.

68. The pharmaceutical composition of claim 66 or claim 67, wherein the pharmaceutical composition is formulated for systemic, oral, nasal, pulmonary, local, or topical administration.

69. A nucleic acid molecule, comprising a sequence of nucleotides that encodes any one of the modified non-complement proteases, or a catalytically active portion thereof, of claims 51-69.

70. A vector, comprising the nucleic acid molecule of claim 69.

71. A cell, comprising the vector of claim 70.