

WHAT IS CLAIMED:

1. A modified membrane type serine protease 1 (MTSP-1) polypeptide, comprising amino acid modifications corresponding to:

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D, or

Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E, or

Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192D, or

Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96P/F97W/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192E, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D, or

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Q192D, or
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192D, or
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Q192D, or
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Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/F97G/T98P/F99L/C122S/G151H/
Q175L/Q192D, or
Q38H/I41S/D60bA/F60eV/Y60gF/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192T,
or
Q38H/I41A/D60bV/F60eR/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192
D, or
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or
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or
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Q38H/I41A/D60bE/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192
D, or
Q38H/I41A/D60bT/F60eK/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192
D, or
Q38H/I41A/D60bT/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192
D, or

Q38H/I41S/D60bS/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E,
or
Q38H/I41S/D60bT/F60eS/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
or
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or
Q38H/I41S/D60bT/F60eT/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192V,
or
Q38H/I41S/D60bF/F60eV/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192A,
or
Q38H/I41A/D60bE/F60eH/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175
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/Q192D, or
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D, or
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or
Q38H/I41A/D60bT/F60eR/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V, or
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Q38H/H40P/I41A/F60eQ/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192D,
or
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Q38H/I41A/D60bY/F60eT/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192V,
or

Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192V, or
Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175A/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192E, or
Q38H/I41A/D60bE/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41A/D60bT/F60eK/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41A/D60bV/F60eI/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/L52M/D60bG/ins97aV/F97D/T98P/F99L/M117K/C122S/I136L/Q192G/D217A, or
Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/M117L/C122S/I136T/Q192G/D217I, or
Q38H/I41A/D60bW/ins97aV/F97D/T98P/F99L/C122S/I136M/Q192G/D217N, or
Q38H/I41S/P49Q/D60bS/F93L/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217Q, or
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Q38H/I41S/D60bS/F93L/D96Y/ins97aV/F97D/T98P/F99L/C122S/I136F/Q192G/D217V, or
Q38H/I41T/D60bH/ins97aV/F97D/T98P/F99L/C122S/I136F/L153P/Q192G/D217Y, or
Q38H/I41S/D60bT/F93L/ins97aV/F97D/T98P/F99L/S115N/C122S/Q192V/F208L/D217Q, or
Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217V, or
Q38H/I41S/D60bG/ins97aV/F97D/T98P/F99L/M117T/C122S/N164D/Q192G/D217E, or
Q38H/I41S/D60bT/F60eT/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192V, or
Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192D, or
Q38H/I41A/D60bV/F60eR/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/L52M/D60bH/D96V/ins97aV/F97D/T98P/F99L/C122S/T150A/Q192G/Q209L/D217T, or
Q38H/I41S/D60bT/S90T/F97D/ins97aV/T98P/F99L/C122S/S127N/I136F/Q192G/D217Q, or
Q38H/I41S/D60bT/F93S/ins97aV/F97D/T98P/F99L/C122S/I136L/Q192G/D217A, or
L33M/Q38H/I41A/D60bA/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217N, or
Q38H/I41S/D60bY/D96Y/ins97aV/F97D/T98P/F99L/L106M/C122S/I136M/Q192G/Q209L/D217T, or
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G/F99L/C122S/G151N/Q175L/Q192D, or

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Q175L/Q192D, or

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Q175L/Q192D, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96Y/ins97aI/F97E/T98N/F99M/C122S/G151N/
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Q38H/I41A/D60bV/F60eR/Y60gW/D96S/ins97aR/F97A/T98S/F99L/C122S/G151N/
Q175L/Q192T, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151N/
/Q175L/Q192E, or

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Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/ins97aV/F97E/T98G/F99L/C122S/G151H/
Q175L/Q192D, or

Q38H/I41S/D60bA/Y60gG/ins97aV/F97D/T98P/F99L/C122S/H143T/G151N/Q175L/
/Q192A, or

Q38H/I41S/D60bT/F60eH/Y60gF/ins97aV/F97D/T98P/F99L/C122S/H143R/G151N/
Q175L/Q192S, or

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Q175L/Q192T, or

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Q192G, or

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Q175L/Q192A, or

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/Q192G, or

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Q192G, or

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Q175L/Q192R, or

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Q175L/Q192E, or

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Q175L/Q192D, or

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Q192D, or

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Q175L/Q192D, or

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/Q175L/Q192E, or

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Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/C122S/G151H/Q175L/Q192E, or

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Q38H/I41S/D60bT/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192E, or

Q38H/I41S/D60bT/F60eG/Y60gW/D96V/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D, or

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Q38H/I41S/D60bT/F60eG/D96P/F97N/T98G/F99L/C122S/G151Q/Q175L/Q192D, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97D/ins97aE/T98G/F99M/C122S/G151N/Q175L/Q192R, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97E/ins97aT/T98G/F99M/C122S/G151N/Q175L/Q192G, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97E/ins97aS/T98G/F99M/C122S/G151N/Q175L/Q192G, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96W/F97D/ins97aD/T98G/F99L/C122S/G151N/Q175L/Q192G, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97Y/ins97aE/T98G/F99M/C122S/G151N/Q175L/Q192R, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96W/F97D/ins97aT/T98G/F99L/C122S/G151N/Q175L/Q192G, or

Q38H/I41S/D60bT/F60eK/Y60gF/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97S/ins97aH/T98G/F99L/C122S/G151N/Q175L/Q192G, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97Y/ins97aN/T98G/F99M/C122S/G151N/Q175L/Q192G, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97S/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97Y/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97N/ins97aE/T98S/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97R/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41A/D60bT/F60eK/Y60gF/F97T/ins97aE/T98G/F99L/C122S/H143R/G151N/Q175L/Q192V, or

Q38H/I41S/F60eT/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eK/D96V/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/M117K/C122S/G151H/Q175L/Q192D, or

L36Q/Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/T150S/G151H/Q175L/Q192D/Q209L, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41S/Y60gW/C122S/G151H/Q192A, or

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/F99L/C122S/G151H/Q175L/Q192D, or

Q38H/I41S/D96S/ins97aK/C122S/G151N/Q192A, or

Q38H/I41A/D96A/ins97aA/C122S/G151D/Q192T, or

Q38H/I41S/D96Q/ins97aT/C122S/G151N/Q192A, or

Q38H/I41T/D96M/ins97aA/C122S/G151D, or

Q38H/I41S/D96K/ins97aT/C122S/G151K/Q192A, or

Q38H/I41A/D96R/ins97aQ/C122S, or

Q38H/I41S/D96V/ins97aA/C122S/G151N/Q192A, or

Q38H/I41T/D96K/ins97aL/C122S/G151N/Q192A, or

Q38H/I41S/D96Q/ins97aA/C122S/Q192T, or

Q38H/I41S/D96K/ins97aS/C122S/G151P/Q192S, or
Q38H/I41S/D96G/ins97aG/C122S/G151N/Q192A, or
Q38H/I41S/D96K/ins97aD/C122S/G151N/Q192S, or
Q38H/I41S/ins97aV/A112V/C122S/Q192A/Q209L, or
Q38H/I41T/D96R/ins97aG/C122S/G151S, or the same modifications except C122S is not modified and is C122C,

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 consists of the sequence of amino acids set forth in any of SEQ ID NOs: 1-4 or comprises the protease domain of SEQ ID NO: 2 or 4.

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 SEQ ID NO:4.

6. The modified MTSP-1 polypeptide of claim 5, that comprise a modification corresponding to I41S.

7. The modified MTSP-1 polypeptide of any of claims 1-5, comprising modifications corresponding to any of:

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D, or
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E, or
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192D, or
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41A/D60bV/F60eR/Y60gW/D96P/F97W/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192E, or

Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97E/ins97aV/T98G/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96L/F97D/ins97aG/T98N/F99L/C122S/G151H/Q175L/Q192E, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L, or
Q38H/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/F99L/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/C122S/G151H/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D, or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q192D, or
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D, or
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D, or
Q38H/I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V, or
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V, or the same modifications
except C122S is not modified and is C122C.

8. The modified MTSP-1 polypeptide of any of claims 1-5, comprising modifications corresponding to
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/
Q192D or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/G151H/Q175L/Q192D,
wherein the unmodified MTSP-1 polypeptide consists of the protease domain of SEQ ID
NO:2 or SEQ ID NO:4.

9. The modified MTSP-1 polypeptide of any of claims 1-5, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in any of SEQ ID NOs: 22-37, 39, 40, 48-57, 59, 64, 65, 73, 289, 294, 295, 301, 306-317, 320, 322, 328, 329, 337, 339, 340, 342-345, 349-351, 354-356, 358, 361, 362, 364, 366, 369, 374-380, 382, 386, 388-393, 395, 396, 398-401, 403, 404, 406-437, 439-450, 453, 456, 462-475, 479, 480, 493-496, 569, 612, 629-632, 634, 636, 639-641, 644-646, 657, and 675, or the same sequence of amino acid residues except C122S is not modified and is C122C.

10. The modified MTSP-1 polypeptide of any of claims 1-5, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:35.

11. The modified MTSP-1 polypeptide of any of claims 1-5, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:35, except that the residue at position 122, by chymotrypsin numbering, is cysteine (C).

12. The modified MTSP-1 polypeptide of any of claims 1-4 and 6-11, wherein the unmodified MTSP-1 polypeptide consists of the sequence of amino acid residues set forth in SEQ ID NO:2 or 4.

13. The modified MTSP-1 polypeptide of any of claims 1-12 that is modified by a polymer to increase serum half-life or to reduce immunogenicity or both.

14. The modified MTSP-1 polypeptide of claim 13 that is PEGylated.

15. The modified MTSP-1 polypeptide of claim 11 that is PEGylated.
16. The modified MTSP-1 polypeptide of any of claims 13-15, comprising a PEG that has a molecular weight from 3 kD to 50 kD.
17. The modified MTSP-1 polypeptide of claim 16, comprising a PEG that has a molecular weight of 40 kD.
18. The modified MTSP-1 polypeptide of any of claims 13-17, comprising a branched PEG.
19. The modified MTSP-1 polypeptide of any of claims 14-18, wherein the PEG is linked via a cysteine residue in the modified MTSP-1 polypeptide.
20. The modified MTSP-1 polypeptide of any of claims 13-19, comprising a PEG-maleimide linked via a cysteine residue in the modified MTSP-1 polypeptide.
21. A modified MTSP-1 polypeptide comprising the sequence of amino acid residues set forth in SEQ ID NO:35, 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.
22. The modified MTSP-1 polypeptide of claim 21, wherein the PEG is a branched PEG.
23. The modified MTSP-1 polypeptide of claim 21 or claim 22, wherein the PEG is a PEG-maleimide.
24. The modified MTSP-1 polypeptide of any of claims 21-23, wherein the PEG has a molecular weight from 3 kDa to 50 kDa.
25. The modified MTSP-1 polypeptide of any of claims 21-24 that is a mature MTSP-1 polypeptide.
26. A fusion protein, comprising the modified MTSP-1 polypeptide or a catalytically active portion of a modified MTSP-1 polypeptide of any of claims 1-25 that is linked to a multimerization domain or a protein transduction domain (PTD).
27. The fusion protein of claim 26, wherein the polypeptide is linked to a multimerization domain that is an Fc domain.
28. A nucleic acid molecule, comprising a sequence of nucleotides encoding a modified MTSP-1 polypeptide of any of claims 1-25 or fusion protein of claim 26 or claim 27.
29. A vector, comprising the nucleic acid molecule of claim 28.
30. The vector of claim 29 that is a eukaryotic vector.
31. The vector of claim 29 that is a herpes virus simplex vector, or a vaccinia virus vector, or an adenovirus associated virus (AAV) vector, or an adenoviral vector, or a retroviral vector, or an insect vector.
32. An isolated cell or a cell culture, comprising the nucleic acid molecule of claim 28 or the vector of any of claims 29-31, wherein the isolated cell is not a human zygote.

33. Use of a modified membrane type serine protease 1 (MTSP-1) polypeptide of any of claims 1-25 or the fusion protein of claim 26 or claim 27 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.

34. The use of claim 33, 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.

35. The use of claim 33, wherein the disease or condition is an ocular disease or is rejection or inflammation due to a transplanted organ.

36. The use of claim 35, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.

37. The use of claim 36, wherein the disease or condition is a macular degeneration.

38. The use of claim 37, wherein the macular degeneration is age-related macular degeneration (AMD).

39. The use of claim 35, wherein the disease or condition is delayed renal graft function (DGF).

40. The use of any of claims 33-39 wherein the modified MTSP-1 polypeptide is PEGylated.

41. The use of any of claims 33-40, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:35 or the polypeptide comprises the sequence of amino acid residues of SEQ ID NO:35, except that residue 122 is cysteine (C).

42. The use of any of claims 39-41, wherein the modified MTSP-1 polypeptide comprises the modifications
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/G151H/Q175L/Q192D
or
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D.

43. The use of any of claims 33-42, wherein the modified MTSP-1 polypeptide is PEGylated.

44. 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 1-25 or fusion protein of claim 26 or claim 27 into a cell;
culturing the cell under conditions, whereby the polypeptide is expressed; and
isolating the expressed polypeptide.

45. The method of claim 44, wherein nucleic acid encoding the modified MTSP-1 polypeptide is operatively linked to a nucleic acid encoding a Small Ubiquitin-like Modifier (SUMO) tag.

46. Use of the nucleic acid molecule of claim 28 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.

47. The use of claim 46, 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.

48. The use of claim 46, wherein the disease or condition is an ocular disease or is rejection or inflammation due to a transplanted organ.

49. The use of claim 48, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.

50. The use of claim 49, wherein the disease or condition is age-related macular degeneration (AMD).

51. A pharmaceutical composition, comprising the modified MTSP-1 polypeptide of any one of claims 1-25, or the fusion protein of claim 26 or claim 27, or the nucleic acid molecule of claim 28, or the vector of any of claims 29-31, in a pharmaceutically acceptable vehicle.

52. A modified membrane type serine protease 1 (MTSP-1) polypeptide of any of claims 1-25, or the fusion protein of claim 26 or claim 27, or the nucleic acid molecule of claim 28, or the vector of any of claims 29-31 for use in therapy.