

## WHAT IS CLAIMED:

1. A modified membrane type serine protease 1 (MTSP-1) polypeptide, comprising the amino acid modification G151N or H, whereby the modified MTSP-1 polypeptide has increased activity and/or specificity for a complement protein compared to the active form of the unmodified MTSP-1 polypeptide, wherein:
  - amino acid modifications are selected from among replacements, insertions, and/or deletions in the unmodified MTSP-1 polypeptide;
  - the complement protein is C3;
  - the modified MTSP-1 polypeptide cleaves a target site in C3 that inactivates C3 to thereby inhibit or reduce complement activation;
  - residues are numbered by chymotrypsin numbering;
  - corresponding residues are determined by alignment and chymotrypsin numbering;and
  - the unmodified MTSP-1 polypeptide comprises the sequence of amino acids set forth in any of SEQ ID NOs: 1-4, or a catalytically active fragment or form thereof that includes the amino acid modification position(s).
2. The modified MTSP-1 polypeptide of claim 1, wherein the target site in C3 comprises residues 737-744 of SEQ ID NO:9.
3. The modified MTSP-1 polypeptide of claim 2, wherein the cleavage is between residues 740 and 741 of SEQ ID NO:9, whereby cleavage occurs at  
Q H A R ↓ A S H L.
4. The modified MTSP-1 polypeptide of any of claims 1-3, wherein the unmodified MTSP-1 polypeptide consists of the sequence of amino acids set forth in any of SEQ ID NOs:1-4.
5. The modified MTSP-1 polypeptide of any of claims 1-3, wherein the unmodified MTSP-1 polypeptide consists of the sequence of amino acids set forth in in SEQ ID NO:2 or SEQ ID NO:4.
6. The modified MTSP-1 polypeptide of any of claims 1-5, wherein the modified MTSP-1 polypeptide contains up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid replacements, insertions, or deletions, compared to the unmodified MTSP-1 polypeptide of any of SEQ ID NOs: 1-4 or a catalytically active portion thereof.
7. The modified MTSP-1 polypeptide of claim 6, further comprising a replacement at one or more of positions corresponding to I41, F99, and Q192.
8. The modified MTSP-1 polypeptide of any of claims 1-7, comprising a replacement at a position corresponding to I41, wherein the replacement is S, D, R, or E.
9. The modified MTSP-1 polypeptide of any of claims 1-8, comprising a replacement at a position corresponding to Q192, wherein the replacement is T, D, or E.
10. The modified MTSP-1 polypeptide of any of claims 1-6, comprising modifications corresponding to I41E/F99L/C122S/G151N/Q192T, or I41D/C122S/G151N/Q192T, or I41S/F99L/C122S/G151N/Q192V, or I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E, or I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D, or I41D/Y59F/D96E/F99L/C122S/G151N/Q192T, or I41D/Y59F/C122S/G151N/Q192T, or

I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or I41T/D60bW/F60eH/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192G, or I41S/F99L/C122S/G151N/Q175M/Q192G/D217V, or comprising the same modifications except wherein C122S is C122C.

11. The modified MTSP-1 polypeptide of any of claims 1-6, comprising modifications corresponding to any of:

I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E, or

I41E/F99L/C122S/G151N/Q192T, or

I41D/C122S/G151N/Q192T, or

I41S/F99L/C122S/G151N/Q192V, or

I41D/Y59F/D96E/F99L/C122S/G151N/Q192T, or

I41D/Y59F/C122S/G151N/Q192T, or

I41T/F97W/F99L/C122S/G151N/Q175M/Q192G/D217L, or

I41G/F97S/F99L/C122S/G151N/Q175L/Q192G/D217I, or

I41T/F97L/F99L/C122S/G151N/Q175S/Q192S/D217W, or

or comprising the same modifications except C122S is not modified and is C122C.

12. The modified MTSP-1 polypeptide of any of claims 1-6, comprising modifications corresponding to I41D/C122S/G151N/Q192T or I41D/G151N/Q192T or I41E/F99L/C122S/G151N/Q192T or I41E/F99L/G151N/Q192T, wherein the unmodified MTSP-1 polypeptide comprises the protease domain of SEQ ID NO:2 or SEQ ID NO:4.

13. The modified MTSP-1 polypeptide of any of claims 1-6, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in any of SEQ ID NOs: 6, 21, 23, 24, 27, 29, 31, 32, 35-37, 39-47, 49-54, 56, 77, 81, 160-162, 165, 168, 179, 187, 198, 199, 204, 270, 271, 285, 287, 297, 301-308, 317-319, 323-325, 327-330, 332-335, 337, 339-345, 374-381, 398-400, 408-420, 423-444, 446-455, 457-491, 493-500, 502, 506, 509-511, 519, 522, 525-528, 530-532, 540, 542-544, 548, 549, 556-559, 563, 565, 568-571, 576-582, 586, 587, 590, 592, 594, 596, 598, 600-609, 612, 629, 631, 635, 638-640, 642, 643, 645, 646, and 686-690, or the same sequences of amino acid residues, except the residue at position C122 is C (Cys).

14. The modified MTSP-1 polypeptide of any of claims 1-6, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in any of SEQ ID NOs: 24, 32, 35-37, 40, 42-46, 50, 52, 53, 81, 165, 187, 306, 319, 324, 329, 330, 332, 335, 339, 340, 344, 345, 377, 379, 380, 398, 400, 408-416, 419, 420, 424-438, 440, 441, 443, 447-450, 453, 455, 465-467, 469-474, 476, 478, 481, 484, 487, 488, 491, 493-496, 568, 569, 612, 635, 642, 686 and 689, or the same sequences of amino acid residues, except the residue at position C122 is C (Cys).

15. The modified MTSP-1 polypeptide of any of claims 1-6, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:42.

16. The modified MTSP-1 polypeptide of any of claims 1-6, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:42, except that the residue at position 122, by chymotrypsin numbering, is cysteine (C).

17. The modified MTSP-1 polypeptide of any of claims 1-16, wherein the unmodified MTSP-1 polypeptide consists of the sequence of amino acid residues set forth in SEQ ID NO: 2 or 4.

18. The modified MTSP-1 polypeptide of any of claims 1-17 that is modified by a polymer to increase serum half-life or to reduce immunogenicity or both.

19. The modified MTSP-1 polypeptide of claim 18 that is PEGylated.

20. The modified MTSP-1 polypeptide of claim 16 that is PEGylated.

21. The modified MTSP-1 polypeptide of any of claims 17-20, comprising a PEG that has a molecular weight from 3 kD to 50 kD.

22. The modified MTSP-1 polypeptide of claim 21, comprising a PEG that has a molecular weight of 40 kD.

23. The modified MTSP-1 polypeptide of any of claims 18-22, comprising a branched PEG.

24. The modified MTSP-1 polypeptide of any of claims 19-23, wherein the PEG is linked via a cysteine residue in the modified MTSP-1 polypeptide.

25. The modified MTSP-1 polypeptide of any of claims 19-24, comprising a PEG-maleimide linked via a cysteine residue in the modified MTSP-1 polypeptide.

26. A modified MTSP-1 polypeptide comprising the sequence of amino acid residues set forth in SEQ ID NO:42, except that the residue at position 122, by chymotrypsin numbering, is cysteine (C);

the modified MTSP-1 polypeptide is PEGylated; and

the PEG is linked via the cysteine residue in the modified MTSP-1 polypeptide.

27. The modified MTSP-1 polypeptide of claim 26, wherein the PEG is a branched PEG.

28. The modified MTSP-1 polypeptide of claim 26 or claim 27, wherein the PEG is a PEG-maleimide.

29. The modified MTSP-1 polypeptide of any of claims 26-28, wherein the PEG has a molecular weight from 3 kDa to 50 kDa.

30. The modified MTSP-1 polypeptide of any of claims 26-29 that is a mature MTSP-1 polypeptide.

31. A fusion protein, comprising a modified MTSP-1 polypeptide or a catalytically active portion of a modified MTSP-1 polypeptide of any of claims 1-30 that is linked to a multimerization domain or a protein transduction domain (PTD) or to a Small Ubiquitin-like Modifier (SUMO) tag.

32. The fusion protein of claim 31, wherein the polypeptide is linked to a multimerization domain that is an Fc domain.

33. A nucleic acid molecule, comprising a sequence of nucleotides encoding a modified MTSP-1 polypeptide of any of claims 1-30 or fusion protein of claim 31 or claim 32.

34. A vector, comprising the nucleic acid molecule of claim 33.

35. The vector of claim 34 that is a eukaryotic vector.
36. The vector of claim 34 that is a herpes virus simplex vector, a vaccinia virus vector, an adenoviral vector, an adenovirus associated vector (AAV), a retroviral vector, or an insect vector.
37. An isolated cell or a cell culture, comprising the nucleic acid molecule of claim 33, or a vector any of claims 34-36, wherein the isolated cell is not a zygote.
38. Use of a modified membrane type serine protease 1 (MTSP-1) polypeptide of any of claims 1-30 or the fusion protein of claim 31 or claim 32 in the preparation of a medicament for the treatment of a disease or pathological condition mediated by or involving complement activation, wherein inhibition of complement activation effects treatment or amelioration of the disease or pathological condition.
39. The use of claim 38, wherein the complement-mediated disease or condition is selected from among sepsis, Rheumatoid arthritis (RA), an ocular disease, 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), and Ischemia-reperfusion injury.
40. The use of claim 38, wherein the disease or condition is an ocular disease or is rejection or inflammation due to a transplanted organ.
41. The use of claim 40, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.
42. The use of claim 41, wherein the disease or condition is a macular degeneration.
43. The use of claim 41, wherein the macular degeneration is age-related macular degeneration (AMD).
44. The use of claim 43, wherein the disease or condition is delayed renal graft function (DGF).
45. The use of any of claims 38-44 wherein the modified MTSP-1 polypeptide is PEGylated.
46. The use of any of claims 38-45, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:42 or the modified MTSP-1 polypeptide comprises the sequence of amino acid residues of SEQ ID NO:42, except that residue 122 is cysteine (C).
47. The use of any of claims 38-46, wherein the modified MTSP-1 polypeptide comprises the modifications I41D/C122S/G151N/Q192T or I41D/G151N/Q192T.
48. The use of any of claims 38-47, wherein the modified MTSP-1 polypeptide is PEGylated.
49. A method of making a modified MTSP-1 polypeptide, comprising:
  - introducing a nucleic acid or vector encoding the modified MTSP-1 polypeptide of any of claims 1-30 or fusion protein of claim 31 or claim 32 into a cell;
  - culturing the cell under conditions, whereby the polypeptide is expressed; and
  - isolating the expressed polypeptide.

50. The method of claim 49, wherein nucleic acid encoding the modified MTSP-1 polypeptide is operatively linked to a nucleic acid encoding a Small Ubiquitin-like Modifier (SUMO) tag.

51. Use of the nucleic acid molecule of claim 33 in the preparation of a medicament for the treatment of a disease or pathological condition mediated by or involving complement activation, wherein inhibition of complement activation effects treatment or amelioration of the disease or pathological condition.

52. The use of claim 51, wherein the complement-mediated disease or condition is selected from among sepsis, Rheumatoid arthritis (RA), an ocular disease, 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), and Ischemia-reperfusion injury.

53. The use of claim 51, wherein the disease or condition is an ocular disease or is rejection or inflammation due to a transplanted organ.

54. The use of claim 53, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.

55. The use of claim 54, wherein the disease or condition is age-related macular degeneration (AMD).

56. A pharmaceutical composition, comprising the modified MTSP-1 polypeptide of any of claims 1-30 or fusion protein of claim 31 or claim 32, or the nucleic acid molecule of claim 33, or the vector of any of claims 34-36, in a pharmaceutically acceptable vehicle.

57. A modified membrane type serine protease 1 (MTSP-1) polypeptide of any of claims 1-30 or fusion protein of claim 31 or claim 32, or the nucleic acid molecule of claim 33, or the vector of any of claims 34-36 for use in therapy.