

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2018290281 B2**

- (54) Title
Modified membrane type serine protease 1 (MTSP-1) polypeptides and methods of use
- (51) International Patent Classification(s)
C07K 14/435 (2006.01) **A61K 38/48** (2006.01)
- (21) Application No: **2018290281** (22) Date of Filing: **2018.06.21**
- (87) WIPO No: **WO18/237201**
- (30) Priority Data
- | | | |
|-------------------|-------------------|--------------|
| (31) Number | (32) Date | (33) Country |
| 62/664,051 | 2018.04.27 | US |
| 62/523,735 | 2017.06.22 | US |
- (43) Publication Date: **2018.12.27**
- (44) Accepted Journal Date: **2021.12.16**
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- (56) Related Art
US 20140242062 A1
WO 2008045148 A2



- (51) **International Patent Classification:**
A61K 38/48 (2006.01) C07K 14/435 (2006.01)
- (21) **International Application Number:**
PCT/US2018/038844
- (22) **International Filing Date:**
21 June 2018 (21.06.2018)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
62/523,735 22 June 2017 (22.06.2017) US
62/664,051 27 April 2018 (27.04.2018) US
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- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

(54) **Title:** MODIFIED MEMBRANE TYPE SERINE PROTEASE 1 (MTSP-1) POLYPEPTIDES AND METHODS OF USE

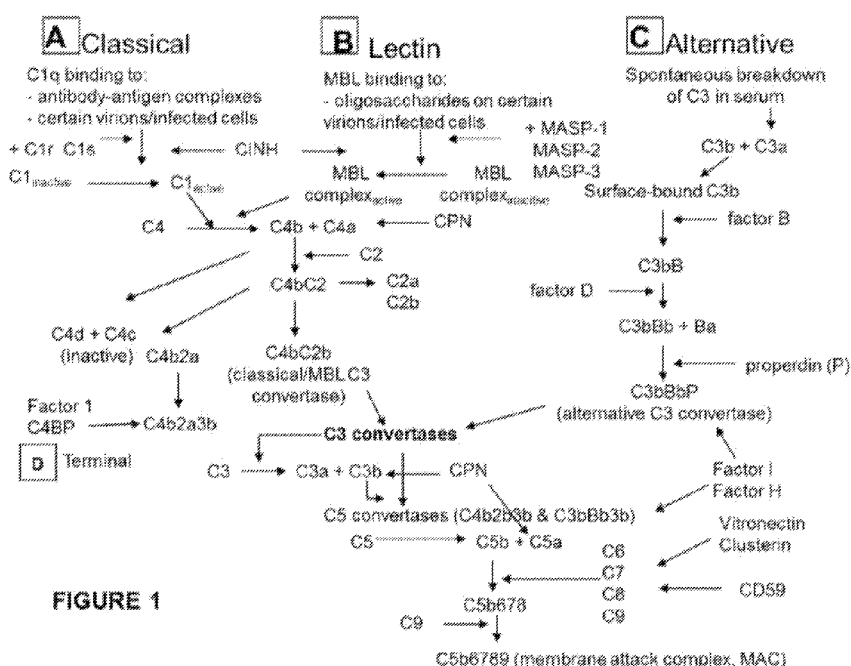


FIGURE 1

(57) **Abstract:** Provided are MTSP-1 polypeptides modified to have altered activity and/or specificity so that they cleave a complement protein, such as complement protein C3, to inhibit its activity and thereby inhibit complement activation. The modified MTSP-1 polypeptides that inhibit complement activation can be used for treatment of diseases and conditions in which complement activation plays a role. Such diseases and conditions include inflammatory diseases and diseases with an inflammatory component. Exemplary of these disorders are ischemic and reperfusion disorders, including myocardial infarction and stroke, sepsis, autoimmune diseases, ophthalmic disorders, such as diabetic retinopathies and macular degeneration, including age-related macular degeneration (AMD), and transplanted organ rejection, such as renal delayed graft function (DGF).

SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *with sequence listing part of description (Rule 5.2(a))*

MODIFIED MEMBRANE TYPE SERINE PROTEASE 1 (MTSP-1)**POLYPEPTIDES AND METHODS OF USE****RELATED APPLICATIONS**

Benefit of priority is claimed to U.S. provisional application Serial No. 62/523,735, filed June 22, 2017, to Madison, Edwin L., Soros, Vanessa, and Popkov, Mikhail, entitled "MODIFIED MEMBRANE TYPE SERINE PROTEASE 1 (MTSP-1) POLYPEPTIDES AND METHODS OF USE." Benefit of priority also is claimed to U.S. provisional application Serial No. 62/664,051, filed April 27, 2018, to Madison, Edwin L., Soros, Vanessa, and Popkov, Mikhail, entitled "MODIFIED MEMBRANE TYPE SERINE PROTEASE 1 (MTSP-1) POLYPEPTIDES AND METHODS OF USE." Where permitted, the subject matter of each of these applications is incorporated by reference in its entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING PROVIDED ELECTRONICALLY

An electronic version of the Sequence Listing is filed herewith, the contents of which are incorporated by reference in their entirety. The electronic file was created on June 18, 2018, is 1.4 megabytes in size, and is titled 4939SEQPC001.txt.

FIELD OF THE INVENTION

Provided are modified MTSP-1 polypeptides that cleave a complement protein, thereby, inhibiting complement activation. By virtue of this inhibition the modified MTSP-1 polypeptides can be used for treatment diseases and conditions mediated by complement or in which complement activation plays role. These disease and conditions, include, but are not limited to, ophthalmic indications, including macular degeneration, such as age-related macular degeneration (AMD), diabetic retinopathies, and Stargardt disease, renal delayed graft function (DGF), ischemic and reperfusion disorders, including myocardial infarction and stroke, sepsis, autoimmune diseases, inflammatory diseases and diseases with an inflammatory component, including Alzheimer's Disease and other neurodegenerative disorders.

BACKGROUND

The complement (C) system is part of the immune system and plays a role in eliminating invading pathogens and in initiating the inflammatory response. The complement system of humans and other mammals involves more than 30 soluble and

membrane-bound proteins that participate in an orderly sequence of reactions resulting in complement activation. The blood complement system has a wide array of functions associated with a broad spectrum of host defense mechanisms including anti-microbial and anti-viral actions. Products derived from the activation of C

5 components include the non-self-recognition molecules C3b, C4b and C5b, as well as the anaphylatoxins C3a, C4a and C5a that influence a variety of cellular immune responses. These anaphylatoxins also act as pro-inflammatory agents.

The complement system is composed of an array of enzymes and non-enzymatic proteins and receptors. Complement activation occurs by one of three

10 primary modes known as the "classical" pathway, the "alternative" pathway and the "lectin" pathway (see FIGURE 1). Complement typically is activated or triggered by 1 of these 3 pathways, which as shown in FIGURE 1, converge at C3 activation. In a fourth complement-activation mechanism, referred to as the intrinsic pathway, serine proteases associated with the coagulation/fibrinolytic cascade activate the

15 complement system directly through cleavage of C3 or C5, independently of the classical, alternate, and lectin pathways. These pathways can be distinguished by the process that initiates complement activation. The classical pathway is initiated by antibody-antigen complexes or aggregated forms of immunoglobulins; the alternative pathway is initiated by the recognition of structures on microbial and cell surfaces;

20 and the lectin pathway, which is an antibody-independent pathway, is initiated by the binding of mannan binding lectin (MBL, also designated mannose binding protein) to carbohydrates such as those that are displayed on the surface of bacteria or viruses. Activation of the cascades results in production of complexes involved in proteolysis or cell lysis and peptides involved in opsonization, anaphylaxis and chemotaxis.

25 The complement cascade, which is a central component of an animal's immune response, is an irreversible cascade. Numerous protein cofactors regulate the process. Inappropriate regulation, typically inappropriate activation, of the process can be a facet of or can occur in a variety of disorders that involve inappropriate inflammatory and immune responses, such as those observed in acute and chronic

30 inflammatory diseases and other conditions involving an inappropriate immune response. These diseases and disorders include autoimmune diseases, such as

rheumatoid arthritis and lupus, cardiac disorders and other inflammatory diseases, such as sepsis and ischemia-reperfusion injury.

Because of the involvement of the complement pathways in a variety of diseases and conditions, components of the complement pathways are targets for therapeutic intervention, particularly for inhibition of the pathway. Examples of such therapeutics include synthetic and natural small molecule therapeutics, antibody inhibitors, and recombinant soluble forms of membrane complement regulators. There are limitations to strategies for preparing such therapeutics. Small molecules have short half-lives *in vivo* and need to be continually infused to maintain complement inhibition thereby limiting their role, especially in chronic diseases. Therapeutic antibodies can result in an immune response in a subject, and thus can lead to complications in treatment, particularly treatments designed to modulate immune responses. Thus, there exists a need for therapeutics for treatment of complement-mediated diseases and diseases in which complement activation plays a role. These include acute and chronic inflammatory diseases. Accordingly, among the objectives herein, it is an objective to provide such therapeutics to target the activation of the complement cascade and to provide therapeutics and methods of treatment of diseases.

SUMMARY

Modified MTSP-1 polypeptides, comprising one or more of amino acid modifications I41S, Q38H, D60bT, F60eS or R, Y60gW, ins97aV, D96K, F97G, G151H or N and Q192T, whereby the modified MTSP-1 polypeptide has increased activity and/or specificity for a complement protein compared to the unmodified active form of the MTSP-1 polypeptide, where the amino acid modifications are selected from among replacements, insertions and deletions in the primary amino acid sequence of the unmodified MTSP-1 polypeptide; the modified MTSP-1 polypeptide cleaves a complement protein to thereby inhibit or reduce complement activation compared to an active form of the unmodified MTSP-1 polypeptide that does not contain the amino acid modification(s); residues are numbered by chymotrypsin numbering; corresponding residues are determined by alignment and chymotrypsin numbering; the unmodified MTSP-1 polypeptide comprises the sequence of amino acids set forth in any of SEQ ID NOs. 1-4 (wild-type full-length MTSP-1, wild-type

protease domain MTSP-1, wild-type mature MTSP-1, full-length MTSP-1 with C122S, protease domain MTSP-1 with C122S, mature MTSP-1 with C122S) or a catalytically active fragment or form thereof that includes the amino acid modification(s). Modifications are in the primary sequence, and include insertions, replacements and deletions. The modified MTSP-1 polypeptides include modifications that improve or alter activity, and other properties, including properties that improve their use as pharmaceuticals. For example, the modified MTSP-1 polypeptides can be conjugated to moieties that increase stability, serum half-life, shelf-life and other such properties. These modifications include conjugation to polymers, such as PEGylation moieties, other polypeptides for targeting, identifying and purifying, to the modified MTSP-1.

The complement protein for which modified MTSP-1 polypeptides provided herein are modified to inactivate is C3, such that the modified MTSP-1 polypeptides cleave a site that inactivates C3. By virtue of inactivation of C3, complement activation is reduced or inhibited. By virtue of inhibition or reduction of complement activation, any disease, condition or disorder in which complement plays a role or in which a reduction of complement activation can treat or reduce symptoms or pathology of the disease or disorder, can be treated with the modified MTSP-1 polypeptides provided herein. Target sites in C3 for inactivation cleavage include residues 737-744; cleavage within these residues, such as between residues 740 and 741 of SEQ ID NO:9 (Q H A R ↓ A S H L), inactivates C3. Activity/specificity for the cleavage of C3 can be increased compared to an active form of the unmodified MTSP-1 polypeptide that does not contain the amino acid modification(s). The modified MTSP-1 polypeptides provided herein are designed to have increased activity for cleavage of C3 that is least 1-fold greater or more than 1-fold greater than an active form, such as the full length or protease domain, of the unmodified MTSP-1 polypeptide of SEQ ID NO:4 (the protease domain with the free cysteine, C122 by chymotrypsin numbering, replaced by S). Cleavage activity for inactivating C3 can be increased by any amount, such as at least 0.5-fold, 1-fold, 1.2 fold, 1.5-fold, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10- fold or more than the unmodified modified MTSP-1 polypeptide of SEQ ID NO: 4. The unmodified MTSP-1 polypeptide is selected from among polypeptides of SEQ ID NOs.: 1-4 and catalytically active portions thereof.

The modified MTSP-1 polypeptide, which includes at least one modification, such as I41S, Q38H, D60bT, F60eS or R, Y60gW, ins97aV, D96K, F97G, G151H or N and Q192T, or combinations of these or other replacements as described herein, has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity with the polypeptides of any of SEQ ID NOs.: 1-4.

The modified MTSP-1 polypeptide can have at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 modifications, including insertions, deletions and replacements in the primary sequence in the polypeptides of any of SEQ ID NOs: 1-4 and catalytically active portions thereof.

For example, provided are modified MTSP-1 polypeptides that comprise a modification corresponding to any one or more of I41S, Q38H, D60bT, F60eS, oY60gW, ins97aV, D96K, F97G, G151H, G151N, Q192T, Q192D and/or Q192E.

The modified MTSP-1 polypeptides further can include additional replacements corresponding to and selected from one or more of F60eR, Y59F, F99L, T98P,

Q175L or selected from one or more modifications at a position corresponding to D217, such as D217V, I, L, W or M, I41D, E, T, G or R. As above, corresponding positions are determined by chymotrypsin numbering. Exemplary

modified MTSP-1 polypeptides include modified MTSP-1 polypeptides that contain I41E/F99L/C122S/G151N/Q192T; I41D/C122S/G151N/Q192T;

I41S/F99L/C122S/G151N/Q192V; or I41E/F99L/C122S/G151N/Q192T or the same modifications except C122S is C122C. Other exemplary modified MTSP-1 polypeptide include modifications corresponding to any of:

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

I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D,

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

I41D/Y59F/C122S/G151N/Q192T.

Also provided are modified MTSP-1 polypeptides that include modifications corresponding to any of:

I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E, 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/Q175
L/Q192D, or
- Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L
/Q192E, or
- 5 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/Q175
L/Q192D, or
- Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L
10 /Q192D, or
- Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175
L/Q192D, or
- Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/
Q175L/Q192D, or
- 15 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/
20 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
- 25 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/
Q175L/Q192D, 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/
30 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
- 5 I41E/F99L/C122S/G151N/Q192T, or I41D/C122S/G151N/Q192T, or
I41S/F99L/C122S/G151N/Q192V, or I41E/F99L/C122S/G151N/Q192T, 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
- 10 /Q192D, 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
- 15 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
- 20 192D, 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
- 25 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
- 30 I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D, or
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
 I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V, or
 I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V, or
 I41S/D96M/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V, or
 5 I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192V/D217I, or
 I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192H, or
 I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192N/D217V, or
 I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D, or
 Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V, or
 10 I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192V, or
 I41S/P49S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V, or
 I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192N/I217V, or
 I41T/F97W/F99L/C122S/G151N/Q175M/Q192G/D217L, or
 I41G/F97L/F99L/C122S/Q175A/Q192T/D217V, or
 15 I41G/F97V/F99L/C122S/G151Q/Q175M/Q192A/D217L, or
 I41G/F97I/F99L/C122S/G151L/Q175M/Q192S/D217V, or
 I41G/F97S/F99L/C122S/G151N/Q175L/Q192G/D217I, or
 I41T/F97L/F99L/C122S/G151N/Q175S/Q192S/D217W, or
 I41D/F97T/F99M/C122S/Q192V/D217M, or the same modifications except C122S is
 20 not modified and is C122C.

- Also provided are modified MTSP-1 polypeptides that include modifications selected from among combinations that include one or more of modifications Q38H, I41S, D60bT, F60eS, Y60gW, D96K, F97G, Ins97aV and G151H as follows:
- G151H, Ins97aV, Ins97aV/G151H, F97G, F97G/G151H, F97G/Ins97aV,
 25 F97G/Ins97aV/G151H, D96K, D96K/G151H, D96K/Ins97aV,
 D96K/Ins97aV/G151H, D96K/F97G, D96K/F97G/G151H, D96K/F97G/Ins97aV,
 D96K/F97G/Ins97aV/G151H, Y60gW, Y60gW/G151H, Y60gW/Ins97aV,
 Y60gW/Ins97aV/G151H, Y60gW/F97G, Y60gW/F97G/G151H,
 Y60gW/F97G/Ins97aV, Y60gW/F97G/Ins97aV/G151H, Y60gW/D96K,
 30 Y60gW/D96K/G151H, Y60gW/D96K/Ins97aV, Y60gW/D96K/Ins97aV/G151H,
 Y60gW/D96K/F97G, Y60gW/D96K/F97G/G151H, Y60gW/D96K/F97G/Ins97aV,
 Y60gW/D96K/F97G/Ins97aV/G151H, F60eS, F60eS/G151H, F60eS/Ins97aV,

- F60eS/Ins97aV/G151H, F60eS/F97G, F60eS/F97G/G151H, F60eS/F97G/Ins97aV,
F60eS/F97G/Ins97aV/G151H, F60eS/D96K, F60eS/D96K/G151H,
F60eS/D96K/Ins97aV, F60eS/D96K/Ins97aV/G151H, F60eS/D96K/F97G,
F60eS/D96K/F97G/G151H, F60eS/D96K/F97G/Ins97aV,
- 5 F60eS/D96K/F97G/Ins97aV/G151H, F60eS/Y60gW, F60eS/Y60gW/G151H,
F60eS/Y60gW/Ins97aV, F60eS/Y60gW/Ins97aV/G151H, F60eS/Y60gW/F97G,
F60eS/Y60gW/F97G/G151H, F60eS/Y60gW/F97G/Ins97aV,
F60eS/Y60gW/F97G/Ins97aV/G151H, F60eS/Y60gW/D96K,
F60eS/Y60gW/D96K/G151H, F60eS/Y60gW/D96K/Ins97aV,
- 10 F60eS/Y60gW/D96K/Ins97aV/G151H, F60eS/Y60gW/D96K/F97G,
F60eS/Y60gW/D96K/F97G/G151H, F60eS/Y60gW/D96K/F97G/Ins97aV,
F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, D60bT, D60bT/G151H,
D60bT/Ins97aV, D60bT/Ins97aV/G151H, D60bT/F97G, D60bT/F97G/G151H,
D60bT/F97G/Ins97aV, D60bT/F97G/Ins97aV/G151H, D60bT/D96K,
- 15 D60bT/D96K/G151H, D60bT/D96K/Ins97aV, D60bT/D96K/Ins97aV/G151H,
D60bT/D96K/F97G, D60bT/D96K/F97G/G151H, D60bT/D96K/F97G/Ins97aV,
D60bT/D96K/F97G/Ins97aV/G151H, D60bT/Y60gW, D60bT/Y60gW/G151H,
D60bT/Y60gW/Ins97aV, D60bT/Y60gW/Ins97aV/G151H, D60bT/Y60gW/F97G,
D60bT/Y60gW/F97G/G151H, D60bT/Y60gW/F97G/Ins97aV,
- 20 D60bT/Y60gW/F97G/Ins97aV/G151H, D60bT/Y60gW/D96K,
D60bT/Y60gW/D96K/G151H, D60bT/Y60gW/D96K/Ins97aV,
D60bT/Y60gW/D96K/Ins97aV/G151H, D60bT/Y60gW/D96K/F97G,
D60bT/Y60gW/D96K/F97G/G151H, D60bT/Y60gW/D96K/F97G/Ins97aV,
D60bT/Y60gW/D96K/F97G/Ins97aV/G151H, D60bT/F60eS, D60bT/F60eS/G151H,
- 25 D60bT/F60eS/Ins97aV, D60bT/F60eS/Ins97aV/G151H, D60bT/F60eS/F97G,
D60bT/F60eS/F97G/G151H, D60bT/F60eS/F97G/Ins97aV,
D60bT/F60eS/F97G/Ins97aV/G151H, D60bT/F60eS/D96K,
D60bT/F60eS/D96K/G151H, D60bT/F60eS/D96K/Ins97aV,
D60bT/F60eS/D96K/Ins97aV/G151H, D60bT/F60eS/D96K/F97G,
- 30 D60bT/F60eS/D96K/F97G/G151H, D60bT/F60eS/D96K/F97G/Ins97aV,
D60bT/F60eS/D96K/F97G/Ins97aV/G151H, D60bT/F60eS/Y60gW,
D60bT/F60eS/Y60gW/G151H, D60bT/F60eS/Y60gW/Ins97aV,

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D60bT/F60eS/Y60gW/F97G/Ins97aV/G151H, D60bT/F60eS/Y60gW/D96K,
D60bT/F60eS/Y60gW/D96K/G151H, D60bT/F60eS/Y60gW/D96K/Ins97aV,
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D60bT/F60eS/Y60gW/D96K/F97G/G151H,
D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV,
D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, I41S, I41S/G151H,
I41S/Ins97aV, I41S/Ins97aV/G151H, I41S/F97G, I41S/F97G/G151H,
10 I41S/F97G/Ins97aV, I41S/F97G/Ins97aV/G151H, I41S/D96K, I41S/D96K/G151H,
I41S/D96K/Ins97aV, I41S/D96K/Ins97aV/G151H, I41S/D96K/F97G,
I41S/D96K/F97G/G151H, I41S/D96K/F97G/Ins97aV,
I41S/D96K/F97G/Ins97aV/G151H, I41S/Y60gW, I41S/Y60gW/G151H,
I41S/Y60gW/Ins97aV, I41S/Y60gW/Ins97aV/G151H, I41S/Y60gW/F97G,
15 I41S/Y60gW/F97G/G151H, I41S/Y60gW/F97G/Ins97aV,
I41S/Y60gW/F97G/Ins97aV/G151H, I41S/Y60gW/D96K,
I41S/Y60gW/D96K/G151H, I41S/Y60gW/D96K/Ins97aV,
I41S/Y60gW/D96K/Ins97aV/G151H, I41S/Y60gW/D96K/F97G,
I41S/Y60gW/D96K/F97G/G151H, I41S/Y60gW/D96K/F97G/Ins97aV,
20 I41S/Y60gW/D96K/F97G/Ins97aV/G151H, I41S/F60eS, I41S/F60eS/G151H,
I41S/F60eS/Ins97aV, I41S/F60eS/Ins97aV/G151H, I41S/F60eS/F97G,
I41S/F60eS/F97G/G151H, I41S/F60eS/F97G/Ins97aV,
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I41S/F60eS/Y60gW, I41S/F60eS/Y60gW/G151H, I41S/F60eS/Y60gW/Ins97aV,
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I41S/F60eS/Y60gW/D96K/G151H, I41S/F60eS/Y60gW/D96K/Ins97aV,
I41S/F60eS/Y60gW/D96K/Ins97aV/G151H, I41S/F60eS/Y60gW/D96K/F97G,

- I41S/F60eS/Y60gW/D96K/F97G/G151H, I41S/F60eS/Y60gW/D96K/F97G/Ins97aV,
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I41S/D60bT/G151H, I41S/D60bT/Ins97aV, I41S/D60bT/Ins97aV/G151H,
I41S/D60bT/F97G, I41S/D60bT/F97G/G151H, I41S/D60bT/F97G/Ins97aV,
5 I41S/D60bT/F97G/Ins97aV/G151H, I41S/D60bT/D96K, I41S/D60bT/D96K/G151H,
I41S/D60bT/D96K/Ins97aV, I41S/D60bT/D96K/Ins97aV/G151H,
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10 I41S/D60bT/Y60gW/Ins97aV/G151H, I41S/D60bT/Y60gW/F97G,
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20 I41S/D60bT/F60eS/F97G/G151H, I41S/D60bT/F60eS/F97G/Ins97aV,
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I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV,

- I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV/G151H,
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I41S/D60bT/F60eS/Y60gW/D96K/F97G/G151H,
I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV,
- 5 I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H, Q38H/G151H,
Q38H/Ins97aV, Q38H/Ins97aV/G151H, Q38H/F97G, Q38H/F97G/G151H,
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- 10 Q38H/D96K/F97G/Ins97aV/G151H, Q38H/Y60gW, Q38H/Y60gW/G151H,
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- 15 Q38H/Y60gW/D96K/Ins97aV/G151H, Q38H/Y60gW/D96K/F97G,
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- 20 Q38H/F60eS/F97G/Ins97aV/G151H, Q38H/F60eS/D96K,
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- 25 Q38H/F60eS/Y60gW/G151H, Q38H/F60eS/Y60gW/Ins97aV,
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- 30 Q38H/F60eS/Y60gW/D96K/Ins97aV/G151H, Q38H/F60eS/Y60gW/D96K/F97G,
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Q38H/F60eS/Y60gW/D96K/F97G/Ins97aV,

- Q38H/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/D60bT,
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10 Q38H/D60bT/Y60gW/Ins97aV/G151H, Q38H/D60bT/Y60gW/F97G,
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- 5 Q38H/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV,
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- 10 Q38H/I41S/D96K/Ins97aV, Q38H/I41S/D96K/Ins97aV/G151H,
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- 15 Q38H/I41S/Y60gW/F97G/G151H, Q38H/I41S/Y60gW/F97G/Ins97aV,
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- 20 Q38H/I41S/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/I41S/F60eS,
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- 25 Q38H/I41S/F60eS/D96K/G151H, Q38H/I41S/F60eS/D96K/Ins97aV,
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- 30 Q38H/I41S/F60eS/Y60gW/Ins97aV/G151H, Q38H/I41S/F60eS/Y60gW/F97G,
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Q38H/I41S/F60eS/Y60gW/D96K/Ins97aV,
Q38H/I41S/F60eS/Y60gW/D96K/Ins97aV/G151H,
Q38H/I41S/F60eS/Y60gW/D96K/F97G,
- 5 Q38H/I41S/F60eS/Y60gW/D96K/F97G/G151H,
Q38H/I41S/F60eS/Y60gW/D96K/F97G/Ins97aV,
Q38H/I41S/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/I41S/D60bT,
Q38H/I41S/D60bT/G151H, Q38H/I41S/D60bT/Ins97aV,
Q38H/I41S/D60bT/Ins97aV/G151H, Q38H/I41S/D60bT/F97G,
- 10 Q38H/I41S/D60bT/F97G/G151H, Q38H/I41S/D60bT/F97G/Ins97aV,
Q38H/I41S/D60bT/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/D96K,
Q38H/I41S/D60bT/D96K/G151H, Q38H/I41S/D60bT/D96K/Ins97aV,
Q38H/I41S/D60bT/D96K/Ins97aV/G151H, Q38H/I41S/D60bT/D96K/F97G,
Q38H/I41S/D60bT/D96K/F97G/G151H, Q38H/I41S/D60bT/D96K/F97G/Ins97aV,
- 15 Q38H/I41S/D60bT/D96K/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/Y60gW,
Q38H/I41S/D60bT/Y60gW/G151H, Q38H/I41S/D60bT/Y60gW/Ins97aV,
Q38H/I41S/D60bT/Y60gW/Ins97aV/G151H, Q38H/I41S/D60bT/Y60gW/F97G,
Q38H/I41S/D60bT/Y60gW/F97G/G151H,
Q38H/I41S/D60bT/Y60gW/F97G/Ins97aV,
- 20 Q38H/I41S/D60bT/Y60gW/F97G/Ins97aV/G151H,
Q38H/I41S/D60bT/Y60gW/D96K, Q38H/I41S/D60bT/Y60gW/D96K/G151H,
Q38H/I41S/D60bT/Y60gW/D96K/Ins97aV,
Q38H/I41S/D60bT/Y60gW/D96K/Ins97aV/G151H,
Q38H/I41S/D60bT/Y60gW/D96K/F97G,
- 25 Q38H/I41S/D60bT/Y60gW/D96K/F97G/G151H,
Q38H/I41S/D60bT/Y60gW/D96K/F97G/Ins97aV,
Q38H/I41S/D60bT/Y60gW/D96K/F97G/Ins97aV/G151H,
Q38H/I41S/D60bT/F60eS, Q38H/I41S/D60bT/F60eS/G151H,
Q38H/I41S/D60bT/F60eS/Ins97aV, Q38H/I41S/D60bT/F60eS/Ins97aV/G151H,
- 30 Q38H/I41S/D60bT/F60eS/F97G, Q38H/I41S/D60bT/F60eS/F97G/G151H,
Q38H/I41S/D60bT/F60eS/F97G/Ins97aV,
Q38H/I41S/D60bT/F60eS/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS/D96K,

- Q38H/I41S/D60bT/F60eS/D96K/G151H, Q38H/I41S/D60bT/F60eS/D96K/Ins97aV,
 Q38H/I41S/D60bT/F60eS/D96K/Ins97aV/G151H,
 Q38H/I41S/D60bT/F60eS/D96K/F97G,
 Q38H/I41S/D60bT/F60eS/D96K/F97G/G151H,
 5 Q38H/I41S/D60bT/F60eS/D96K/F97G/Ins97aV,
 Q38H/I41S/D60bT/F60eS/D96K/F97G/Ins97aV/G151H,
 Q38H/I41S/D60bT/F60eS/Y60gW, Q38H/I41S/D60bT/F60eS/Y60gW/G151H,
 Q38H/I41S/D60bT/F60eS/Y60gW/Ins97aV,
 Q38H/I41S/D60bT/F60eS/Y60gW/Ins97aV/G151H,
 10 Q38H/I41S/D60bT/F60eS/Y60gW/F97G,
 Q38H/I41S/D60bT/F60eS/Y60gW/F97G/G151H,
 Q38H/I41S/D60bT/F60eS/Y60gW/F97G/Ins97aV,
 Q38H/I41S/D60bT/F60eS/Y60gW/F97G/Ins97aV/G151H,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96K,
 15 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/G151H,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV/G151H,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/G151H,
 20 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, and the same
 modifications except C122S is not modified and is C122C.

- Also provided are modified MTSP-1 polypeptides that include modifications
 corresponding to any of: T98P/F99LQ175L/Q192D, optionally C122S, and one or
 25 more selected from among: Q38H, I41S, D60bT, F60eS, Y60gW, D96K, F97G,
 Ins97aV and G151H as follows:

- T98P/F99L/C122S/G151H/Q175L/Q192D,
 Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
 Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 30 F97G/T98P/F99L/C122S/Q175L/Q192D,
 F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
 F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,

- F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D96K/T98P/F99L/C122S/Q175L/Q192D,
D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
- 5 D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
- 10 Y60gW/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
- 15 Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
- 20 Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
- 25 Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/T98P/F99L/C122S/Q175L/Q192D,
F60eS/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
- 30 F60eS/F97G/T98P/F99L/C122S/Q175L/Q192D,
F60eS/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,

- F60eS/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/D96K/T98P/F99L/C122S/Q175L/Q192D,
F60eS/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
5 F60eS/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
F60eS/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
10 F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
15 F60eS/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
20 F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
25 F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/T98P/F99L/C122S/Q175L/Q192D,
D60bT/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
30 D60bT/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,

- D60bT/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/D96K/T98P/F99L/C122S/Q175L/Q192D,
D60bT/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
5 D60bT/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
10 D60bT/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
15 D60bT/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
20 D60bT/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
25 D60bT/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
30 D60bT/F60eS/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,

- D60bT/F60eS/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/D96K/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
5 D60bT/F60eS/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
10 D60bT/F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
15 D60bT/F60eS/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
20 D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
25 D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/T98P/F99L/C122S/Q175L/Q192D,
I41S/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
30 I41S/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,

- I41S/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
5 I41S/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
10 I41S/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
15 I41S/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
20 I41S/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
25 I41S/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
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25 Q38H/D60bT/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/D60bT/F60eS/T98P/F99L/C122S/Q175L/Q192D,
Q38H/D60bT/F60eS/T98P/F99L/C122S/G151H/Q175L/Q192D,
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Q38H/D60bT/F60eS/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
30 Q38H/D60bT/F60eS/F97G/T98P/F99L/C122S/Q175L/Q192D,
Q38H/D60bT/F60eS/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/D60bT/F60eS/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,

- Q38H/D60bT/F60eS/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
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Q38H/D60bT/F60eS/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/D60bT/F60eS/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
5 Q38H/D60bT/F60eS/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
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10 D, Q38H/D60bT/F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
Q38H/D60bT/F60eS/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
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15 Q38H/D60bT/F60eS/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
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20 Q38H/D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
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,Q38H/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192
25 D,Q38H/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q1
75L/Q192D, Q38H/I41S/T98P/F99L/C122S/Q175L/Q192D,
Q38H/I41S/T98P/F99L/C122S/G151H/Q175L/Q192D,
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- Q38H/I41S/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
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10 Q38H/I41S/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
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- Q38H/I41S/F60eS/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
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10 Q38H/I41S/F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
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20 Q38H/I41S/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
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25 Q38H/I41S/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/
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Q38H/I41S/D60bT/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
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30 Q38H/I41S/D60bT/F97G/T98P/F99L/C122S/Q175L/Q192D,
Q38H/I41S/D60bT/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/I41S/D60bT/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,

- Q38H/I41S/D60bT/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
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Q38H/I41S/D60bT/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
- 5 Q38H/I41S/D60bT/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
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Q38H/I41S/D60bT/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
- 10 Q38H/I41S/D60bT/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
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- 15 Q38H/I41S/D60bT/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/I41S/D60bT/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Q38H/I41S/D60bT/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192
D, Q38H/I41S/D60bT/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
Q38H/I41S/D60bT/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
- 20 Q38H/I41S/D60bT/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
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- 25 Q38H/I41S/D60bT/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/
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- 30 Q38H/I41S/D60bT/F60eS/F97G/T98P/F99L/C122S/Q175L/Q192D,
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 10 Q192D, Q38H/I41S/D60bT/F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
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 L/Q192D,Q38H/I41S/D60bT/F60eS/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192
 D,Q38H/I41S/D60bT/F60eS/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192
 20 D,Q38H/I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q19
 2D,Q38H/I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q1
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 H/Q175L/Q192D,Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99
 25 L/C122S/Q175L/Q192D,Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T9
 8P/F99L/C122S/G151H/Q175L/Q192D, and the same modifications except C122S is
 not modified and is C122C.

Other exemplary modified MTSP-1 polypeptides can contain replacements,
 insertions and/or deletions corresponding to:

- 30 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, including those in which the unmodified MTSP-1 polypeptide comprises or is the protease domain of SEQ ID NO:2 or SEQ ID NO:4. Other such exemplary modified MTSP-1 polypeptides include, but are not limited to:

modified MTSP-1 polypeptides comprising modifications selected from among

- 5 combinations of modifications in which the protease domain cleaves human C3 *in vitro* with an EC₅₀ of less than 10 nM:

ins97aA/F97G/T98L/C122S/Q175M/Q192A/D217I/K224R,

Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L,

Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151H/Q175L

10 /Q192E,

Q38G/H40R/I41H/D60bN/F97D/F99L/C122S/Q175L/Q192G,

Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L,

Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151H/Q175L
/Q192E,

15 Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97D/ins97aE/T98S/F99L/C122S/G151H/Q175L/
Q192A,

Q38F/I41A/D60bT/F60eG/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E,

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

Q38H/I41A/D60bV/F60eT/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E,

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

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

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

25 Q38Y/I41A/D60bL/F60eQ/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175M/Q192A,

Q38H/I41S/D60bF/F60eV/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192A,

Q38H/I41A/D60bV/F60eA/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V,

Q38H/I41A/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G/F99L/C122S/G151H/Q175L/
Q192D,

30 Q38H/I41S/D60bT/F60eS/Y60gW/D96L/ins97aG/F97D/T98N/F99L/C122S/G151H/Q175L/
Q192E,

Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151H/Q175L
/Q192D,

Q38F/I41S/D60bF/F60eR/Y60gF/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192V,

- Q38H/I41S/D60bY/D96Y/ins97aV/F97D/T98P/F99L/L106M/C122S/I136M/Q192G/Q209L/D217T,
 Q38H/I41A/D60bV/F60eR/Y60gW/D96S/ins97aR/F97A/T98S/F99L/C122S/G151N/Q175L/Q192T,
- 5 Q38H/I41A/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G/F99L/C122S/G151N/Q175L/Q192D,
 Q38H/I41A/D60bT/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D,
 Q38H/I41A/D60bV/F60eR/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D,
 ins97aY/F97G/T98V/C122S/Q175M/Q192S/D217V,
- 10 Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/M117L/C122S/I136T/Q192G/D217I,
 Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151H/Q175L/Q192D,
 Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151N/Q175L/Q192D,
 Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192A,
- 15 H40R/I41H/F97D/F99L/C122S/Q175M/Q192G/D217V/K224Y,
 I41G/F97I/F99L/C122S/G151L/Q175M/Q192S/D217V,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D,
- 20 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/T150S/G151H/Q175L/Q192D/Q209L,
 Q38H/I41A/D60bV/F60eI/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D,
 Q38H/I41A/D60bW/ins97aV/F97D/T98P/F99L/C122S/I136M/Q192G/D217N,
- 25 Q38H/I41S/D60bF/F60eT/ins97aV/F97D/T98P/F99L/C122S/H143Q/G151N/Q175L/Q192G,
 Q38Y/I41S/D60bT/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D,
 Q38H/I41A/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192A,
 I41T/D60bW/F60eH/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192G,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97Y/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D,
- 30 Q192D,
 Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97S/ins97aH/T98G/F99L/C122S/G151N/Q175L/Q192G,
 Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E,
 I41S/F99L/C122S/G151N/Q175M/Q192G/D217V,
- 35 Q38R/I41S/D60bY/F60eD/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175M/Q192A,

Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/T98G/F99L/C122S/G151N/Q175L/Q192D,
 H40R/I41H/Y60gH/F97D/F99L/C122S/Q175M/Q192G/D217I/K224L,
 Q38H/I41A/D60bV/F60eR/Y60gW/F97D/F99L/C122S/G151H/Q175L/Q192D,
 Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/Q175L/Q192D,
 5 Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97Y/ins97aN/T98G/F99M/C122S/G151N/Q175
 L/Q192G,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97N/ins97aE/T98S/F99L/C122S/G151H/Q175L/
 Q192D,
 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/
 10 Q192D, and the same modifications except C122S is not modified and is C122C.

Exemplary of modified MTSP-1 polypeptides provided herein are those that contain or have the sequences set forth in any of SEQ ID NOs.: 6, 8, 21-59 and 63-81. This includes the modified MTSP-1 polypeptide whose sequence is set forth in SEQ ID NO: 35 or in SEQ ID NO: 42. MTSP-1 polypeptides that contain the modifications
 15 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/
 Q192D (with or without the C122S) are exemplary of such polypeptides.

For all of the modified MTSP-1 polypeptides provided herein, the unmodified MTSP-1 polypeptides include those that contain or have the sequence of amino acid residues set forth in SEQ ID NO:2 or 4 (protease domain). Included are full-length,
 20 two chain forms, two chain activated forms, and single chain forms that contain the protease domain or a catalytically active portion thereof.

The modified MTSP-1 polypeptides are selected to cleave and inactivate C3 so that, *in vivo*, complement activation is reduced. Modified MTSP-1 polypeptides provided herein include those that cleave within residues QHARASHL (residues 737-
 25 744) of human C3 (SEQ ID NO:9), such as those in which P1-P1' is RA.

All or any of the modified MTSP-1 polypeptides provided herein can include structural modifications and post-translational modifications such as additions of a polymer(s) to increase serum half-life and/or to reduce immunogenicity or both. Structural modifications include alterations in glycosylation, such as addition of
 30 glycosylation sites or types of glycosylation, and additions of polymers, such as dextran, sialylation and PEGylation. Any of the modified MTSP-1 polypeptides can be PEGylated to increase half-life and/or serum stability, particularly for indications in which extended duration of action is desired. The modified MTSP-1 polypeptide

can be further modified, such as by addition or elimination of lysines or other residues to alter PEGylation or by addition of or elimination of glycosylation sites.

Also, provided are fusion proteins, containing a modified MTSP-1 polypeptide or a catalytically active portion of a modified MTSP-1 polypeptide provided herein
5 fused or otherwise conjugated via a chemical or physical linker or bond to a non-MTSP-1 protease polypeptide or a portion thereof. Exemplary of such non-protease polypeptides is a multimerization domain, such as an Fc domain, or a protein transduction domain (PTD).

Also provided are nucleic acid molecules encoding any of the modified
10 MTSP-1 polypeptides and fusion proteins provided herein. Vectors containing the nucleic acid molecules also are provided. The vectors can be prokaryotic vectors or eukaryotic vectors, and include expression vectors, viral vectors, and vectors for gene therapy. Viral vectors include, but are not limited to, a herpes virus simplex vector, or a vaccinia virus vector, or an adenoviral vector, or a retroviral vector, or an insect
15 vector.

Provided are isolated cells, isolated non-human cells (that cannot develop into a zygote or into a human by any method available to those of skill in the art) and cell cultures that contain the nucleic acid molecule or nucleic acid molecules or vectors encoding the modified MTSP-1 polypeptides provided herein. Methods for making
20 the modified MTSP-1 polypeptides are provided, and include amino acid synthesis methods, and recombinant DNA methods. These include introducing a nucleic acid or vector encoding a modified MTSP-1 polypeptide provided herein into a cell; culturing the cell under conditions, whereby the polypeptide is expressed; and optionally, isolating or purifying the expressed modified MTSP-1 polypeptide. Cells
25 include any suitable cells or cell lines, including eukaryotic cells or prokaryotic cells. These include bacterial cells, mammalian cells, and yeast cells. For example, the cell can be a CHO cell, a BHK cell, *saccharomyces*, *Pichia* and such mammalian cells. Cells and methods for producing recombinant therapeutic polypeptides are well known to those of skill in the art.

30 The nucleic acids, vectors and polypeptides can be used for treating or in methods of a disease or condition mediated by or involving complement activation, wherein inhibition of complement activation effects treatment or amelioration of the

disease or condition. The nucleic acids and vectors can be used for gene therapy, or the polypeptides can be administered. Suitable routes of administration include parenteral, local, systemic and transdermal routes. These include intravenous, intramuscular, subcutaneous, and intravitreal administration.

- 5 Provided are methods of treating a disease or condition mediated by or involving complement activation where inhibition or reduction of activation effects treatment or some amelioration of symptoms or prevents (reduces the risk) of such disease or condition. The nucleic acid or vector or polypeptide is administered to a subject to treat or prevent (reduce the risk or symptoms) of the disease or condition.
- 10 Complement-mediated diseases or disorders or conditions include, but are not limited to, inflammatory disease and conditions, sepsis, rheumatoid arthritis (RA), an ophthalmic or ocular disease, a cardiovascular disease, membranoproliferative glomerulonephritis (MPGN), ophthalmic or ocular diseases or disorders, multiple sclerosis (MS), myasthenia gravis (MG), asthma, inflammatory bowel disease,
- 15 immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), transplanted organ rejection, and ischemia-reperfusion injury.

 The disease or condition can be an ocular or ophthalmic disease or rejection or inflammation due to a transplanted organ. Exemplary of such diseases, disorders or conditions is a diabetic retinopathy or a macular degeneration, including age-related

20 macular degeneration (AMD) and delayed renal graft function (DGF).

 The polypeptides provided herein can be used for inhibiting complement activation by contacting a modified MTSP-1 polypeptide with a complement protein C3, whereby complement protein C3 is cleaved such that complement activation is reduced or inhibited. The subjects for treatment with the polypeptides, methods and

25 uses herein can be any animal, including humans, and domesticated animals, particularly, dogs, cats and other pets and farm animals. Inhibition of complement activation can reduce the risk of developing (prevent) a disease, condition or disorder or lessen the disease, condition or disorder if it develops, or treat the disease or disorder or condition. Inhibition of complement activation, among its effects, leads to

30 a reduction of inflammatory symptoms associated with a complement-mediated disease or disorder selected from among an inflammatory disorder, a neurodegenerative disorder and a cardiovascular disorder. As noted above,

complement-mediated diseases or disorders or conditions include, but are not limited to, sepsis, Rheumatoid arthritis (RA), ocular or ophthalmic disorders, membranoproliferative glomerulonephritis (MPGN), Multiple Sclerosis (MS), delayed rejection of or inflammation of transplanted organs or tissues, Myasthenia
5 gravis (MG), asthma, inflammatory bowel disease, immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), and Ischemia-reperfusion injury, and any others known to those of skill in the art.

The complement-mediated disease, condition or disorder can result from a treatment of a subject. For example, ischemia-reperfusion injury can be caused by an
10 event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis. Treatment with a modified MTSP-1 polypeptide provided herein can be effected prior to a treatment of a subject that results in or has risk of causing a complement mediated disorder, condition or disease.

15 Provided are uses of the modified MTSP-1 polypeptides provided herein and methods of treating a disease or condition mediated by or involving complement activation, by administering a modified MTSP-1 polypeptide provided herein, where inhibition of complement activation effects treatment or amelioration of the disease or condition. The modified MTSP-1 polypeptides also can be administered to reduce the
20 risk (prevent) of a developing a disease or condition or to reduce the symptoms of such disease, disorder or condition development. Complement-mediated diseases, conditions or disorders include any noted above or below. Included are ocular or ophthalmic diseases or rejection of or inflammation due to a transplanted organ. Such diseases and conditions include diabetic retinopathy and a macular degeneration, such as AMD, and delayed renal graft function (DGF). The modified MTSP-1
25 polypeptide (or encoding nucleic acid molecule or vector) can be administered by any suitable route, including those discussed above and elsewhere herein, such as parenterally, such as administered intravenously, or subcutaneously. For treatment of ophthalmic disorders the modified MTSP-1 polypeptides can be administered locally,
30 such as by intravitreal injection or by topical application to the eye. The modified MTSP-1 polypeptide can be modified for introduction into the eye, such as by fusion to a protein transduction domain to facilitate transduction into the vitreous humor.

For any application, method or use, the modified MTSP-1 polypeptide can be modified to increase serum half-life, such as by PEGylation.

Also provided are combinations and kits, that include: (a) a modified MTSP-1 polypeptide provided herein; and (b) a second agent or agents for treating a complement-mediated disease or disorder. Second agents include, but are not limited to anti-inflammatory agent(s) and anticoagulant(s), such as, but not limited to, any one or more of a non-steroidal anti-inflammatory drug (NSAID), antimetabolite, corticosteroid, analgesic, cytotoxic agent, pro-inflammatory cytokine inhibitor, anti-inflammatory cytokines, B cell targeting agents, compounds targeting T antigens, adhesion molecule blockers, chemokine receptor antagonists, kinase inhibitors, PPAR- γ (gamma) ligands, complement inhibitors, heparin, warfarin, acenocoumarol, phenindione, EDTA, citrate, oxalate, argatroban, lepirudin, bivalirudin, and ximelagatran.

The methods, uses or combinations include those in which the modified MTSP-1 polypeptide comprises the modification I41D or I41S, particularly I41S, and particularly modified MTSP-1 polypeptides containing the modifications 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 or I41D/C122S/G151N/Q192T or I41D/G151N/Q192T. The replacement C122S (with reference to the protease domain) is included to eliminate a free cysteine to reduce aggregation. The unmodified MTSP-1 polypeptide includes the protease domain, such as that of sequence of amino acid residues set forth in SEQ ID NO:4, such as a modified MTSP-1 polypeptide that contains the sequence of amino acid residues set forth in any of SEQ ID NOs:35 and 42.

Provided are methods of treating DGF by intravenously administering a modified MTSP-1 polypeptide provided herein, such as a modified MTSP-1 polypeptide that contains the sequence of amino acid residues set forth in any of SEQ ID NOs:35 and 42 or a catalytically active portion thereof, such as a modified MTSP-1 polypeptide that comprises the replacements Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D. Dosages include any suitable dose and any suitable dosage regimen.

A single dosage includes 0.1 mg to 1 mg. Treatment can be once or can be repeated a plurality of times, such as every 2 days, 3 days, 4 days, 5 days, 6 days, weekly, bi-weekly or monthly. The modified MTSP-1 polypeptides can be modified, such as by PEGylation or multimerization to effect increased half-life or increased

5 bioavailability.

Provided are uses of the modified MTSP-1 polypeptides and/or methods of treating an ophthalmic disorder or ocular disorder, by administering a modified MTSP-1 polypeptide provided herein such as systemically or to the eye. Ophthalmic disorders include diabetic retinopathy and macular degeneration, such as AMD.

10 Suitable dosages can be empirically determined, and include a single dosage that is 0.1 to 1 mg. Exemplary of modified MTSP-1 polypeptides for use for these indications are any provided herein that cleave C3. These include modified MTSP-1 polypeptides that contains the sequence of amino acid residues set forth in any of SEQ ID NOs:35 and 42 or a catalytically active portion thereof, such as, but are not
15 limited to, a modified MTSP-1 polypeptide that comprises the replacements, or insertions and/or deletions:

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/
20 Q192D

or the modified MTSP-1 polypeptide comprises the replacements:

I41D/G151N/Q192T or I41D/C122S/G151N/Q192T. The polypeptides can be administered to the eye as described above, such as by intravitreal injection or other local method. Treatment can be once or repeated a plurality of times, such as every 2
25 days, 3 days, 4 days, 5 days, 6 days, weekly, bi-weekly or monthly. The modified MTSP-1 polypeptides include those of SEQ ID NO:35 or a catalytically active portion thereof or full-length forms or catalytically active portions thereof. The modified MTSP-1 polypeptides can be modified, such as by PEGylation or multimerization to effect increased half-life or increased bioavailability.

30 For any application, the modified MTSP-1 polypeptide can be a single chain or two chain form of the modified MTSP-1 polypeptide or a zymogen form that is activated *in vivo*. The protease domains are active as single chains. The modified

MTSP-1 polypeptides can include other modifications, such as PEGylation to alter or improve pharmacological properties.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 depicts an overview of the classical, lectin, and alternative complement pathways and the activation of the terminal complement complex, the membrane attack complex (MAC). The figure depicts many of the more than 30 proteins that participate in the complement cascade, their action within the cascade, and where applicable, their points of convergence among the complement pathways. For example, the three pathways converge upon the generation of a C3 convertase, which cleaves C3 to form a C5 convertase yielding the formation of the MAC complex. The figure also depicts the generation of many of the complement cleavage products.

DETAILED DESCRIPTION

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I. EXAMPLES

A. DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the invention(s) belong. All patents, patent applications, published applications and

publications, GENBANK sequences, websites and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there is a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information is known and can be readily accessed, such as by searching the internet and/or appropriate databases. Reference thereto evidences the availability and public dissemination of such information.

As used herein, cleavage refers to the breaking of peptide bonds by a protease. The cleavage site motif for a protease involves residues N- and C-terminal to the scissile bond (the unprimed and primed sides, respectively, with the cleavage site for a protease defined as ... P3-P2-P1-P1'-P2'-P3' ..., and cleavage occurs between the P1 and P1' residues). In human C3, cleavage by a C3 convertase occurs between residues R and S (see residues 746-751 of SEQ ID NO: 9, cleavage between residue 748 and 749 of the sequence in human C3) of C3:

P3 P2 P1 P1' P2' P3'
Leu Ala Arg ↓ Ser Asn Leu.

Typically, cleavage of a substrate in a biochemical pathway is an activating cleavage or an inhibitory cleavage. An activating cleavage refers to cleavage of a polypeptide from an inactive form to an active form. This includes, for example, cleavage of a zymogen to an active enzyme. An activating cleavage also is cleavage whereby a protein is cleaved into one or more proteins that themselves have activity. For example, the complement system is an irreversible cascade of proteolytic cleavage events whose termination results in the formation of multiple effector molecules that stimulate inflammation, facilitate antigen phagocytosis, and lyse some cells directly. Thus, cleavage of C3 by a C3 convertase into C3a and C3b is an activation cleavage. In contrast, the modified MTSP-1 polypeptides provided herein effect inhibitory cleavage of C3, such as by cleavage in a target site that inactivates C3.

As used herein, an inhibitory cleavage or inactivation cleavage is cleavage of a protein into one or more degradation products that are not functional. Inhibitory

cleavage results in the diminishment or reduction of an activity of a protein.

Typically, a reduction of an activity of a protein reduces the pathway or process for which the protein is involved. In one example, the cleavage of any one or more complement proteins that is an inhibitory cleavage results in the concomitant

5 reduction or inhibition of any one or more of the classical, lectin, or alternative functional pathways of complement. To be inhibitory, the cleavage reduces activity by at least or at least about 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more compared to a native form of the protein. The percent cleavage of a protein that is required for the cleavage to be inhibitory varies among
10 proteins but can be determined by assaying for an activity of the protein.

As used herein, “complement activation” refers to the activation of complement pathways, for example complement activation refers to an increase in the functions or activities of any one or more of the complement pathways by a protease or an increase in the activity of any of the proteins in the complement pathway.

15 Complement activation can lead to complement-mediated cell lysis or can lead to cell or tissue destruction. Inappropriate complement activation on host tissue plays an important role in the pathology of many autoimmune and inflammatory diseases, and also is responsible for or associated with many disease states associated with bioincompatibility. It is understood that activation can mean an increase in existing
20 activity as well as the induction of a new activity. A complement activation can occur *in vitro* or *in vivo*. Exemplary functions of complement that can be assayed and that are described herein include hemolytic assays, and assays to measure any one or more of the complement effector molecules such as by SDS PAGE followed by Western Blot or Coomassie Brilliant Blue staining or by ELISA. In some embodiments,
25 complement activation is inhibited by a protease, such as a protease described herein, by 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% or 99% or more compared to the activity of complement in the absence of a protease.

As used herein, “inhibiting complement activation” or “complement inactivation” refers to the reduction or decrease of a complement-mediated function
30 or activity of any one or more of the complement pathways by a protease or in the activity of any of the proteins in a pathway. A function or activity of complement can occur *in vitro* or *in vivo*. Exemplary functions of complement that can be assayed and

that are described herein include hemolytic assays, and assays to measure any one or more of the complement effector molecules such as by SDS PAGE followed by Western Blot or Coomassie Brilliant Blue staining or by ELISA. A protease can inhibit complement activation by 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more. In other embodiments, complement activation is inhibited by a protease by 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% or 99% or more compared to the activity of complement in the absence of a protease.

As used herein, a "complement protein" or a "complement component" is a protein of the complement system that functions in the host's defense against infections and in the inflammatory process. Complement proteins include those that function in the classical pathway, those that function in the alternative pathway, and those that function in the lectin pathway. Among the complement proteins are proteases that participate in the complement pathways. In addition, as used herein, complement proteins include any of the "cleavage products" (also referred to as "fragments") that are formed upon activation of the complement cascade. Also included among complement proteins are inactive or altered forms of complement proteins, such as iC3b and C3a-desArg. Thus, complement proteins include, but are not limited to: C1q, C1r, C1s, C2, C3, C3a, C3b, C3c, C3dg, C3g, C3d, C3f, iC3, C3a-desArg, C4, C4a, C4b, iC4, C4a-desArg, C5, C5a, C5a-des-Arg, C6, C7, C8, C9, MASP-1, MASP-2, MBL, Factor B, Factor D, Factor H, Factor I, CR1, CR2, CR3, CR4, properdin, C1Inh, C4bp, MCP, DAF, CD59 (MIRL), clusterin and HRF and allelic and species variants of any complement protein.

As used herein, a "native" form of a complement protein is one which can be isolated from an organism such as a vertebrate in the absence of complement activation, and which has not been intentionally modified by man in the laboratory. Examples of native complement proteins include C1q, C1r, C1s, C2, C3, C4, Factor B, Factor D, properdin, C5, C6, C7, C8, and C9.

Generally, "native complement proteins" are inactive and acquire activity upon activation. Activation can require activation cleavage, maturation cleavage and/or complex formation with other proteins. An exception to this is Factor I and Factor D which have enzymatic activity in their native form. In some examples, activation of a native complement protein occurs following cleavage of the protein.

For example, complement zymogens such as C3 are proteases which are themselves activated by protease cleavage such that cleavage of C3 by the C3 convertase C4b2b generates the active fragments C3a and C3b. In another example, cleavage of an inactive native complement protein results in changes in the structural stability of a protein resulting in activation of the protein. For example, C3 contains an internal thioester bond which in the native protein is stable, but can become highly reactive and activated following conformational changes that result from cleavage of the protein. Thus, the cleavage products of C3 are biologically active. Activation of C3 also can occur spontaneously in the absence of cleavage. It is the spontaneous conversion of the thioester bond in native C3 that is an initiating event of the alternative pathway of complement. In other examples, activation of a native complement protein occurs following the release of a complexed regulatory molecule that inhibits the activity of an otherwise active native complement protein. For example, C1inh binds to and inactivates C1s and C1r, unless they are in complex with C1q.

As used herein, "maturation cleavage" is a general term that refers to any cleavage required for activation of a zymogen. This includes cleavage that leads to a conformational change resulting in activity (*i.e.*, activation cleavage). It also includes cleavage in which a critical binding site is exposed or a steric hindrance is exposed or an inhibitory segment is removed or moved.

As used herein, "altered form" of a complement protein refers to a complement protein that is present in a non-native form resulting from modifications in its molecular structure. For example, C3 reaction of the thioester with water can occur in the absence of convertase cleavage, giving a hydrolyzed inactive form of C3 termed iC3. In another example, anaphylatoxins including C3a, C5a, and C4a can be desarginated by carboxypeptidase N into more stable, less active forms.

As used herein, a "fragment" or "cleavage product" of a complement protein is a region or segment of a complement protein that contains a portion of the polypeptide sequence of a native complement protein. A fragment of a complement protein usually results following the activation of a complement cascade. Generally, a fragment results from the proteolytic cleavage of a native complement protein. For example, complement protein C3 is enzymatically cleaved by a C3 convertase,

resulting in two fragments: C3a which constitutes the N-terminal portion of C3; and C3b which constitutes the C-terminal portion and contains the serine protease site. A fragment of a complement protein also results from the proteolytic cleavage of another fragment of a complement protein. For example, C3b, a fragment generated from the cleavage of C3, is cleaved by Factor I to generate the fragments iC3b and C3f. Generally cleavage products of complement proteins are biologically active products and function as cleavage effector molecules of the complement system. Hence a fragment or portion of complement protein includes cleavage products of complement proteins and also portions of the proteins that retain or exhibit at least one activity of a complement protein.

As used herein, "cleavage effector molecules" or "cleavage effector proteins" refers to the active cleavage products generated as a result of the triggered-enzyme cascade of the complement system. A cleavage effector molecule, a fragment or a cleavage product resulting from complement activation can contribute to any of one or more of the complement-mediated functions or activities, which include opsonization, anaphylaxis, cell lysis and inflammation. Examples of cleavage or effector molecules include, but are not limited to, C3a, C3b, C4a, C4b, C5a, C5b-9, and Bb. Cleavage effector molecules of the complement system, by virtue of participation in the cascade, exhibit activities that include stimulating inflammation, facilitating antigen phagocytosis, and lysing some cells directly. Complement cleavage products promote or participate in the activation of the complement pathways.

As used herein, "anaphylatoxins" are cleavage effector proteins that trigger degranulation of, or release of substances from, mast cells or basophils, which participate in the inflammatory response, particularly as part of defense against parasites. If the degranulation is too strong, it can cause allergic reactions. Anaphylatoxins include, for example, C3a, C4a and C5a. Anaphylatoxins also indirectly mediate spasms of smooth muscle cells (such as bronchospasms), increases in permeability of blood capillaries, and chemotaxis.

As used herein, "chemotaxis" refers to receptor-mediated movement of leukocytes towards a chemoattractant typically in the direction of the increasing

concentration thereof, such as in the direction of increasing concentration of an anaphylatoxin.

As used herein, "opsonization" refers to the alteration of the surface of a pathogen or other particle so that it can be ingested by phagocytes. A protein that
5 binds or alters the surface of a pathogen is termed an opsonin. Antibody and complement proteins opsonize extracellular bacteria for uptake and destruction by phagocytes such as neutrophils and macrophages.

As used herein, "cell lysis" refers to the breaking open of a cell by the destruction of its wall or membrane. Hemolysis of red blood cells is a measure of cell
10 lysis.

As used herein, "complement protein C3" or "C3" refers to complement protein C3 of the complement system that functions in the host defense against infections and in the inflammatory process. Human complement protein C3 is a 1663 amino acid single-chain pre-proprotein or zymogen set forth in SEQ ID NO: 9 that
15 that contains a 22 amino acid signal peptide (amino acids 1-22 of SEQ ID NO: 9) and a tetra-arginine sequence (amino acids 668-671 of SEQ ID NO: 9) that is removed by a furin-like enzyme resulting in a mature two chain protein containing a beta chain (amino acids 23-667 of SEQ ID NO: 9) and an alpha chain (amino acids 672-1663 of SEQ ID NO: 9) linked by a disulfide bond between residues C559 and C816.
20 Complement protein C3 is further activated by proteolytic cleavage by a C3 convertase (C4b2b or C3bBb) between amino acids 748 and 749 of SEQ ID NO: 9 generating the anaphylatoxin C3a and the opsonin C3b.

As used herein, a "zymogen" refers to a protein that is activated by proteolytic cleavage, including maturation cleavage, such as activation cleavage, and/or complex
25 formation with other protein(s) and/or cofactor(s). A zymogen is an inactive precursor of a protein. Such precursors are generally larger, although not necessarily larger, than the active form. With reference to MTSP-1 or complement protein C3, zymogens are converted to active enzymes by specific cleavage, including catalytic and autocatalytic cleavage, or by binding of an activating co-factor, which generates
30 an active enzyme. A zymogen, thus, is an enzymatically inactive protein that is converted to a proteolytic enzyme by the action of an activator. Cleavage can be effected autocatalytically. A number of complement proteins are zymogens; they are

inactive, but become cleaved and activated upon the initiation of the complement system following infection. Zymogens, generally, are inactive and can be converted to mature active polypeptides by catalytic or autocatalytic cleavage of the proregion from the zymogen.

5 As used herein, a “proregion,” “propeptide,” or “pro sequence,” refers to a region or a segment of a protein that is cleaved to produce a mature protein. This can include segments that function to suppress enzymatic activity by masking the catalytic machinery and thus preventing formation of the catalytic intermediate (*i.e.*, by sterically occluding the substrate binding site). A proregion is a sequence of amino
10 acids positioned at the amino terminus of a mature biologically active polypeptide and can be as little as a few amino acids or can be a multidomain structure.

 As used herein, an “activation sequence” refers to a sequence of amino acids in a zymogen that is the site required for activation cleavage or maturation cleavage to form an active protease. Cleavage of an activation sequence can be catalyzed
15 autocatalytically or by activating partners.

 Activation cleavage is a type of maturation cleavage in which a conformational change required for activity occurs. This is a classical activation pathway, for example, for serine proteases in which a cleavage generates a new N-terminus which interacts with the conserved regions of catalytic machinery, such as
20 catalytic residues, to induce conformational changes required for activity. Activation can result in production of multi-chain forms of the proteases. In some instances, single chain forms of the protease can exhibit proteolytic activity.

 As used herein, “domain” refers to a portion of a molecule, such as proteins or the encoding nucleic acids, that is structurally and/or functionally distinct from other
25 portions of the molecule and is identifiable. An exemplary polypeptide domain is a part of the polypeptide that can form an independently folded structure within a polypeptide made up of one or more structural motifs (*e.g.*, combinations of alpha helices and/or beta strands connected by loop regions) and/or that is recognized by a particular functional activity, such as enzymatic activity, dimerization or substrate-
30 binding. A polypeptide can have one or more, typically more than one, distinct domains. For example, the polypeptide can have one or more structural domains and one or more functional domains. A single polypeptide domain can be distinguished

based on structure and function. A domain can encompass a contiguous linear sequence of amino acids. Alternatively, a domain can encompass a plurality of non-contiguous amino acid portions, which are non-contiguous along the linear sequence of amino acids of the polypeptide. Typically, a polypeptide contains a plurality of domains. For example, serine proteases can be characterized based on the sequence of protease domain(s). Those of skill in the art are familiar with polypeptide domains and can identify them by virtue of structural and/or functional homology with other such domains. For exemplification herein, definitions are provided, but it is understood that it is well within the skill in the art to recognize particular domains by name. If needed, appropriate software can be employed to identify domains.

As used herein, a "structural region" of a polypeptide is a region of the polypeptide that contains at least one structural domain.

As used herein, a "protease domain" is the catalytically active portion of a protease. Reference to a protease domain of a protease includes the single, two- and multi-chain forms of any of these proteins. A protease domain of a protein contains all of the requisite properties of that protein required for its proteolytic activity, such as for example, its catalytic center.

As used herein, a "catalytically active portion" or "catalytically active domain" of a protease, for example an MTSP-1 polypeptide, refers to the protease domain, or any fragment or portion thereof that retains protease activity. For example, a catalytically active portion of a MTSP-1 polypeptide can be a MTSP-1 protease domain including an isolated single chain form of the protease domain or an activated two-chain form. The zymogen form of each protein is single chain form, which can be converted to the active two chain form by cleavage. The protease domain also can be converted to a two chain form. Significantly, at least *in vitro*, the single chain forms of the proteases and catalytic domains or proteolytically active portions thereof (typically C-terminal truncations) exhibit protease activity.

As used herein, a "nucleic acid encoding a protease domain or catalytically active portion of a protease" refers to a nucleic acid encoding only the recited single chain protease domain or active portion thereof, and not the other contiguous portions of the protease as a continuous sequence.

As used herein, recitation that a polypeptide consists essentially of the protease domain means that the only portion of the polypeptide is a protease domain or a catalytically active portion thereof. The polypeptide can optionally, and generally will, include additional non-protease-derived sequences of amino acids.

5 As used herein, an “active site of a protease” refers to the substrate binding site where catalysis of the substrate occurs. The structure and chemical properties of the active site allow the recognition and binding of the substrate and subsequent hydrolysis and cleavage of the scissile bond in the substrate. The active site of a protease contains amino acids that contribute to the catalytic mechanism of peptide
10 cleavage, as well as amino acids that contribute to substrate sequence recognition, such as amino acids that contribute to extended substrate binding specificity.

As used herein, target site in C3 refers to a site that, when cleaved, inactivates C3. Exemplary of such site is:

Q H A R ↓ A S H L (residues 737-744 of SEQ ID NO:9)
15 P4P3P2P1 ↓P1' P4'.

As used herein, the “substrate recognition site” or “cleavage sequence” refers to the sequence recognized by the active site of a protease that is cleaved by a protease. Typically, a cleavage sequence for a serine protease is six residues in length to match the extended substrate specificity of many proteases, but can be longer or
20 shorter depending upon the protease. Typically, for example, for a serine protease, a cleavage sequence is made up of the P1-P4 and P1'-P4' amino acids in a substrate, where cleavage occurs after the P1 position. Typically, a cleavage sequence for a serine protease is six residues in length to match the extended substrate specificity of many proteases, but can be longer or shorter depending upon the protease.

25 As used herein, “target substrate” refers to a substrate that is cleaved by a protease. Typically, the target substrate is specifically cleaved at its substrate recognition site by a protease. Minimally, a target substrate includes the amino acids that make up the cleavage sequence. Optionally, a target substrate includes a peptide containing the cleavage sequence and any other amino acids. A full-length protein,
30 allelic variant, isoform, or any portion thereof, containing a cleavage sequence recognized by a protease, is a target substrate for that protease. For example, for purposes herein in which complement inactivation is intended, a target substrate is

complement protein C3, or any portion or fragment thereof containing a cleavage sequence recognized by a MTSP-1 polypeptide. Such target substrates can be purified proteins, or can be present in a mixture, such as a mixture *in vitro* or a mixture *in vivo*. Mixtures can include, for example, blood or serum or breast milk, or other tissue fluids. Additionally, a target substrate includes a peptide or protein containing an additional moiety that does not affect cleavage of the substrate by a protease. For example, a target substrate can include a four amino acid peptide or a full-length protein chemically linked to a fluorogenic moiety. The proteases can be modified to exhibit greater substrate specificity for a target substrate.

As used herein, “MTSP-1” or “MTSP1” or “membrane-type serine protease” “MTSP-1 polypeptide” refers to any MTSP-1 polypeptide including, but not limited to, a recombinantly produced polypeptide, a synthetically produced polypeptide and a MTSP-1 polypeptide extracted or isolated from cells or tissues including, but not limited to, epithelial cells, cancer cells, liver and blood. Alternative names that are used interchangeably for MTSP-1 include membrane-type serine protease and matriptase and Epithin and TMPRSS1 and Suppressor of tumorigenicity 14 protein and Prostamin and Serine protease 14 (ST14) and Serine protease TADG-15 and Tumor-associated differentially-expressed gene 15 (TADG-15) protein. MTSP-1 includes related polypeptides from different species including, but not limited to animals of human and non-human origin. Human MTSP-1 includes MTSP-1, allelic variants, isoforms, synthetic molecules from nucleic acids, protein isolated from human tissue and cells, and modified forms thereof.

Exemplary unmodified human MTSP-1 polypeptides include, but are not limited to, unmodified and wild-type MTSP-1 polypeptides (SEQ ID NO:1) and the protease domain (such as the single-chain protease domain of MTSP-1 set forth in SEQ ID NO: 2). One of skill in the art would recognize that the referenced positions of the full length wild-type MTSP-1 polypeptide (SEQ ID NO:1) differ by 614 amino acid residues when compared to the MTSP-1 protease domain (SEQ ID NO:2). Thus, the first amino acid residue of SEQ ID NO:2 “corresponds to” the six hundred and fifteenth (615th) amino acid residue of SEQ ID NO:1. In another embodiment, an MTSP-1 polypeptide can be any one or more of the allelic variants of MTSP-1 as set forth in SEQ ID NO:99.

An MTSP-1 protease occurs as a single chain zymogen, and as an activated two-chain polypeptide. Reference to MTSP-1 includes active single-chain and two-chain forms thereof. The MTSP-1 polypeptides provided herein can be further modified, such as by chemical modification or post-translational modification. Such
5 modifications include, but are not limited to, glycosylation, PEGylation, albumination, farnesylation, carboxylation, hydroxylation, phosphorylation, HESylation, PASylation, and other polypeptide modifications known in the art.

MTSP-1 includes MTSP-1 from any species, including human and non-human species. MTSP-1 polypeptides of non-human origin include, but are not limited to,
10 murine and rat MTSP-1 polypeptides. Exemplary MTSP-1 polypeptides of non-human origin include, for example, mouse (*Mus musculus*, SEQ ID NO:12) and rat (*Rattus norvegicus*, SEQ ID NO:13).

Reference to MTSP-1 polypeptides also includes precursor polypeptides and mature MTSP-1 polypeptides in single-chain or two-chain forms, truncated forms
15 thereof that have activity, the isolated protease domain and includes allelic variants and species variants, variants encoded by splice variants, and other variants, including polypeptides that have at least or at least about 40%, 45%, 50%, 55%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more sequence identity to full length form (SEQ ID NO:1 or 3) or the protease domain thereof (SEQ
20 ID NO: 2 or 4). MTSP-1 polypeptides include, but are not limited to, tissue-specific isoforms and allelic variants thereof, synthetic molecules prepared by translation of nucleic acids, proteins generated by chemical synthesis, such as syntheses that include ligation of shorter polypeptides, through recombinant methods, proteins isolated from human and non-human tissue and cells, chimeric MTSP-1 polypeptides and modified
25 forms thereof. MTSP-1 polypeptides also include fragments or portions of MTSP-1 that are of sufficient length or include appropriate regions to retain at least one activity (upon activation if needed) of a full-length mature polypeptide. In one example the portion of MTSP-1 is the protease domain, such as, for example, the protease domain set forth in SEQ ID NO: 2 which corresponds to amino acids 615-
30 855 of the WT MTSP-1 sequence set forth in SEQ ID NO: 1. MTSP-1 polypeptides also include those that contain chemical or posttranslational modifications and those that do not contain chemical or posttranslational modifications. Such modifications

include, but are not limited to, PEGylation, albumination, glycosylation, farnesylation, carboxylation, hydroxylation, phosphorylation, HESylation, PASylation, and other polypeptide modifications known in the art.

As used herein, “MTSP-1 protease” or “MTSP-1 protease domain” refers to any MTSP-1 polypeptide including, but not limited to, a recombinantly produced polypeptide, a synthetically produced polypeptide and a MTSP-1 polypeptide extracted or isolated from cells or tissues including, but not limited to, liver and blood. MTSP-1 protease includes related polypeptides from different species including, but not limited to animals of human and non-human origin. A human MTSP-1 protease or MTSP-1 protease domain includes MTSP-1, allelic variants, isoforms, synthetic molecules from nucleic acids, protein isolated from human tissue and cells, and modified forms thereof. Exemplary reference human MTSP-1 protease domains include, but are not limited to, unmodified and wild-type MTSP-1 protease domain (SEQ ID NO:2) and an alternate protease domain (such as the MTSP-1 protease domain set forth in SEQ ID NO: 4). One of skill in the art would recognize that the referenced positions of the MTSP-1 protease domain (SEQ ID NO:2) differ by 614 amino acid residues when compared to the full length MTSP-1 polypeptide (SEQ ID NO:1), which is the MTSP-1 polypeptide containing the full length WT sequence. Thus, the first amino acid residue of SEQ ID NO:2 “corresponds to” the six hundred and fifteenth (615th) amino acid residue of SEQ ID NO:1.

As used herein, a “modification” is in reference to modification of a sequence of amino acids of a polypeptide or a sequence of nucleotides in a nucleic acid molecule and includes deletions, insertions, and replacements of amino acids or nucleotides, respectively. Modified MT-SP1 polypeptides refer to MT-SP1 polypeptides containing alterations in the primary sequence of the polypeptide. Methods of modifying a polypeptide are routine to those of skill in the art, such as by using recombinant DNA methodologies. Reference to other modifications, such as post-translational modifications, and conjugation to moieties, such as polymers, such as PEG moieties, and tags for detection or isolation, are specified as such.

As used herein, “substitution” or “replacement” refers to the replacing of one or more nucleotides or amino acids in a native, target, wild-type or other nucleic acid or polypeptide sequence with an alternative nucleotide or amino acid, without

changing the length (as described in numbers of residues) of the molecule. Thus, one or more substitutions in a molecule does not change the number of amino acid residues or nucleotides of the molecule. Amino acid replacements compared to a particular polypeptide can be expressed in terms of the number of the amino acid residue along the length of the polypeptide sequence. For example, a modified polypeptide having a modification in the amino acid at the 35th position of the amino acid sequence that is a substitution/replacement of Arginine (Arg; R) with glutamine (Gln; Q) can be expressed as R35Q, Arg35Gln, or 35Q. Simply R35 can be used to indicate that the amino acid at the modified 35th position is an arginine.

As used herein, a “modified MTSP-1” or “modified MTSP-1 polypeptide” refers to a MTSP-1 protease that exhibits altered activity, such as altered substrate specificity, compared to the unmodified form. Such proteases include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more modifications (*i.e.*, changes in amino acids) compared to a wild type MTSP-1 such that an activity, such as substrate specificity or selectivity, of the MTSP-1 protease for cleaving complement protein C3 is altered. A modified MTSP-1 can be a full-length MTSP-1 protease, or can be a portion thereof of a full length protease, such as the protease domain of MTSP-1, as long as the modified MTSP-1 protease contains modifications in regions that alter the activity or substrate specificity of the protease and the protease is proteolytically active. A modified MTSP-1 protease, or a modified MTSP-1 protease domain, also can include other modifications in regions that do not impact on substrate specificity of the protease. Hence, a modified MTSP-1 polypeptide typically has 60%, 70%, 80 %, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to a corresponding sequence of amino acids of a wild type MTSP-1 polypeptide. A modified full-length MTSP-1 polypeptide or a catalytically active portion thereof or a protease domain thereof of a modified MTSP-1 polypeptide can include polypeptides that are fusion proteins as long as the fusion protein possesses the target specificity.

As used herein, chymotrypsin numbering refers to the amino acid numbering of a mature chymotrypsin polypeptide of SEQ ID NO: 1. Alignment of a protease domain of another protease, such as for example, the protease domain of MTSP-1, can be made with chymotrypsin. In such an instance, the amino acids of MTSP-1 that

correspond to amino acids of chymotrypsin are given the numbering of the chymotrypsin amino acids. Corresponding positions can be determined by such alignment by one of skill in the art using manual alignments or by using the numerous alignment programs available (for example, BLASTP). Corresponding positions also

5 can be based on structural alignments, for example by using computer simulated alignments of protein structure. Recitation that amino acids of a polypeptide correspond to amino acids in a disclosed sequence refers to amino acids identified upon alignment of the polypeptide with the disclosed sequence to maximize identity or homology (where conserved amino acids are aligned) using a standard alignment

10 algorithm, such as the GAP algorithm. The corresponding chymotrypsin numbers of amino acid positions 615-855 of the MTSP-1 polypeptide set forth in SEQ ID NO:1 are provided in Table 1. The amino acid positions relative to the sequence set forth in SEQ ID NO:1 are in normal font, the amino acid residues at those positions are in bold, and the corresponding chymotrypsin numbers are in italics. For example, upon

15 alignment of the serine protease domain of MTSP-1 (SEQ ID NO: 2) with mature chymotrypsin, V at position 1 in the MTSP-1 protease domain is given the chymotrypsin numbering of V16. Subsequent amino acids are numbered accordingly. In one example, an F at amino acid position 708 of full-length MTSP-1 (SEQ ID NO:1) or at position 94 of the protease domain of MTSP-1 (SEQ ID NO:2),

20 corresponds to F99 based on chymotrypsin numbering. Where a residue exists in a protease, but is not present in chymotrypsin, the amino acid residue is given a letter notation. For example, residues in chymotrypsin that are part of a loop with amino acid 60 based on chymotrypsin numbering, but are inserted in the MTSP-1 sequence compared to chymotrypsin, are referred to for example as D60b or R60c. These

25 residues correspond to D661 and R662, respectively, by numbering relative to the mature MTSP-1 sequence (human) set forth in SEQ ID NO:1.

Table 1. Chymotrypsin numbering of MTSP-1

615	616	617	618	619	620	621	622	623	624	625	626	627	628	629
V	V	G	G	T	D	A	D	E	G	E	W	P	W	Q
<i>16</i>	<i>17</i>	<i>18</i>	<i>19</i>	<i>20</i>	<i>21</i>	<i>22</i>	<i>23</i>	<i>24</i>	<i>25</i>	<i>26</i>	<i>27</i>	<i>28</i>	<i>29</i>	<i>30</i>
630	631	632	633	634	635	636	637	638	639	640	641	642	643	644
V	S	L	H	A	L	G	Q	G	H	I	C	G	A	S
<i>31</i>	<i>32</i>	<i>33</i>	<i>34</i>	<i>35</i>	<i>36</i>	<i>37</i>	<i>38</i>	<i>39</i>	<i>40</i>	<i>41</i>	<i>42</i>	<i>43</i>	<i>44</i>	<i>45</i>

645	646	647	648	649	650	651	652	653	654	655	656	657	658	659
L	I	S	P	N	W	L	V	S	A	A	H	C	Y	I
46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
660	661	662	663	664	665	666	667	668	669	670	671	672	673	674
D	D	R	G	F	R	Y	S	D	P	T	Q	W	T	A
60a	60b	60c	60d	60e	60f	60g	60h	60i	61	62	63	64	65	66
675	676	677	678	679	680	681	682	683	684	685	686	687	688	689
F	L	G	L	H	D	Q	S	Q	R	S	A	P	G	V
67	68	69	70	71	72	73	74	74a	75	76	77	78	79	80
690	691	692	693	694	695	696	697	698	699	700	701	702	703	704
Q	E	R	R	L	K	R	I	I	S	H	P	F	F	N
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95
705	706		707	708	709	710	711	712	713	714	715	716	717	718
D	F		T	F	D	Y	D	I	A	L	L	E	L	E
96	97	97a	98	99	100	101	102	103	104	105	106	107	108	109
719	720	721	722	723	724	725	726	727	728	729	730	731	732	733
K	P	A	E	Y	S	S	M	V	R	P	I	C	L	P
110	111	112	113	114	115	116	117	118	119	120	121	122	123	124
734	735	736	737	738	739	740	741	742	743	744	745	746	747	748
D	A	S	H	V	F	P	A	G	K	A	I	W	V	T
	126	127	128	129	130	131	132	133	134	135	136	137	138	139
749	750	751	752	753	754	755	756	757		758	759	760	761	762
G	W	G	H	T	Q	Y	G	G		T	G	A	L	I
140	141	142	143	144	145	146	147	148	149	150	151	152	153	154
763	764	765	766	767	768	769	770	771	772	773	774	775	776	777
L	Q	K	G	E	I	R	V	I	N	Q	T	T	C	E
155	156	157	158	159	160	161	162	163	164	165	166	167	168	169
778	779	780	781	782	783	784	785	786	787	788	789	790	791	792
N	L	L	P	Q	Q	I	T	P	R	M	M	C	V	G
170	171	172	173	174	175	176	177	178	179	180	181	182	183	184
793	794	795	796	797	798	799	800	801	802	803	804	805	806	807
F	L	S	G	G	V	D	S	C	Q	G	D	S	G	G
184a	185	186	186a	187	188	189	190	191	192	193	194	195	196	197
808	809	810	811	812	813	814	815	816	817	818	819	820	821	822
P	L	S	S	V	E	A	D	G	R	I	F	Q	A	G
198	199	200	201	202	203	204	204a	205	206	207	208	209	210	211

823	824	825	826	827	828	829	830	831	832	833	834	835	836	837
V	V	S	W	G	D	G	C	A	Q	R	N	K	P	G
212	213	214	215	216	217	218	219	220	221	222	223	224	225	226
838	839	840	841	842	843	844	845	846	847	848	849	850	851	852
V	Y	T	R	L	P	L	F	R	D	W	I	K	E	N
227	228	229	230	231	232	233	234	235	236	237	238	239	240	241
853	854	855												
T	G	V												
242	243	244												

As used herein, k_{cat} is a measure of the catalytic activity of an enzyme; the units of k_{cat} are seconds⁻¹. The reciprocal of k_{cat} is the time required by an enzyme molecule to "turn over" one substrate molecule; k_{cat} measures the number of substrate molecules turned over per enzyme molecule per second. k_{cat} also is called the turnover number.

As used herein, specificity for a target substrate refers to a preference for cleavage of a target substrate by a protease compared to a another substrate, referred to as a non-target substrate. Specificity is reflected in the specificity constant (k_{cat}/K_m), which is a measure of the affinity of a protease for its substrate and the efficiency of the enzyme. k_{cat}/K_m is a measure of enzyme efficiency; a large value of k_{cat} (rapid turnover) or a small value of K_m (high affinity for substrate) makes k_{cat}/K_m large.

As used herein, a specificity constant for cleavage is (k_{cat}/K_m), wherein K_m is the Michaelis-Menton constant ($[S]$ at one half V_{max}) and k_{cat} is the $V_{\text{max}}/[E_T]$, where E_T is the final enzyme concentration. The parameters k_{cat} , K_m and k_{cat}/K_m can be calculated by graphing the inverse of the substrate concentration versus the inverse of the velocity of substrate cleavage, and fitting to the Lineweaver-Burk equation ($1/\text{velocity}=(K_m/V_{\text{max}})(1/[S]) + 1/V_{\text{max}}$; where $V_{\text{max}}=[E_T]k_{\text{cat}}$). Any method to determine the rate of increase of cleavage over time in the presence of various concentrations of substrate can be used to calculate the specificity constant. For example, a substrate is linked to a fluorogenic moiety, which is released upon cleavage by a protease. By determining the rate of cleavage at different enzyme concentrations, k_{cat} can be determined for a particular protease. The specificity

constant can be used to determine the preference of a protease for one target substrate over another substrate.

As used herein, substrate specificity refers to the preference of a protease for one target substrate over another. Substrate specificity can be measured as a ratio of specificity constants.

As used herein, a substrate specificity ratio is the ratio of specificity constants and can be used to compare specificities of two or more proteases or a protease for two more substrates. For example, substrate specificity of a protease for competing substrates or of competing proteases for a substrate can be compared by comparing k_{cat}/K_m . For example, a protease that has a specificity constant of $2 \times 10^6 \text{ M}^{-1}\text{sec}^{-1}$ for a target substrate and $2 \times 10^4 \text{ M}^{-1}\text{sec}^{-1}$ for a non-target substrate is more specific for the target substrate. Using the specificity constants from above, the protease has a substrate specificity ratio of 100 for the target substrate.

As used herein, preference or substrate specificity for a target substrate can be expressed as a substrate specificity ratio. The particular value of the ratio that reflects a preference is a function of the substrates and proteases at issue. A substrate specificity ratio that is greater than 1 signifies a preference for a target substrate and a substrate specificity less than 1 signifies a preference for a non-target substrate. Generally, a ratio of at least or about 1 reflects a sufficient difference for a protease to be considered a candidate therapeutic.

As used herein, altered specificity refers to a change in substrate specificity of a modified protease compared to a starting wild type protease. Generally, the change in specificity is a reflection of the change in preference of a modified protease for a target substrate compared to a wild type substrate of the protease (herein referred to as a non-target substrate). Typically, modified MTSP-1 proteases provided herein exhibit increased substrate specificity for complement protein C3 compared to the substrate specificity of the wild type MTSP-1 protease. For example, a modified protease that has a substrate specificity ratio of 100 for a target substrate versus a non-target substrate exhibits a 10-fold increased specificity compared to a scaffold protease with a substrate specificity ratio of 10. In another example, a modified protease that has a substrate specificity ratio of 1 compared to a ratio of 0.1, exhibits a 10-fold increase in substrate specificity. To exhibit increased specificity compared to

a scaffold protease, a modified protease has a 1.5-fold, 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold or more greater substrate specificity for any one of more of the complement proteins.

As used herein, “selectivity” can be used interchangeably with specificity
5 when referring to the ability of a protease to choose and cleave one target substrate from among a mixture of competing substrates. Increased selectivity of a protease for a target substrate compared to any other one or more target substrates can be determined, for example, by comparing the specificity constants of cleavage of the target substrates by a protease. For example, if a protease has a specificity constant of
10 cleavage of $2 \times 10^6 \text{ M}^{-1}\text{sec}^{-1}$ for a target substrate and $2 \times 10^4 \text{ M}^{-1}\text{sec}^{-1}$ for any other one of more substrates, the protease is more selective for the target substrate.

As used herein, an “activity” or a “functional activity” of a polypeptide, such as a protease, refers to any activity exhibited by the polypeptide. Such activities can be empirically determined. Exemplary activities include, but are not limited to, ability
15 to interact with a biomolecule, for example, through substrate-binding, DNA binding, or dimerization, enzymatic activity, for example, kinase activity or proteolytic activity. For a protease (including protease fragments), activities include, but are not limited to, the ability to specifically bind a particular substrate, affinity and/or specificity of substrate-binding (*e.g.*, high or low affinity and/ or specificity), effector
20 functions, such as the ability to promote substrate (*e.g.*, protein, *i.e.* C3) inhibition, neutralization, cleavage or clearance, and *in vivo* activities, such as the ability to promote protein cleavage or clearance. Activity can be assessed *in vitro* or *in vivo* using recognized assays, such as ELISA, flow cytometry, surface plasmon resonance or equivalent assays to measure on- or off-rate, immunohistochemistry and
25 immunofluorescence histology and microscopy, cell-based assays, and binding assays. For example, for a protease, *e.g.*, a modified MTSP-1 protease, activities can be assessed by measuring substrate protein cleavage, turnover, residual activity, stability and/or levels *in vitro* and/or *in vivo*. The results of such *in vitro* assays that indicate that a polypeptide exhibits an activity can be correlated to activity of the
30 polypeptide *in vivo*, in which *in vivo* activity can be referred to as therapeutic activity, or biological activity. Activity of a modified polypeptide can be any level of percentage of activity of the unmodified polypeptide, including, but not limited to, at

or about 1% of the activity, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100%, 200%, 300%, 400%, 500%, or more of activity compared to the unmodified polypeptide. Assays to determine functionality or activity of modified (or variant) proteases are well-known in the art.

Functional activities include, but are not limited to, biological activity, catalytic or enzymatic activity, antigenicity (ability to bind to or compete with a polypeptide for binding to an anti-polypeptide antibody), immunogenicity, ability to form multimers, and the ability to specifically bind to a receptor or ligand for the polypeptide.

As used herein, a functional activity with reference to a complement protein refers to a complement-mediated function including, but not limited to, anaphylaxis, opsonization, chemotaxis, or cell lysis. Nonlimiting assays for testing activities of complement include hemolysis of red blood cells, and detection of complement effector molecules such as by ELISA or SDS-PAGE.

As used herein, catalytic activity or cleavage activity refers to the activity of a protease as assessed in *in vitro* proteolytic assays that detect proteolysis of a selected substrate. Cleavage activity can be measured by assessing catalytic efficiency of a protease.

As used herein, activity towards a target substrate refers to cleavage activity and/or functional activity, or other measurement that reflects the activity of a protease on or towards a target substrate. A functional activity of a complement protein target substrate by a protease can be measured by assessing an IC_{50} in a complement assay such as red blood cell lysis, or other such assays known by one of skill in the art or provided herein to assess complement activity. Cleavage activity can be measured by assessing catalytic efficiency of a protease. For purposes herein, an activity is increased if a protease exhibits greater proteolysis or cleavage of a target substrate and/or modulates (*i.e.*, activates or inhibits) a functional activity of a complement protein as compared to in the absence of the protease.

As used herein, "increased activity" with reference to a modified MTSP-1 polypeptide means that, when tested under the same conditions, the modified MTSP-1 polypeptide exhibits greater activity compared to an unmodified MTSP-1 polypeptide

not containing the amino acid replacement(s). For example, a modified MTSP-1 polypeptide exhibits at least or about at least 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more of the activity of the unmodified or reference MTSP-1 polypeptide.

As used herein, the term “the same,” when used in reference to antibody binding affinity, means that the EC_{50} , association constant (K_a) or dissociation constant (K_d) is within about 1 to 100 fold or 1 to 10 fold of that of the reference antibody (1-100 fold greater affinity or 1-100 fold less affinity, or any numerical value or range or value within such ranges, than the reference antibody).

As used herein, binding activity refers to characteristics of a molecule, *e.g.*, a polypeptide, relating to whether or not, and how, it binds one or more binding partners. Binding activities include the ability to bind the binding partner(s), the affinity with which it binds to the binding partner (*e.g.*, high affinity), the strength of the bond with the binding partner and/or specificity for binding with the binding partner.

As used herein, EC_{50} , also called the apparent K_d , is the concentration (*e.g.*, nM) of protease, where 50% of the maximal activity is observed on a fixed amount of substrate (*e.g.*, the concentration of modified MTSP-1 polypeptide required to cleave through 50% of the available hC3). Typically, EC_{50} values are determined from sigmoidal dose-response curves, where the EC_{50} is the concentration at the inflection point. A high protease affinity for its substrate correlates with a low EC_{50} value and a low affinity corresponds to a high EC_{50} value. Affinity constants can be determined by standard kinetic methodology for protease reactions, for example, immunoassays, such as ELISA, followed by curve-fitting analysis.

As used herein, “affinity constant” refers to an association constant (K_a) used to measure the affinity or molecular binding strength between a protease and a substrate. The higher the affinity constant the greater the affinity of the protease for the substrate. Affinity constants are expressed in units of reciprocal molarity (*i.e.*, M⁻¹) and can be calculated from the rate constant for the association-dissociation reaction as measured by standard kinetic methodology for protease-substrate reactions (*e.g.*, immunoassays, surface plasmon resonance, or other kinetic interaction assays).

known in the art). The binding affinity of an protease also can be expressed as a dissociation constant, or K_d . The dissociation constant is the reciprocal of the association constant, $K_d = 1/K_a$. Hence, an affinity constant also can be represented by the K_d . Affinity constants can be determined by standard kinetic methodology for protease reactions, for example, immunoassays, surface plasmon resonance (SPR) (Rich and Myszka (2000) *Curr. Opin. Biotechnol* 11:54; Englebienne (1998) *Analyst* 123:1599), isothermal titration calorimetry (ITC) or other kinetic interaction assays known in the art (see, *e.g.*, Paul, ed., *Fundamental Immunology*, 2nd ed., Raven Press, New York, pages 332-336 (1989)). Instrumentation and methods for real time detection and monitoring of binding rates are known and are commercially available (*e.g.*, BIAcore 2000, BIAcore AB, Uppsala, Sweden and GE Healthcare Life Sciences; Malmqvist (2000) *Biochem. Soc. Trans.* 27:335).

Methods for calculating affinity are well-known, such as methods for determining EC_{50} values or methods for determining association/dissociation constants. For example, in terms of EC_{50} , high binding affinity means that the protease specifically binds to a target protein with an EC_{50} that is less than about 10 ng/mL, 9 ng/mL, 8 ng/mL, 7 ng/mL, 6 ng/mL, 5 ng/mL, 4 ng/mL, 3 ng/mL, 2 ng/mL, 1 ng/mL or less. High binding affinity also can be characterized by an equilibrium dissociation constant (K_d) of 10^{-6} M or lower, such as 10^{-7} M, 10^{-8} M, 10^{-10} M, 10^{-11} M or 10^{-12} M or lower. In terms of equilibrium association constant (K_a), high binding affinity is generally associated with K_a values of greater than or equal to about 10^6 M⁻¹, greater than or equal to about 10^7 M⁻¹, greater than or equal to about 10^8 M⁻¹, or greater than or equal to about 10^9 M⁻¹, 10^{10} M⁻¹, 10^{11} M⁻¹ or 10^{12} M⁻¹. Affinity can be estimated empirically or affinities can be determined comparatively, *e.g.*, by comparing the affinity of two or more antibodies for a particular antigen, for example, by calculating pairwise ratios of the affinities of the antibodies tested. For example, such affinities can be readily determined using conventional techniques, such as by ELISA; equilibrium dialysis; surface plasmon resonance; by radioimmunoassay using radiolabeled target antigen; or by another method known to the skilled artisan. The affinity data can be analyzed, for example, by the method of Scatchard *et al.*, *Ann N.Y. Acad. Sci.*, 51:660 (1949) or by curve fitting analysis, for example, using a 4 Parameter Logistic nonlinear regression model using the equation: $y = ((A -$

$D/(1+((x/C)^B))) + D$, where A is the minimum asymptote, B is the slope factor, C is the inflection point (EC_{50}), and D is the maximum asymptote.

As used herein, "ED₅₀" is the dose (*e.g.*, mg/kg or nM) of a protease (*e.g.*, a modified MTSP-1 protease) that produces a specified result (*e.g.*, cleavage of the complement protein C3) in 50% of the total population (*e.g.*, total amount of C3 present in the sample).

As used herein, "substantially the same" when used in reference to EC_{50} , association constant (K_a) or dissociation constant (K_d), or ED₅₀ effective dose means that the K_a , K_d , EC_{50} or ED₅₀ is within about 5 to 5000 fold greater or less than the K_a , K_d , EC_{50} or ED₅₀, of the reference MTSP-1 (5-5000 fold greater or 5-5000 fold less than the reference MTSP-1, *i.e.*, wild-type MTSP-1).

As used herein, the term "surface plasmon resonance" refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example, using the BIAcore system (GE Healthcare Life Sciences).

As used herein, a human protein is one encoded by a nucleic acid molecule, such as DNA, present in the genome of a human, including all allelic variants and conservative variations thereof. A variant or modification of a protein is a human protein if the modification is based on the wild type or prominent sequence of a human protein.

As used herein, the residues of naturally occurring α -amino acids are the residues of those 20 α -amino acids found in nature which are incorporated into protein by the specific recognition of the charged tRNA molecule with its cognate mRNA codon in humans.

As used herein, non-naturally occurring amino acids refer to amino acids that are not genetically encoded.

As used herein, "nucleic acid" refers to at least two linked nucleotides or nucleotide derivatives, including a deoxyribonucleic acid (DNA) and a ribonucleic acid (RNA) and analogs thereof, joined together, typically by phosphodiester linkages. Also included in the term "nucleic acid" are analogs of nucleic acids such as peptide nucleic acid (PNA), phosphorothioate DNA, and other such analogs and derivatives or combinations thereof. Nucleic acids also include DNA and RNA

derivatives containing, for example, a nucleotide analog or a "backbone" bond other than a phosphodiester bond, for example, a phosphotriester bond, a phosphoramidate bond, a phosphorothioate bond, a thioester bond, or a peptide bond (peptide nucleic acid). The term also includes, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, single (sense or antisense) and double-stranded nucleic acids. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine and deoxythymidine. For RNA, the uracil base is uridine. Nucleic acids can be single or double-stranded. When referring to probes or primers, which are optionally labeled, such as with a detectable label, such as a fluorescent or radiolabel, single-stranded molecules are contemplated. Such molecules are typically of a length such that their target is statistically unique or of low copy number (typically less than 5, generally less than 3) for probing or priming a library. Generally a probe or primer contains at least 14, 16 or 30 contiguous nucleotides of sequence complementary to or identical to a gene of interest. Probes and primers can be 10, 20, 30, 50, 100 or more nucleotides long.

As used herein, an isolated nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. An "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. Exemplary isolated nucleic acid molecules provided herein include isolated nucleic acid molecules encoding a MTSP-1 protease provided.

As used herein, "synthetic," with reference to, for example, a synthetic nucleic acid molecule or a synthetic gene or a synthetic peptide refers to a nucleic acid molecule or polypeptide molecule that is produced by recombinant methods and/or by chemical synthesis methods.

As used herein, "polypeptide" refers to two or more amino acids covalently joined. The terms "polypeptide" and "protein" are used interchangeably herein.

As used herein, a "peptide" refers to a polypeptide that is from 2 to about or 40 amino acids in length.

As used herein, the amino acids which occur in the various sequences of amino acids provided herein are identified according to their known, three-letter or one-letter abbreviations (Table 2). The nucleotides which occur in the various nucleic acid fragments are designated with the standard single-letter designations used

5 routinely in the art.

As used herein, an “amino acid” is an organic compound containing an amino group and a carboxylic acid group. A polypeptide contains two or more amino acids. For purposes herein, amino acids include the twenty naturally-occurring amino acids (Table 2), non-natural amino acids and amino acid analogs (*i.e.*, amino acids wherein the α -carbon has a side chain).

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As used herein, the amino acids, which occur in the various amino acid sequences of polypeptides herein, are identified according to their well-known, three-letter or one-letter abbreviations (see Table 2). The nucleotides, which occur in the various nucleic acid molecules and fragments, are designated with the standard single-

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As used herein, “amino acid residue” refers to an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are presumed to be in the “L” isomeric form. Residues in the “D” isomeric form, which are so designated, can be substituted for any L-amino acid residue as long as the desired functional property is retained by the polypeptide. NH_2 refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in *J. Biol. Chem.*, 243: 3557-3559 (1968), and adopted in 37 C.F.R. §§ 1.821-1.822,

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25 abbreviations for amino acid residues are shown in Table 2:

Table 2 – Table of Correspondence

SYMBOL		
1-Letter	3-Letter	AMINO ACID
Y	Tyr	Tyrosine
G	Gly	Glycine
F	Phe	Phenylalanine
M	Met	Methionine
A	Ala	Alanine
S	Ser	Serine
I	Ile	Isoleucine

SYMBOL		
1-Letter	3-Letter	AMINO ACID
L	Leu	Leucine
T	Thr	Threonine
V	Val	Valine
P	Pro	Proline
K	Lys	Lysine
H	His	Histidine
Q	Gln	Glutamine
E	Glu	Glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	Tryptophan
R	Arg	Arginine
D	Asp	Aspartic acid
N	Asn	Asparagine
B	Asx	Asn and/or Asp
C	Cys	Cysteine
X	Xaa	Unknown or other

All sequences of amino acid residues represented herein by a formula have a left to right orientation in the conventional direction of amino-terminus to carboxyl-terminus. In addition, the phrase “amino acid residue” is defined to include the amino acids listed in the Table of Correspondence (Table 2), modified, non-natural and unusual amino acids. Furthermore, a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues or to an amino-terminal group such as NH_2 or to a carboxyl-terminal group such as COOH .

As used herein, “naturally occurring amino acids” refer to the 20 L-amino acids that occur in polypeptides. As used herein, the residues of naturally occurring α -amino acids are the residues of those 20 α -amino acids found in nature which are incorporated into protein by the specific recognition of the charged tRNA molecule with its cognate mRNA codon in humans.

As used herein, “non-natural amino acid” refers to an organic compound that has a structure similar to a natural amino acid but has been modified structurally to mimic the structure and reactivity of a natural amino acid. Non-naturally occurring amino acids, thus, include, for example, amino acids or analogs of amino acids other than the 20 naturally occurring amino acids and include, but are not limited to, the D-stereoisomers of amino acids. Exemplary non-natural amino acids are known to those

of skill in the art, and include, but are not limited to, para-acetyl Phenylalanine, para-azido Phenylalanine, 2-Aminoadipic acid (Aad), 3-Aminoadipic acid (bAad), β -alanine/ β -Amino-propionic acid (Bala), 2-Aminobutyric acid (Abu), 4-Aminobutyric acid/piperidinic acid (4Abu), 6-Aminocaproic acid (Acp), 2-Aminoheptanoic acid (Ahe), 2-Aminoisobutyric acid (Aib), 3-Aminoisobutyric acid (Baib), 2-Aminopimelic acid (Apm), 2,4-Diaminobutyric acid (Dbu), Desmosine (Des), 2,2'-Diaminopimelic acid (Dpm), 2,3-Diaminopropionic acid (Dpr), N-Ethylglycine (EtGly), N-Ethylasparagine (EtAsn), Hydroxylysine (Hyl), allo-Hydroxylysine (Ahyl), 3-Hydroxyproline (3Hyp), 4-Hydroxyproline (4Hyp), Isodesmosine (Ide), allo-Isoleucine (Aile), N-Methylglycine, sarcosine (MeGly), N-Methylisoleucine (MeIle), 6-N-Methyllysine (MeLys), N-Methylvaline (MeVal), Norvaline (Nva), Norleucine (Nle), and Ornithine (Orn). Exemplary non-natural amino acids are described herein and are known to those of skill in the art.

As used herein, an isokinetic mixture is one in which the molar ratios of amino acids has been adjusted based on their reported reaction rates (see, *e.g.*, Ostresh *et al.* (1994) *Biopolymers* 34:1681).

As used herein, a DNA construct is a single or double stranded, linear or circular DNA molecule that contains segments of DNA combined and juxtaposed in a manner not found in nature. DNA constructs exist as a result of human manipulation, and include clones and other copies of manipulated molecules.

As used herein, a DNA segment is a portion of a larger DNA molecule having specified attributes. For example, a DNA segment encoding a specified polypeptide is a portion of a longer DNA molecule, such as a plasmid or plasmid fragment, which, when read from the 5' to 3' direction, encodes the sequence of amino acids of the specified polypeptide.

As used herein, the term ortholog means a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

As used herein, the term polynucleotide means a single- or double-stranded polymer of deoxyribonucleotides or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and can be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic

molecules. The length of a polynucleotide molecule is given herein in terms of nucleotides (abbreviated “nt”) or base pairs (abbreviated “bp”). The term nucleotides is used for single- and double-stranded molecules where the context permits. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term base pairs. It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide can differ slightly in length and that the ends thereof can be staggered; thus all nucleotides within a double-stranded polynucleotide molecule cannot be paired. Such unpaired ends will, in general, not exceed 20 nucleotides in length.

As used herein, alignment of a sequence refers to the use of homology to align two or more sequences of nucleotides or amino acids. Typically, two or more sequences that are related by 50% or more identity are aligned. An aligned set of sequences refers to 2 or more sequences that are aligned at corresponding positions and can include aligning sequences derived from RNAs, such as ESTs and other cDNAs, aligned with genomic DNA sequence. Related or variant polypeptides or nucleic acid molecules can be aligned by any method known to those of skill in the art. Such methods typically maximize matches, and include methods, such as using manual alignments and by using the numerous alignment programs available (*e.g.*, BLASTP) and others known to those of skill in the art. By aligning the sequences of polypeptides or nucleic acids, one skilled in the art can identify analogous portions or positions, using conserved and identical amino acid residues as guides. Further, one skilled in the art also can employ conserved amino acid or nucleotide residues as guides to find corresponding amino acid or nucleotide residues between and among human and non-human sequences. Corresponding positions also can be based on structural alignments, for example by using computer simulated alignments of protein structure. In other instances, corresponding regions can be identified. One skilled in the art also can employ conserved amino acid residues as guides to find corresponding amino acid residues between and among human and non-human sequences.

As used herein, “sequence identity” refers to the number of identical or similar amino acids or nucleotide bases in a comparison between a test and a reference polypeptide or polynucleotide. Sequence identity can be determined by sequence alignment of nucleic acid or protein sequences to identify regions of similarity or

identity. For purposes herein, sequence identity is generally determined by alignment to identify identical residues. The alignment can be local or global. Matches, mismatches and gaps can be identified between compared sequences. Gaps are null amino acids or nucleotides inserted between the residues of aligned sequences so that identical or similar characters are aligned. Generally, there can be internal and terminal gaps. Sequence identity can be determined by taking into account gaps as the number of identical residues/ length of the shortest sequence x 100. When using gap penalties, sequence identity can be determined with no penalty for end gaps (*e.g.*, terminal gaps are not penalized). Alternatively, sequence identity can be determined without taking into account gaps as the number of identical positions/length of the total aligned sequence x 100.

As used herein, “at a position corresponding to” or recitation that nucleotides or amino acid positions “correspond to” nucleotides or amino acid positions in a disclosed sequence, such as set forth in the Sequence listing, refers to nucleotides or amino acid positions identified upon alignment with the disclosed sequence to maximize identity using a standard alignment algorithm, such as the GAP algorithm. For purposes herein, alignment of a MTSP-1 sequence is to the amino acid sequence of the protease domain of human MTSP-1 set forth in SEQ ID NO: 2, or particularly a reference MTSP-1 of SEQ ID NO:4. By aligning the sequences, one skilled in the art can identify corresponding residues, for example, using conserved and identical amino acid residues as guides. In general, to identify corresponding positions, the sequences of amino acids are aligned so that the highest order match is obtained (see, *e.g.*: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part I*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo *et al.* (1988) *SIAM J Applied Math* 48:1073). Alternatively, the skilled person can number the residues by chymotrypsin number, thereby identify corresponding residues. For closely related sequences, a computer algorithm is not needed; alignment can be done visually.

As used herein, a “global alignment” is an alignment that aligns two sequences from beginning to end, aligning each letter in each sequence only once. An alignment is produced, regardless of whether or not there is similarity or identity between the sequences. For example, 50% sequence identity based on “global alignment” means that in an alignment of the full sequence of two compared sequences each of 100 nucleotides in length, 50% of the residues are the same. It is understood that global alignment also can be used in determining sequence identity even when the length of the aligned sequences is not the same. The differences in the terminal ends of the sequences will be taken into account in determining sequence identity, unless the “no penalty for end gaps” is selected. Generally, a global alignment is used on sequences that share significant similarity over most of their length. Exemplary algorithms for performing global alignment include the Needleman-Wunsch algorithm (Needleman *et al.* (1970) *J. Mol. Biol.* 48: 443). Exemplary programs for performing global alignment are publicly available and include the Global Sequence Alignment Tool available at the National Center for Biotechnology Information (NCBI) website (ncbi.nlm.nih.gov/), and the program available at deepc2.psi.iastate.edu/aat/align/align.html.

As used herein, a “local alignment” is an alignment that aligns two sequence, but only aligns those portions of the sequences that share similarity or identity. Hence, a local alignment determines if sub-segments of one sequence are present in another sequence. If there is no similarity, no alignment will be returned. Local alignment algorithms include BLAST or Smith-Waterman algorithm (*Adv. Appl. Math.* 2: 482 (1981)). For example, 50% sequence identity based on “local alignment” means that in an alignment of the full sequence of two compared sequences of any length, a region of similarity or identity of 100 nucleotides in length has 50% of the residues that are the same in the region of similarity or identity.

For purposes herein, sequence identity can be determined by standard alignment algorithm programs used with default gap penalties established by each supplier. Default parameters for the GAP program can include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov *et al.* (1986) *Nucl. Acids Res.* 14: 6745, as described by Schwartz and Dayhoff, eds., *Atlas of Protein Sequence and Structure*,

National Biomedical Research Foundation, pp. 353-358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps. Whether any two nucleic acid molecules have nucleotide sequences or any two polypeptides have amino acid sequences that are at least 80%,
5 85%, 90%, 95%, 96%, 97%, 98% or 99% "identical," or other similar variations reciting a percent identity, can be determined using known computer algorithms based on local or global alignment (*see e.g.*,
wikipedia.org/wiki/Sequence_alignment_software, providing links to dozens of known and publicly available alignment databases and programs). Generally, for
10 purposes herein sequence identity is determined using computer algorithms based on global alignment, such as the Needleman-Wunsch Global Sequence Alignment tool available from NCBI/BLAST
(blast.ncbi.nlm.nih.gov/Blast.cgi?CMD=Web&Page_TYPE=BlastHome); LAlign (William Pearson implementing the Huang and Miller algorithm (*Adv. Appl. Math.*
15 (1991) 12:337-357)); and the program from Xiaoqui Huang available at
deepc2.psi.iastate.edu/aat/align/align.html. Generally, when comparing nucleotide sequences herein, an alignment with penalty for end gaps is used. Local alignment also can be used when the sequences being compared are substantially the same length.

20 Therefore, as used herein, the term "identity" represents a comparison or alignment between a test and a reference polypeptide or polynucleotide. In one non-limiting example, "at least 90% identical to" refers to percent identities from 90% to 100% relative to the reference polypeptide or polynucleotide. Identity at a level of 90% or more is indicative of the fact that, assuming for exemplification purposes a
25 test and reference polypeptide or polynucleotide length of 100 amino acids or nucleotides are compared, no more than 10% (*i.e.*, 10 out of 100) of amino acids or nucleotides in the test polypeptide or polynucleotide differs from that of the reference polypeptides. Similar comparisons can be made between a test and reference polynucleotides. Such differences can be represented as point mutations randomly
30 distributed over the entire length of an amino acid sequence or they can be clustered in one or more locations of varying length up to the maximum allowable, *e.g.*, 10/100 amino acid difference (approximately 90% identity). Differences also can be due to

deletions or truncations of amino acid residues. Differences are defined as nucleic acid or amino acid substitutions, insertions or deletions. Depending on the length of the compared sequences, at the level of homologies or identities above about 85-90%, the result can be independent of the program and gap parameters set; such high levels of identity can be assessed readily, often without relying on software.

As used herein, a disulfide bond (also called an S-S bond or a disulfide bridge) is a single covalent bond derived from the coupling of thiol groups. Disulfide bonds in proteins are formed between the thiol groups of cysteine residues, and stabilize interactions between polypeptide domains.

As used herein, “coupled” or “conjugated” means attached via a covalent or noncovalent interaction.

As used herein, “primer” refers to a nucleic acid molecule that can act as a point of initiation of template-directed DNA synthesis under appropriate conditions (*e.g.*, in the presence of four different nucleoside triphosphates and a polymerization agent, such as DNA polymerase, RNA polymerase or reverse transcriptase) in an appropriate buffer and at a suitable temperature. It will be appreciated that certain nucleic acid molecules can serve as a “probe” and as a “primer.” A primer, however, has a 3' hydroxyl group for extension. A primer can be used in a variety of methods, including, for example, polymerase chain reaction (PCR), reverse-transcriptase (RT)-PCR, RNA PCR, LCR, multiplex PCR, panhandle PCR, capture PCR, expression PCR, 3' and 5' RACE, *in situ* PCR, ligation-mediated PCR and other amplification protocols.

As used herein, “primer” refers to an oligonucleotide containing two or more deoxyribonucleotides or ribonucleotides, typically more than three, from which synthesis of a primer extension product can be initiated. Experimental conditions conducive to synthesis include the presence of nucleoside triphosphates and an agent for polymerization and extension, such as DNA polymerase, and a suitable buffer, temperature and pH.

As used herein, “primer pair” refers to a set of primers that includes a 5' (upstream) primer that hybridizes with the 5' end of a sequence to be amplified (*e.g.* by PCR) and a 3' (downstream) primer that hybridizes with the complement of the 3' end of the sequence to be amplified.

As used herein, "specifically hybridizes" refers to annealing, by complementary base-pairing, of a nucleic acid molecule (*e.g.* an oligonucleotide) to a target nucleic acid molecule. Those of skill in the art are familiar with *in vitro* and *in vivo* parameters that affect specific hybridization, such as length and composition of the particular molecule. Parameters particularly relevant to *in vitro* hybridization further include annealing and washing temperature, buffer composition and salt concentration. Exemplary washing conditions for removing non-specifically bound nucleic acid molecules at high stringency are 0.1 x SSPE, 0.1% SDS, 65°C, and at medium stringency are 0.2 x SSPE, 0.1% SDS, 50°C. Equivalent stringency conditions are known in the art. The skilled person can readily adjust these parameters to achieve specific hybridization of a nucleic acid molecule to a target nucleic acid molecule appropriate for a particular application.

As used herein, substantially identical to a product means sufficiently similar so that the property of interest is sufficiently unchanged so that the substantially identical product can be used in place of the product.

As used herein, it also is understood that the terms "substantially identical" or "similar" varies with the context as understood by those skilled in the relevant art.

As used herein, the wild-type form of a polypeptide or nucleic acid molecule is a form encoded by a gene or by a coding sequence encoded by the gene. Typically, a wild-type form of a gene, or molecule encoded thereby, does not contain mutations or other modifications that alter function or structure. The term wild-type also encompasses forms with allelic variation as occurs among and between species.

As used herein, a predominant form of a polypeptide or nucleic acid molecule refers to a form of the molecule that is the major form produced from a gene. A "predominant form" varies from source to source. For example, different cells or tissue types can produce different forms of polypeptides, for example, by alternative splicing and/or by alternative protein processing. In each cell or tissue type, a different polypeptide can be a "predominant form."

As used herein, an allelic variant or allelic variation references any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and can result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the

encoded polypeptide) or can encode polypeptides having altered amino acid sequence. The term “allelic variant” also is used herein to denote a protein encoded by an allelic variant of a gene. Typically the reference form of the gene encodes a wild type form and/or predominant form of a polypeptide from a population or single reference member of a species. Typically, allelic variants, which include variants between and among species, have at least 80%, 90% or greater amino acid identity with a wild type and/or predominant form from the same species; the degree of identity depends upon the gene and whether comparison is interspecies or intraspecies. Generally, intraspecies allelic variants have at least or at least about 80%, 85%, 90% or 95% identity or greater with a wild type and/or predominant form, including at least or at least about 96%, 97%, 98%, 99% or greater identity with a wild type and/or predominant form of a polypeptide.

As used herein, “allele,” which is used interchangeably herein with “allelic variant” refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for that gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide or several nucleotides, and can include substitutions, deletions and insertions of nucleotides. An allele of a gene also can be a form of a gene containing a mutation.

As used herein, species variants refer to variants in polypeptides among different species, including different mammalian species, such as mouse and human. Generally, species variants have about or at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or more sequence identity. Corresponding residues between and among species variants can be determined by comparing and aligning sequences to maximize the number of matching nucleotides or residues, for example, such that identity between the sequences is equal to or greater than 95%, equal to or greater than 96%, equal to or greater than 97%, equal to or greater than 98% or equal to greater than 99%. The position of interest is then given the number assigned in the reference nucleic acid molecule. Alignment can be

effected manually or by eye, particularly, where sequence identity is greater than 80%.

As used herein, a splice variant refers to a variant produced by differential processing of a primary transcript of genomic DNA that results in more than one type
5 of mRNA.

As used herein, modification is in reference to modification of a sequence of amino acids of a polypeptide or a sequence of nucleotides in a nucleic acid molecule and includes deletions, insertions, and replacements of amino acids and nucleotides, respectively.

10 For purposes herein, amino acid substitutions, deletions and/or insertions, can be made in any of MTSP-1 polypeptide or catalytically active fragment thereof provided that the resulting protein exhibits protease activity or other activity (or, if desired, such changes can be made to eliminate activity). Modifications can be made by making conservative amino acid substitutions and also non-conservative amino
15 acid substitutions. For example, amino acid substitutions that desirably or advantageously alter properties of the proteins can be made. In one embodiment, mutations that prevent degradation of the polypeptide can be made. Many proteases cleave after basic residues, such as R and K; to eliminate such cleavage, the basic residue is replaced with a non-basic residue. Interaction of the protease with an
20 inhibitor can be blocked while retaining catalytic activity by effecting a non-conservative change at the site of interaction of the inhibitor with the protease. Other activities also can be altered. For example, receptor binding can be altered without altering catalytic activity.

Amino acid substitutions contemplated include conservative substitutions,
25 such as those set forth in Table 3, which do not eliminate proteolytic activity. As described herein, substitutions that alter properties of the proteins, such as removal of cleavage sites and other such sites also are contemplated; such substitutions are generally non-conservative, but can be readily effected by those of skill in the art.

As used herein, suitable conservative substitutions of amino acids are known
30 to those of skill in this art and can be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not

substantially alter biological activity (see, *e.g.*, Watson *et al.* Molecular Biology of the Gene, 4th Edition, 1987, The Benjamin/Cummings Pub. Co., p.224). Such substitutions can be made in accordance with those set forth in Table 3 as follows:

Table 3	
Original residue	Exemplary conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys
Asn (N)	Gln; His
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
Gly (G)	Ala; Pro
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; Gln; Glu
Met (M)	Leu; Tyr; Ile
Phe (F)	Met; Leu; Tyr
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

Other substitutions also are permissible and can be determined empirically or in accord with known conservative substitutions.

As used herein, the term promoter means a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding region of genes.

As used herein, isolated or purified polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell of tissue from which the protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. Preparations can be determined to be substantially free if they appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis and high performance liquid chromatography (HPLC), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical

and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound, however, can be a mixture of stereoisomers. In such instances, further
5 purification might increase the specific activity of the compound.

The term substantially free of cellular material includes preparations of proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the term substantially free of cellular material includes preparations of protease proteins having
10 less than about 30% (by dry weight) of non-protease proteins (also referred to herein as a contaminating protein), generally less than about 20% of non-protease proteins or 10% of non-protease proteins or less than about 5% of non-protease proteins. When the protease protein or active portion thereof is recombinantly produced, it also is substantially free of culture medium, *i.e.*, culture medium represents less than, about,
15 or equal to 20%, 10% or 5% of the volume of the protease protein preparation.

As used herein, the term substantially free of chemical precursors or other chemicals includes preparations of protease proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. The term includes preparations of protease proteins having less than about
20 30% (by dry weight), 20%, 10%, 5% or less of chemical precursors or non-protease chemicals or components.

As used herein, production by recombinant means by using recombinant DNA methods refers to the use of the well-known methods of molecular biology for expressing proteins encoded by cloned DNA.

25 As used herein, “expression” refers to the process by which polypeptides are produced by transcription and translation of polynucleotides. The level of expression of a polypeptide can be assessed using any method known in art, including, for example, methods of determining the amount of the polypeptide produced from the host cell. Such methods can include, but are not limited to, quantitation of the
30 polypeptide in the cell lysate by ELISA, Coomassie Blue staining following gel electrophoresis, Lowry protein assay and Bradford protein assay.

As used herein, a “host cell” is a cell that is used to receive, maintain, reproduce and/or amplify a vector. Host cells also can be used to express the polypeptide encoded by the vector. The nucleic acid contained in the vector is replicated when the host cell divides, thereby amplifying the nucleic acids.

5 As used herein, a “vector” or “plasmid” is a replicable nucleic acid from which one or more heterologous proteins can be expressed when the vector is transformed into an appropriate host cell. Reference to a vector includes discrete elements that are used to introduce heterologous nucleic acid into cells for either expression or replication thereof. Reference to a vector also includes those vectors into which a
10 nucleic acid encoding a polypeptide or fragment thereof can be introduced, typically by restriction digest and ligation. Reference to a vector also includes those vectors that contain nucleic acid encoding a protease, such as a modified MTSP-1. The vector is used to introduce the nucleic acid encoding the polypeptide into the host cell for amplification of the nucleic acid or for expression/display of the polypeptide encoded
15 by the nucleic acid. The vectors typically remain episomal, but can be designed to effect integration of a gene or portion thereof into a chromosome of the genome. Also contemplated are vectors that are artificial chromosomes, such as yeast artificial chromosomes and mammalian artificial chromosomes. Selection and use of such vehicles are well-known to those of skill in the art. A vector also includes “virus
20 vectors” and “viral vectors.”

 As used herein, an “expression vector” includes vectors capable of expressing DNA that is operatively linked with regulatory sequences, such as promoter regions, that are capable of effecting expression of such DNA fragments. Such additional segments can include promoter and terminator sequences, and optionally can include
25 one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, and the like. Expression vectors are generally derived from plasmid or viral DNA, or can contain elements of both. Thus, an expression vector refers to a recombinant DNA or RNA construct, such as a plasmid, a phage, recombinant virus or other vector that, upon introduction into an appropriate host cell,
30 results in expression of the cloned DNA. Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic

cells and/or prokaryotic cells and those that remain episomal or those which integrate into the host cell genome.

As used herein, vector also includes “virus vectors” or “viral vectors.” Viral vectors are engineered viruses, eukaryotic and prokaryotic, that can contain
5 heterologous nucleic acid, to effect transfer and expression of thereof in host cells. Viral vectors are characterized as eukaryotic and prokaryotic based upon the host infected by the virus from which the vector is derived, and the type of RNA polymerase (eukaryotic or prokaryotic) that recognizes the viral promoters. Hence, for example, a vector derived from adenovirus is a eukaryotic vector.

10 As used herein, an adenovirus refers to any of a group of DNA-containing viruses that cause conjunctivitis and upper respiratory tract infections in humans. As used herein, naked DNA refers to histone-free DNA that can be used for vaccines and gene therapy. Naked DNA is the genetic material that is passed from cell to cell during a gene transfer processed called transformation. In transformation, purified or
15 naked DNA is taken up by the recipient cell which will give the recipient cell a new characteristic or phenotype.

As used herein, “operably linked” with reference to nucleic acid sequences, regions, elements or domains means that the nucleic acid regions are functionally related to each other. For example, nucleic acid encoding a leader peptide can be
20 operably linked to nucleic acid encoding a polypeptide, whereby the nucleic acids can be transcribed and translated to express a functional fusion protein, wherein the leader peptide effects secretion of the fusion polypeptide. In some instances, the nucleic acid encoding a first polypeptide (*e.g.*, a leader peptide) is operably linked to nucleic acid encoding a second polypeptide and the nucleic acids are transcribed as a single
25 mRNA transcript, but translation of the mRNA transcript can result in one of two polypeptides being expressed. For example, an amber stop codon can be located between the nucleic acid encoding the first polypeptide and the nucleic acid encoding the second polypeptide, such that, when introduced into a partial amber suppressor cell, the resulting single mRNA transcript can be translated to produce either a fusion
30 protein containing the first and second polypeptides, or can be translated to produce only the first polypeptide. In another example, a promoter can be operably linked to

nucleic acid encoding a polypeptide, whereby the promoter regulates or mediates the transcription of the nucleic acid.

As used herein, “primary sequence” refers to the sequence of amino acid residues in a polypeptide or the sequence of nucleotides in a nucleic acid molecule.

5 As used herein, protein binding sequence refers to a protein or peptide sequence that is capable of specific binding to other protein or peptide sequences generally, to a set of protein or peptide sequences or to a particular protein or peptide sequence.

As used herein, a “tag” or an “epitope tag” refers to a sequence of amino acids, typically added to the N- or C- terminus of a polypeptide, such as a MTSP-1
10 provided herein. The inclusion of tags fused to a polypeptide can facilitate polypeptide purification and/or detection. Typically, a tag or tag polypeptide refers to a polypeptide that has enough residues to provide an epitope recognized by an antibody or can serve for detection or purification, yet is short enough such that it
15 does not interfere with activity of the polypeptide to which it is linked. The tag polypeptide typically is sufficiently unique so that an antibody that specifically binds thereto does not substantially cross-react with epitopes in the polypeptide to which it is linked. Epitope tagged proteins can be affinity purified using highly specific antibodies raised against the tags.

20 Suitable tag polypeptides generally have at least 5 or 6 amino acid residues and usually between about 8-50 amino acid residues, typically between 9-30 residues. The tags can be linked to one or more proteins and permit detection of the protein or its recovery from a sample or mixture. Such tags are well-known and can be readily synthesized and designed. Exemplary tag polypeptides include those used for affinity
25 purification and include, Small Ubiquitin-like Modifier (SUMO) tags, FLAG tags, His tags, the influenza hemagglutinin (HA) tag polypeptide and its antibody 12CA5, (Field *et al.* (1988) *Mol. Cell. Biol.* 8:2159-2165); the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto (see, *e.g.*, Evan *et al.* (1985) *Molecular and Cellular Biology* 5 :3610-3616); and the Herpes Simplex virus glycoprotein D
30 (gD) tag and its antibody (Paborsky *et al.* (1990) *Protein Engineering* 3:547-553). An antibody used to detect an epitope-tagged antibody is typically referred to herein as a secondary antibody.

As used herein, metal binding sequence refers to a protein or peptide sequence that is capable of specific binding to metal ions generally, to a set of metal ions or to a particular metal ion.

As used herein the term assessing is intended to include quantitative and
5 qualitative determination in the sense of obtaining an absolute value for the activity of a protease, or a domain thereof, present in the sample, and also of obtaining an index, ratio, percentage, visual or other value indicative of the level of the activity. Assessment can be direct or indirect and the chemical species actually detected need not of course be the proteolysis product itself but can for example be a derivative
10 thereof or some further substance. For example, detection of a cleavage product of a complement protein, such as by SDS-PAGE and protein staining with Coomassie blue.

As used herein, biological activity refers to the *in vivo* activities of a compound or physiological responses that result upon *in vivo* administration of a
15 compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmaceutical activity of such compounds, compositions and mixtures. Biological activities can be observed in *in vitro* systems designed to test or use such activities. Thus, for purposes herein a biological activity of a protease is its catalytic activity in which a polypeptide is hydrolyzed.

As used herein, equivalent, when referring to two sequences of nucleic acids, means that the two sequences in question encode the same sequence of amino acids or equivalent proteins. When equivalent is used in referring to two proteins or peptides, it means that the two proteins or peptides have substantially the same amino acid
20 sequence with only amino acid substitutions (such as, but not limited to, conservative changes such as those set forth in Table 3, above) that do not substantially alter the activity or function of the protein or peptide. When equivalent refers to a property, the property does not need to be present to the same extent (*e.g.*, two peptides can exhibit different rates of the same type of enzymatic activity), but the activities are usually substantially the same. Complementary, when referring to two nucleotide sequences,
25 means that the two sequences of nucleotides are capable of hybridizing, typically with less than 25%, 15% or 5% mismatches between opposed nucleotides. If necessary, the
30

percentage of complementarity will be specified. Typically the two molecules are selected such that they will hybridize under conditions of high stringency.

As used herein, an agent that modulates the activity of a protein or expression of a gene or nucleic acid either decreases or increases or otherwise alters the activity of the protein or, in some manner, up- or down-regulates or otherwise alters expression of the nucleic acid in a cell.

As used herein, a “chimeric protein” or “fusion protein” protease refers to a polypeptide operatively-linked to a different polypeptide. A chimeric or fusion protein provided herein can include one or more proteases or a portion thereof, such as single chain protease domains thereof, and one or more other polypeptides for any one or more of a transcriptional/translational control signals, signal sequences, a tag for localization, a tag for purification, part of a domain of an immunoglobulin G, and/or a targeting agent. These chimeric or fusion proteins include those produced by recombinant means as fusion proteins, those produced by chemical means, such as by chemical coupling, through, for example, coupling to sulfhydryl groups, and those produced by any other method whereby at least one protease, or a portion thereof, is linked, directly or indirectly via linker(s) to another polypeptide.

As used herein, operatively-linked when referring to a fusion protein refers to a protease polypeptide and a non-protease polypeptide that are fused in-frame to one another. The non-protease polypeptide can be fused to the N-terminus or C-terminus of the protease polypeptide.

As used herein, a targeting agent is any moiety, such as a protein or effective portion thereof, that provides specific binding of the conjugate to a cell surface receptor, which in some instances can internalize bound conjugates or portions thereof. A targeting agent also can be one that promotes or facilitates, for example, affinity isolation or purification of the conjugate; attachment of the conjugate to a surface; or detection of the conjugate or complexes containing the conjugate.

As used herein, “linker” refers to short sequences of amino acids that join two polypeptides (or nucleic acid encoding such polypeptides). “Peptide linker” refers to the short sequence of amino acids joining the two polypeptide sequences. Exemplary of polypeptide linkers are linkers joining two antibody chains in a synthetic antibody fragment such as an scFv fragment. Linkers are well-known and any known linkers

can be used in the provided methods. Exemplary of polypeptide linkers are (Gly-Ser)_n amino acid sequences, with some Glu or Lys residues dispersed throughout to increase solubility. Other exemplary linkers are described herein; any of these and other known linkers can be used with the provided compositions and methods.

5 As used herein, derivative or analog of a molecule refers to a portion derived from or a modified version of the molecule.

 As used herein, "disease or disorder" refers to a pathological condition in an organism resulting from cause or condition including, but not limited to, infections, acquired conditions, genetic conditions, conditions related to environmental exposures and human behaviors, and conditions characterized by identifiable symptoms.

10 Diseases or disorders include clinically diagnosed disease as well as disruptions in the normal state of the organism that have not been diagnosed as clinical disease. Diseases and disorders of interest herein are those involving complement activation, including those mediated by complement activation and those in which complement

15 activation plays a role in the etiology or pathology. Diseases and disorders of interest herein include those characterized by complement activation (*e.g.*, age-related macular degeneration and renal delayed graft function).

 As used herein, macular degeneration occurs when the small central portion of the retina, known as the macula, deteriorates. There are two types of AMD: dry

20 (atrophic) and wet (neovascular or exudative). Most AMD starts as the dry type and in 10-20% of individuals, it progresses to the wet type. Age-related macular degeneration is always bilateral (*i.e.*, occurs in both eyes), but does not necessarily progress at the same pace in both eyes.

 As used herein, age-related macular degeneration (AMD) is an inflammatory

25 disease that causes visual impairment and blindness in older people. The proteins of the complement system are central to the development of this disease. Local and systemic inflammation in AMD are mediated by the deregulated action of the alternative pathway of the complement system.

 As used herein, delayed graft function (DGF) is a manifestation of acute

30 kidney injury (AKI) with attributes unique to the transplant process. It occurs post-transplant surgery. Delayed graft function (DGF) is a common complication frequently defined as the need for dialysis during the first post-transplant week.

Intrinsic renal synthesis of the third complement component C3 (C3) contributes to acute rejection by priming a T-cell-mediated response. For example, in brain dead donors, local renal C3 levels are higher at procurement and inversely related to renal function 14 days after transplant.

5 As used herein, a complement-mediated disease or disorder is any disorder in which any one or more of the complement proteins plays a role in the disease, either due to an absence or presence of a complement protein or complement-related protein or activation or inactivation of a complement or complement-related protein. In some embodiments, a complement-mediated disorder is one that is due to a deficiency in a
10 complement protein(s). In other embodiments as described herein a complement-mediated disorder is one that is due to activation or over-activation of a complement protein(s). A complement-mediated disorder also is one that is due to the presence of any one or more of the complement proteins and/or the continued activation of the complement pathway. As used herein, “macular degeneration-related disorder” refers
15 to any of a number of conditions in which the retinal macula degenerates or becomes dysfunctional (*e.g.*, as a consequence of decreased growth of cells of the macula, increased death or rearrangement of the cells of the macula (*e.g.*, RPE cells), loss of normal biological function, or a combination of these events). Macular degeneration results in the loss of integrity of the histoarchitecture of the cells and/or extracellular
20 matrix of the normal macula and/or the loss of function of the cells of the macula. Examples of macular degeneration-related disorder include age-related macular degeneration (AMD), geographic atrophy (GA), North Carolina macular dystrophy, Sorsby's fundus dystrophy, Stargardt's disease, pattern dystrophy, Best disease, dominant drusen, and malattia leventinese (radial drusen). Macular degeneration-
25 related disorder also encompasses extramacular changes that occur prior to, or following dysfunction and/or degeneration of the macula. Thus, the term “macular degeneration-related disorder” also broadly includes any condition which alters or damages the integrity or function of the macula (*e.g.*, damage to the RPE or Bruch's membrane). For example, the term encompasses retinal detachment, chorioretinal
30 degenerations, retinal degenerations, photoreceptor degenerations, RPE degenerations, mucopolysaccharidoses, rod-cone dystrophies, cone-rod dystrophies and cone degenerations.

A macular degeneration-related disorder described herein includes AMD, such as, for example, a macular degeneration-related disorder treated by anti-VEGF treatment, such as, for example, anti-VEGF antibodies, or laser treatment, or an implantable telescope.

5 As used herein, "treating" a subject with a disease or condition means that the subject's symptoms are partially or totally alleviated, or remain static following treatment. Hence treatment encompasses prophylaxis, therapy and/or cure. Prophylaxis refers to prevention of a potential disease and/or a prevention of worsening of symptoms or progression of a disease. Treatment also encompasses any
10 pharmaceutical use of a modified MTSP-1 polypeptide and compositions provided herein.

As used herein, "prevention" or prophylaxis refers to methods in which the risk or probability of developing a disease or condition is reduced.

As used herein, a "therapeutic agent," therapeutic regimen, radioprotectant, or
15 chemotherapeutic mean conventional drugs and drug therapies, including vaccines, which are known to those skilled in the art. Radiotherapeutic agents are well known in the art.

As used herein, "treatment" means any manner in which the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered.
20 Treatment also encompasses any pharmaceutical use of the compositions herein.

As used herein, "amelioration of the symptoms" of a particular disease or disorder by a treatment, such as by administration of a pharmaceutical composition or other therapeutic, refers to any lessening, whether permanent or temporary, lasting or transient, of the symptoms that can be attributed to or associated with administration
25 of the composition or therapeutic.

As used herein, a "pharmaceutically effective agent" includes any therapeutic agent or bioactive agents, including, but not limited to, for example, anesthetics, vasoconstrictors, dispersing agents, and conventional therapeutic drugs, including small molecule drugs and therapeutic proteins.

30 As used herein an "effective amount" of a compound or composition for treating a particular disease is an amount that is sufficient to ameliorate, or in some manner reduce the symptoms associated with the disease. Such amount can be

administered as a single dosage or can be administered according to a regimen, whereby it is effective. The amount can cure the disease but, typically, is administered in order to ameliorate the symptoms of the disease. Typically, repeated administration is required to achieve a desired amelioration of symptoms.

5 As used herein, a “therapeutically effective amount” or a “therapeutically effective dose” refers to the quantity of an agent, compound, material, or composition containing a compound that is at least sufficient to produce a therapeutic effect following administration to a subject. Hence, it is the quantity necessary for preventing, curing, ameliorating, arresting or partially arresting a symptom of a
10 disease or disorder.

 As used herein, a “therapeutic effect” means an effect resulting from treatment of a subject that alters, typically improves or ameliorates, the symptoms of a disease or condition or that cures a disease or condition.

 As used herein, a “prophylactically effective amount” or a “prophylactically
15 effective dose” refers to the quantity of an agent, compound, material, or composition containing a compound that when administered to a subject, have the intended prophylactic effect, *e.g.*, preventing or delaying the onset, or reoccurrence, of disease or symptoms, reducing the likelihood of the onset, or reoccurrence, of disease or
20 symptoms, or reducing the incidence of viral infection. The full prophylactic effect does not necessarily occur by administration of one dose, and can occur only after administration of a series of doses. Thus, a prophylactically effective amount can be administered in one or more administrations.

 As used herein, “administration of a non-complement protease,” such as a modified MTSP-1 protease, refers to any method in which the non-complement
25 protease is contacted with its substrate. Administration can be effected *in vivo* or *ex vivo* or *in vitro*. For example, for *ex vivo* administration a body fluid, such as blood, is removed from a subject and contacted outside the body with the modified non-complement protease, such as a modified MTSP-1 protease. For *in vivo*
30 administration, the modified non-complement protease, such as a modified MTSP-1 protease, can be introduced into the body, such as by local, topical, systemic and/or other route of introduction. *In vitro* administration encompasses methods, such as cell culture methods.

As used herein, "unit dose form" refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art.

As used herein, "patient" or "subject" to be treated includes humans and human or non-human animals. Mammals include; primates, such as humans,
5 chimpanzees, gorillas and monkeys; domesticated animals, such as dogs, horses, cats, pigs, goats and cows; and rodents such as mice, rats, hamsters and gerbils.

As used herein, a "combination" refers to any association between or among two or more items. The association can be spatial or refer to the use of the two or more items for a common purpose. The combination can be two or more separate
10 items, such as two compositions or two collections, a mixture thereof, such as a single mixture of the two or more items, or any variation thereof. The elements of a combination are generally functionally associated or related.

As used herein, a "composition" refers to any mixture of two or more products or compounds (*e.g.*, agents, modulators, regulators, etc.). It can be a solution, a
15 suspension, liquid, powder, a paste, aqueous or non-aqueous formulations or any combination thereof.

As used herein, a stabilizing agent refers to compound added to the formulation to protect either the antibody or conjugate, such as under the conditions (*e.g.*, temperature) at which the formulations herein are stored or used. Thus, included
20 are agents that prevent proteins from degradation from other components in the compositions. Exemplary of such agents are amino acids, amino acid derivatives, amines, sugars, polyols, salts and buffers, surfactants, inhibitors or substrates and other agents as described herein.

As used herein, "fluid" refers to any composition that can flow. Fluids thus
25 encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, an "article of manufacture" is a product that is made and sold. As used throughout this application, the term is intended to encompass a therapeutic agent with a modified MTSP-1 polypeptide or nucleic acid molecule contained in the
30 same or separate articles of packaging.

As used herein, a "kit" refers to a packaged combination, optionally including reagents and other products and/or components for practicing methods using the

elements of the combination. For example, kits containing a modified protease polypeptide, such as a modified MTSP-1 protease provided herein, or nucleic acid molecule provided herein and another item for a purpose including, but not limited to, administration, diagnosis, and assessment of a biological activity or property are provided. Kits optionally include instructions for use.

As used herein, a “cellular extract” refers to a preparation or fraction which is made from a lysed or disrupted cell.

As used herein, “animal” includes any animal, such as, but not limited to; primates including humans, gorillas and monkeys; rodents, such as mice and rats; fowl, such as chickens; ruminants, such as goats, cows, deer and sheep. Non-human animals exclude humans as the contemplated animal. The proteases provided herein are from any source, animal, plant, prokaryotic and fungal. Most proteases are of animal origin, including mammalian origin.

As used herein, a “single dosage” formulation refers to a formulation containing a single dose of therapeutic agent for direct administration. Single dosage formulations generally do not contain any preservatives.

As used herein, a multi-dose formulation refers to a formulation that contains multiple doses of a therapeutic agent and that can be directly administered to provide several single doses of the therapeutic agent. The doses can be administered over the course of minutes, hours, weeks, days or months. Multi-dose formulations can allow dose adjustment, dose-pooling and/or dose-splitting. Because multi-dose formulations are used over time, they generally contain one or more preservatives to prevent microbial growth.

As used herein, a “control” or “standard” refers to a sample that is substantially identical to the test sample, except that it is not treated with a test parameter, or, if it is a plasma sample, it can be from a normal volunteer not affected with the condition of interest. A control also can be an internal control. For example, a control can be a sample, such as a virus, that has a known property or activity.

As used herein, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an” agent includes one or more agents.

As used herein, the term "or" is used to mean "and/or" unless explicitly indicated to refer to alternatives only or if the alternatives are mutually exclusive.

As used herein, ranges and amounts can be expressed as "about" a particular value or range. About also includes the exact amount. Hence "about 5 bases" means
5 "about 5 bases" and also "5 bases."

As used herein, "optional" or "optionally" means that the subsequently described event or circumstance does or does not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not. For example, an optionally substituted group means that the group is
10 unsubstituted or is substituted.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem.* 11:1726).

15 For clarity of disclosure, and not by way of limitation, the detailed description is divided into the subsections that follow.

B. MTSP-1 STRUCTURE AND FUNCTION

MTSP-1 (also called matriptase, TADG-15, suppressor of tumorigenicity 14, ST14; see SEQ ID NOS: 1, 2 and GenBank Accession NOs: AF118224 and
20 AAD42765; U.S. Patent No. 5,792,616; see, also Takeuchi (1999) *Proc. Natl. Acad. Sci. U.S.A.* 96:11054-1161) is a serine protease that cleaves proteins containing the amino acid sequence P4(Arg/Lys)-P3(X)-P2(Ser)-P1(Arg)-P1'(Ala) and P4(X)-P3(Arg/Lys)-P2(Ser)-P1(Arg)-P1'(Ala) where X corresponds to non-basic amino acids (Takeuchi (2000) *J Biol Chem* 275(34):26333-42) and can cleave various
25 synthetic substrates with Arginine or Lysine residues at their P1 sites. MTSP-1 has at least three known physiological substrates, including urokinase-type plasminogen activator (u-PA), hepatocyte growth factor (HGF)/ scatter factor and protease activated receptor-2 (PAR-2) (Takeuchi (2000) *J Biol Chem* 275(34):26333-42; Lee *et al.* (2000) *J Biol Chem* 275:36720-36725). MTSP-1 is found in epithelial cells, and in
30 many cancer tissues. MTSP-1 is involved in normal embryonic development. MTSP-1 co-localizes with E-adherin, a tight junction molecule that is necessary for normal embryonic development in mice.

Provided herein are modified membrane-type serine protease 1 (MTSP-1) polypeptides that are modified so that they cleave inhibitory sequences in C3, such that activation of C3 into C3a and C3b fragments is inhibited. The activity/specificity of the modified MTSP-1 polypeptides provided herein is such that they cleave C3 with greater activity and/or specificity or k_{cat}/K_m compared to the unmodified MTSP-1 polypeptide, particularly of any of SEQ ID NOs: 1-4. The modified MTSP-1 polypeptides also can have reduced activity or specificity or both for a physiological substrate of the unmodified MTSP-1 polypeptide, such as, for example, proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or hepatocyte growth factor (HGF). Thus, the modified MTSP-1 polypeptides provided herein inhibit complement activation in a complement pathway. The Modified MTSP-1 Polypeptides also exhibit increased selectivity for cleaving C3 compared to other MTSP-1 substrates, such as, for example, proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or hepatocyte growth factor (HGF). Therefore, the Modified MTSP-1 Polypeptides provided herein do not exhibit undesired cleavage activities against physiological native MTSP-1 substrates so that they do not exhibit undesirable side effects.

1. Serine Proteases

Serine proteases (SPs), which include secreted enzymes and enzymes sequestered in cytoplasmic storage organelles, have a variety of physiological roles, including in blood coagulation, wound healing, digestion, immune responses and tumor invasion and metastasis. For example, chymotrypsin, trypsin, and elastase function in the digestive tract; Factor 10, Factor 11, Thrombin, and Plasmin are involved in clotting and wound healing; and C1r, C1s, and the C3 convertases play a role in complement activation.

A class of cell surface proteins designated type II transmembrane serine proteases are proteases which are membrane-anchored proteins with extracellular domains. As cell surface proteins, they play a role in intracellular signal transduction and in mediating cell surface proteolytic events. Other serine proteases are membrane bound and function in a similar manner. Others are secreted. Many serine proteases exert their activity upon binding to cell surface receptors, and, hence act at cell

surfaces. Cell surface proteolysis is a mechanism for the generation of biologically active proteins that mediate a variety of cellular functions.

Serine proteases, including secreted and transmembrane serine proteases, are involved in processes that include neoplastic development and progression. While the
5 precise role of these proteases has not been fully elaborated, serine proteases and inhibitors thereof are involved in the control of many intra- and extracellular physiological processes, including degradative actions in cancer cell invasion and metastatic spread, and neovascularization of tumors that are involved in tumor progression. Proteases are involved in the degradation and remodeling of extracellular
10 matrix (ECM) and contribute to tissue remodeling, and are necessary for cancer invasion and metastasis. The activity and/or expression of some proteases have been shown to correlate with tumor progression and development.

More than 20 families (denoted S1-S27) of serine protease have been identified, and they are grouped into 6 clans (SA, SB, SC, SE, SF and SG) on the
15 basis of structural similarity and other functional evidence (Rawlings ND *et al.* (1994) *Meth. Enzymol.* 244: 19-61). There are similarities in the reaction mechanisms of several serine peptidases. Chymotrypsin, subtilisin and carboxypeptidase C clans have a catalytic triad of serine, aspartate and histidine in common: serine acts as a nucleophile, aspartate as an electrophile, and histidine as a base. The geometric
20 orientations of the catalytic residues are similar between families, despite different protein folds. The linear arrangements of the catalytic residues commonly reflect clan relationships. For example the catalytic triad in the chymotrypsin clan (SA) is ordered HDS, but is ordered DHS in the subtilisin clan (SB) and SDH in the carboxypeptidase clan (SC).

25 Examples of serine proteases of the chymotrypsin superfamily include tissue-type plasminogen activator (tPA), trypsin, trypsin-like protease, chymotrypsin, plasmin, elastase, urokinase (or urinary-type plasminogen activator, u-PA), acrosin, activated protein C, C1 esterase, cathepsin G, chymase, and proteases of the blood coagulation cascade including kallikrein, thrombin, and Factors VIIa, IXa, Xa, XIa, and XIIa (Barret, A.J., In: Proteinase Inhibitors, Ed. Barrett, A.J., *Et al.*, Elsevier,
30 Amsterdam, Pages 3-22 (1986); Strassburger, W. *et al.*, (1983) *FEBS Lett.*, 157 :219-223; Dayhoff, M.O., Atlas of Protein Sequence and Structure, Vol 5, National

Biomedical Research Foundation, Silver Spring, Md. (1972); and Rosenberg, R.D. *et al.* (1986) *Hosp. Prac.*, 21: 131-137).

The activity of proteases in the serine protease family is dependent on a set of amino acid residues that form their active site. One of the residues is always a serine; hence their designation as serine proteases. For example, chymotrypsin, trypsin, and elastase share a similar structure and their active serine residue is at the same position (Ser-195) in all three. Despite their similarities, they have different substrate specificities; they cleave different peptide bonds during protein digestion. For example, chymotrypsin prefers an aromatic side chain on the residue whose carbonyl carbon is part of the peptide bond to be cleaved. Trypsin prefers a positively charged Lys or Arg residue at this position. Serine proteases differ markedly in their substrate recognition properties: some are highly specific (*i.e.*, the proteases involved in blood coagulation and the immune complement system); some are only partially specific (*i.e.*, the mammalian digestive proteases trypsin and chymotrypsin); and others, like subtilisin, a bacterial protease, are completely non-specific. Despite these differences in specificity, the catalytic mechanism of serine proteases is well conserved.

The mechanism of cleavage of a target protein by a serine protease is based on nucleophilic attack of the targeted peptidic bond by a serine. Cysteine, threonine or water molecules associated with aspartate or metals also can play this role. In many cases the nucleophilic property of the group is improved by the presence of a histidine, held in a "proton acceptor state" by an aspartate. Aligned side chains of serine, histidine and aspartate build the catalytic triad common to most serine proteases. For example, the active site residues of chymotrypsin, and serine proteases that are members of the same family as chymotrypsin, such as for example MTSP-1, are Asp102, His57, and Ser195.

The catalytic domains of all serine proteases of the chymotrypsin superfamily have sequence homology and structural homology. The sequence homology includes the conservation of: 1) the characteristic active site residues (*e.g.*, Ser195, His57, and Asp102 in the case of trypsin); 2) the oxyanion hole (*e.g.*, Gly193, Asp194 in the case of trypsin); and 3) the cysteine residues that form disulfide bridges in the structure (Hartley, B.S., (1974) *Symp. Soc. Gen. Microbiol.*, 24: 152-182). The structural homology includes 1) a common fold characterized by two Greek key structures

(Richardson, J. (1981) *Adv. Prot. Chem.*, 34:167-339); 2) a common disposition of catalytic residues; and 3) detailed preservation of the structure within the core of the molecule (Stroud, R.M. (1974) *Sci. Am.*, 231: 24-88).

Throughout the chymotrypsin family of serine proteases, the backbone
 5 interaction between the substrate and enzyme is completely conserved, but the side chain interactions vary considerably. The identity of the amino acids that contain the S1-S4 pockets of the active site determines the substrate specificity of that particular pocket. Grafting the amino acids of one serine protease to another of the same fold modifies the specificity of one to the other. Typically, the amino acids of the protease
 10 that contain the S1-S4 pockets are those that have side chains within 4 to 5 angstroms of the substrate. The interactions these amino acids have with the protease substrate are generally called “first shell” interactions because they directly contact the substrate. There, however, can be “second shell” and “third shell” interactions that ultimately position the first shell amino acids. First shell and second shell substrate
 15 binding effects are determined primarily by loops between beta-barrel domains. Because these loops are not core elements of the protein, the integrity of the fold is maintained while loop variants with novel substrate specificities can be selected during the course of evolution to fulfill necessary metabolic or regulatory niches at the molecular level. Typically for serine proteases, the following amino acids in the
 20 primary sequence are determinants of specificity: 195, 102, 57 (the catalytic triad); 189, 190, 191, 192, and 226 (S1); 57, the loop between 58 and 64, and 99 (S2); 192, 217, 218 (S3); the loop between Cys168 and Cys180, 215, and 97 to 100 (S4); and 41 and 151 (S2’), based on chymotrypsin numbering, where an amino acid in an S1 position affects P1 specificity, an amino acid in an S2 position affects P2 specificity,
 25 an amino acid in the S3 position affects P3 specificity, and an amino acid in the S4 position affects P4 specificity. Position 189 in a serine protease is a residue buried at the bottom of the pocket that determines the S1 specificity. Structural determinants for MTSP-1 are listed in Table 4, with protease domains for each of the designated proteases aligned with that of the protease domain of chymotrypsin. The number
 30 underneath the Cys168-Cys182 and 60’s loop column headings indicate the number of amino acids in the loop between the two amino acids and in the loop. The yes/no designation under the Cys191-Cys220 column headings indicates whether the

disulfide bridge is present in the protease. These regions are variable within the family of chymotrypsin-like serine proteases and represent structural determinants in themselves.

2. Structure

5 MTSP-1 cDNA has been cloned from various mammalian species. Exemplary MTSP-1 precursor polypeptides include, but are not limited to, human (SEQ ID NO:1 and encoded by SEQ ID NO:5), mouse (SEQ ID NO:12), and rat (SEQ ID NO:13) MTSP-1 polypeptides. The human MTSP-1 mRNA transcript is normally translated to form a 855 amino acid wild-type protein (SEQ ID NO:1). The nucleic acid
10 molecule whose sequence is set forth in SEQ ID NO:5 (see, also Genbank AF118224) encodes the 855 amino acid MTSP-1 (SEQ ID NO: 1, GenBank AAD42765). MTSP-1 is multidomain proteinase with a C-terminal serine proteinase domain (Friedrich *et al.* (2002) *J Biol Chem* 277(3):2160). A 683 amino acid variant of the protease has been isolated, but this protein appears to be a truncated form or an ectodomain form.
15 As described in further detail below, MTSP-1 is a zymogen or proenzyme that is further processed by proteolytic cleavage at a canonical activation motif to generate a two chain mature MTSP-1 polypeptide.

At least five isoforms, produced by alternative splicing, of human MTSP-1 exist. Forms of MTSP-1 with a molecular mass of approximately 95, 78, 74, 45 and
20 25 kDa, corresponding to the full-length protein (95kDa), residues 149-855 of SEQ ID NO: 1 (78 kDa), residues 190-855 of SEQ ID NO: 1 (73 kDa) or 205-855 of SEQ ID NO: 1 (74 kDa), residues 190-614 of SEQ ID NO: 1 (45.7 kDa), and residues 615-855 of SEQ ID NO: 1 (26 kDa), respectively, have been detected (Ge *et al.*, (2006) *J Biol Chem* 281:7406-7412). Allelic variants and other variants of human MTSP-1 are
25 known. For example, a naturally occurring variant G827R is associated with ichthyosis with hypotrichosis syndrome, characterized by skin hyperkeratosis (Basel-Vanagaite *et al.*, (2007) *Am J Hum Genet* 80:467-477). In another example, a modified MTSP-1 polypeptide containing the amino acid modification C299S (C122S by chymotrypsin numbering) in the sequence of amino acids set forth in SEQ ID
30 NO:1 (corresponding to the sequence of amino acids set forth in SEQ ID NO: 2) is known; the replacement of the free cysteine reduces aggregation of the encoded protein. Additional variants include those containing amino acid modifications

M285I, R381S, H656A, D711A, and S805A in full-length MTSP-1 set forth in SEQ ID NO:1.

MTSP-1 is highly expressed or active in prostate, breast, and colorectal cancers, and it is said to play a role in the metastasis of breast and prostate cancer.

5 MTSP-1 also is expressed in a variety of epithelial tissues with high levels of activity and/or expression in the human gastrointestinal tract and the prostate. Other species of MTSP-1 are known. For example, a mouse homolog of MTSP-1 has been identified and is called epithin. MTSP-1 contains a transmembrane domain, two CUB domains, four LDLR repeats, and a serine protease domain (or peptidase S1 domain) between
10 amino acids 615-854 (set forth as SEQ ID NOS:2 and 7), which is highly conserved among all members of the peptidase S1 family of serine proteases, such as for example with chymotrypsin (SEQ ID NOS:14 and 15). MTSP-1 is synthesized as an 855 amino acid zymogen, and activated to an active double chain enzyme form by cleavage between Arg614 and Val615. In addition, the single chain proteolytic
15 domain alone is catalytically active and functional.

MTSP-1 belongs to the peptidase S1 family of serine proteases (also referred to as the chymotrypsin family), which also includes chymotrypsin and trypsin. Generally, chymotrypsin family members share sequence and structural homology with chymotrypsin. MTSP-1 is numbered herein according to the numbering of
20 mature chymotrypsin, with its protease domain aligned with that of the protease domain of chymotrypsin and its residues numbered accordingly. Based on chymotrypsin numbering, active site residues are Asp102, His57, and Ser195. The linear amino acid sequence can be aligned with that of chymotrypsin and numbered according to the β sheets of chymotrypsin. Insertions and deletions occur in the loops
25 between the beta sheets, but throughout the structural family, the core sheets are conserved. The serine proteases interact with a substrate in a conserved beta sheet manner. Up to 6 conserved hydrogen bonds can occur between the substrate and enzyme. All serine proteases of the chymotrypsin family have a conserved region at their N-terminus of the protease domain that is necessary for catalytic activity (*i.e.*,
30 IIGG, VVGG, or IVGG, where the first amino acid in this quartet is numbered according to the chymotrypsin numbering and given the designation Ile16. This numbering does not reflect the length of the precursor sequence).

The substrate specificity of MTSP-1 in the protease domain has been mapped using a positional scanning synthetic combinatorial library and substrate phage display (Takeuchi *et al.* (2000) *J Biol Chem* 275: 26333). Cleavage residues in substrates recognized by MTSP-1 contain Arg/Lys at P4 and basic residues or Gln at P3, small residues at P2, Arg or Lys at P1, and Ala at P1'. Effective substrates contain Lys-Arg-Ser-Arg in the P4 to P1 sites, respectively. Generally, the substrate specificity for MTSP-1 reveals a trend whereby if P3 is basic, then P4 tends to be non-basic; and if P4 is basic, then P3 tends to be non-basic. Known substrates for MTSP-1, including, for example, proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and hepatocyte growth factor (HGF), conform to the cleavage sequence for MTSP-1 specific substrates.

MTSP-1 can cleave selected synthetic substrates as efficiently as trypsin, but exhibit a more restricted specificity for substrates than trypsin. The catalytic domain of MTSP-1 has the overall structural fold of a (chymo)trypsin-like serine protease, but displays unique properties such as a hydrophobic/acidic S2/S4 subsites and an exposed 60 loop. Similarly, MTSP-1 does not indiscriminately cleave peptide substrates at accessible Lys or Arg residues, but requires recognition of additional residues surrounding the scissile peptide bond. This requirement for an extended primary sequence highlights the specificity of MTSP-1 for its substrates. For example, although MTSP-1 cleaves proteinase activated receptor-2 (PAR-2) (displaying a P4 to P1 target sequence of Ser-Lys-Gly-Arg), the enzyme does not activate proteins closely related to this substrate such as PAR-1, PAR-3, and PAR-4 that do not display target sequences matching the extended MTSP-1 specificity near the scissile bond (see Friedrich *et al.* (2002) *J Biol Chem* 277: 2160).

The protease domain of MTSP-1 (see, *e.g.*, SEQ ID NOS: 2, 4) is composed of a pro-region and a catalytic domain. The catalytically active portion of the polypeptide begins after the autoactivation site at amino acid residue 611 of the mature protein (see, *e.g.*, SEQ ID NOS: 1, 3 at RQAR followed by the residues VVGG). The S1 pocket of MTSP-1 and trypsin are similar with good complementarity for Lys as well as Arg P1 residues, thereby accounting for some similarities in substrate cleavage with trypsin. The accommodation of the P1-Lys residues is mediated by Ser190 whose side chain provides an additional hydrogen

bond acceptor to stabilize the buried α -ammonium group (see Friedrich *et al.* (2002) *J Biol Chem* 277: 2160). The S2 pocket is shaped to accommodate small to medium-sized hydrophobic side chains of P2 amino acids and generally accepts a broad range of amino acids at the P2 position. Upon substrate binding, the S2 sub-site is not rigid
5 as evidenced by the rotation of the Phe99 benzyl group. Association of the substrate amino acids at positions P3 (for either Gln or basic residues) and P4 (for Arg or Lys residues) appears to be mediated by electrostatic interactions in the S3 and S4 pockets with the acidic side chains of Asp-217 and/or Asp-96, which can favorably pre-orient specific basic peptide substrates as they approach the enzyme active site cleft. The
10 side chain of a P3 residue also is able to hydrogen bond the carboxamide group of Gln192 or alternatively, the P3 side chain can extend into the S4 sub-site to form a hydrogen bond with Phe97 thereby weakening the inter-main chain hydrogen bonds with Gly216. In either conformation, a basic P3 side chain is able to interact favorably with the negative potential of the MTSP-1 S4 pocket. The mutual charge
15 compensation and exclusion from the same S4 site explains the low probability of the simultaneous occurrence of Arg/Lys residues at P3 and P4 in good MTSP-1 substrates. Generally, the amino acid positions of MTSP-1 (based on chymotrypsin numbering) that contribute to extended specificity for substrate binding include: 146 and 151 (S1'); 189, 190, 191, 192, 216, 226 (S1); 57, 58, 59, 60, 61, 62, 63, 64, 99
20 (S2); 192, 217, 218, 146 (S3); 96, 97, 98, 99, 100, 168, 169, 170, 170A, 171, 172, 173, 174, 175, 176, 178. 179, 180, 215, 217, 224 (S4). Table 4 summarizes the residues in MTSP-1 for some of the amino acid positions important for specificity interactions with a targeted substrate. Typically, modification of an MTSP-1 protease to alter any one or more of the amino acids in the extended specificity binding pocket
25 or other secondary sites of interaction affect the specificity or selectivity of a protease for a target substrate.

Table 4: Structural Determinants for MTSP-1 substrate cleavage (chymotrypsin numbering)													
Residues that Determine Specificity													
S4					S3		S2			S1			
171	174	180	215	Cys168 Cys182	192	218	99	57	60's loop (58- 64)	189	190	226	Cys191 Cys220
Leu	Gln	Met	Trp	13*	Gln	Asp	Phe	His	16*	Asp	Ser	Gly	yes

* number of residues

3. Function/Activity

Membrane type serine protease 1 (MTSP-1) is a serine protease normally expressed in epithelial tissues, including the skin, and in kidney, lung, prostate and mammary epithelium (Kim *et al.* (1999) *Immunogenetics* 49:420-428; Oberst *et al.* (2001) *Am J Pathol* 158:1301-1311; Takeguchi *et al.* (1999) *Proc Natl Acad Sci* 96:11054-11061) and expressed in a variety of tumor types (Oberst *et al.* (2001) *Am J Pathol* 158:1301-1311). MTSP-1 is essential for post-natal survival; MTSP-1 deficient mice developed to term but died shortly thereafter and were characterized by aberrant skin development, implicating a role for MTSP-1 in epithelial and epidermal barrier function and as important for normal skin and hair development (List *et al.* (2002) *Oncogene* 23(23):2765-3779). Post-natal MTSP-1 ablation caused loss of tight junction formation and mislocalized tight-junction associated proteins in mutant animals (List *et al.* (2009) *Am J Pathology* 175:1453-1463), implicating MTSP-1 as essential in maintenance of mouse epithelia. MTSP-1 also is reported to promote neural progenitor cell migration (Kendall *et al.*, (2008) *Stem Cells* 26(6):1575-86).

MTSP-1 is highly expressed or active in prostate, breast, lung, ovary and colorectal cancers and it may play a role in the metastasis of breast and prostate cancer. MTSP-1 also can be identified in blood vessels associated with tumors. MTSP-1 also is expressed in a variety of epithelial tissues with high levels of activity and/or expression in the human gastrointestinal tract and the prostate. MTSP-1 presence on the tumor or epithelial cell surface allows for interaction with a variety of factors and for proteolytic digestion of a broad range of substrates.

The role of MTSP-1 in cell migration on tumor activity may induce changes in the extracellular environment and the surrounding cells contributing to cell migration, progression, and metastasis. Because of the role of MTSP-1 in vascular diseases and

cancer, MTSP-1 polypeptides provided herein are altered such that they exhibit reduced selectivity towards these proteins.

C. COMPLEMENT INHIBITION BY TARGETING C3

The modified MTSP-1 polypeptides provided herein exhibit increased
5 specificity and/or activity for an inhibitory cleavage sequence in complement protein C3 compared to MTSP-1 polypeptides not containing the amino acid modifications (*e.g.*, wild type human MTSP-1 (see, SEQ ID NO:1) or a reference full-length human MTSP-1 (see, SEQ ID NO:3) or the catalytic domain or protease domain thereof (see, SEQ ID NO:2 or 4)). The reference MTSP-1 polypeptides include the replacement
10 C122S, by chymotrypsin numbering. Replacement with S at residue 122 does not alter specificity or activity on C3, but reduces aggregation. Since C3 is involved in the 3 initiation pathways of complement (see, *e.g.*, FIG. 1), targeting C3 by proteolytic inhibition provides a general and broad therapeutic target for inactivation of the complement cascade. Inactivation cleavage of C3 blocks terminal activity of
15 complement as well as the alternative pathway amplification loop. All three pathways converge at C3 (see, *e.g.*, Figure 1). By virtue of the ability to inhibit complement activation, such modified MTSP-1 polypeptides can be used to treat various diseases, conditions and pathologies associated with complement activation, such as inflammatory responses and autoimmune diseases. Complement activation is associated with
20 the development of diseases and conditions by promoting local inflammation and damage to tissues caused in part by the generation of effector molecules and a membrane attack complex. In one example, such as in many autoimmune diseases, complement produces tissue damage because it is activated under inappropriate circumstances such as by antibody to host tissues. In other situations, complement can
25 be activated normally, such as by septicemia, but still contributes to disease progression, such as in respiratory distress syndrome. Pathologically, complement can cause substantial damage to blood vessels (vasculitis), kidney basement membrane and attached endothelial and epithelial cells (nephritis), joint synovium (arthritis), and erythrocytes (hemolysis) if not adequately controlled. The role of C3 in complement
30 activation is discussed in further detail below.

The modified MTSP-1 polypeptides herein can cleave C3. For example, A single intravenous injection of anti-C3 MTSP-1 variants can eliminate C3 from

plasma *in vivo*; and similarly, a single intravitreal injection can cleave all C3 present in vitreous humor. Since C3 is the first component of the common complement pathway that is required for complement activation via all three “initiation” pathways (classical, alterative, and lectin), inactivation/elimination of C3 is functionally relevant for all three complement pathways.

1. Complement Protein C3 and its Role in Initiating Complement

The complement system involves over 30 soluble and cell-membrane bound proteins that function not only in the antibody-mediated immune response, but also in the innate immune response to recognize and kill pathogens such as bacteria, virus-infected cells, and parasites. Complement activation is initiated on pathogen surfaces through three distinct pathways: the classical pathway, the alternative pathway, and the lectin pathway. These pathways are distinct in that the components required for their initiation are different, but the pathways ultimately generate the same set of effector molecules (*e.g.*, C3 convertases) which cleave complement protein C3 to trigger the formation of the membrane attack complex (MAC) (see, *e.g.*, Figure 1). Thus, complement protein C3 is an attractive target for a therapeutic since modulation of C3 results in modulation of various opsonins, anaphylatoxins and the MAC. Further, naturally occurring complement inhibitor proteins including factor H (FH), CR1, complement receptor Ig (CR1g), DAF and MCP inhibit at the C3 level.

There are three (3) pathways of complement activation (See, Figure 1, which depicts these pathways). The pathways of complement are distinct; each relies on different molecules and mechanisms for initiation. The pathways are similar in that they converge to generate the same set of effector molecules, *i.e.*, C3 convertases. In the classical and lectin pathways C4b2b acts as a C3 convertase; in the alternative pathway, C3bBb is a C3 convertase (see Table5). Cleavage of C3 generates C3b, which acts as an opsonin and as the main effector molecule of the complement system for subsequent complement reactions, and C3a, which is a peptide mediator of inflammation. The addition of C3b to each C3 convertase forms a C5 convertase that generates C5a and C5b. C5a, like C3a, is a peptide mediator of inflammation. C5b mediates the “late” events of complement activation initiating the sequence of reactions culminating in the generation of the membrane attack complex (MAC). Although the three pathways produce different C3 and C5 convertases, all of the

pathways produce the split products of C3 and C5 and form MAC. Alternatively, C3 can be cleaved and activated by extrinsic proteases, such as lysosomal enzymes and elastase (Markiewski and Lambris (2007) *Am J Pathology* 171:715-727; Ricklin and Lambris (2007) *Nat Biotechnol* 25:1265-1275).

Table 5. Complement Cascades			
	Alternative Pathway	Classical Pathway	Lectin Pathway
Activators	Pathogen surface molecules LPS, teichoic acid, zymosan	antigen-bound IgM and IgG; non-immune molecules	Pathogens via recognition of carbohydrates on surface
C3 convertase	C3bBb	C4b2b	C4b2b
C5 convertase	C3bBb3b	C4b2b3b	C4b2b3b
MAC	C5678poly9	C5678poly9	C5678poly9
anaphylatoxins	C3a, C5a	C3a, C4a, C5a	C3a, C4a, C5a

5 a. Classical Pathway

C1q is the first component of the classical pathway of complement. C1q is a calcium-dependent binding protein associated with the collectin family of proteins due to an overall shared structural homology (Malhotra *et al.*, (1994) *Clin Exp Immunol.* 97(2):4-9; Holmskov *et al.* (1994) *Immunol Today* 15(2):67-74).

- 10 Collectins, often called pattern recognition molecules, generally function as opsonins to target pathogens for phagocytosis by immune cells. In contrast to conventional collectins, such as MBL, the carboxy-terminal globular recognition domain of C1q does not have lectin activity but can serve as a “charged” pattern recognition molecule due to marked differences in the electrostatic surface potential of its globular domains
- 15 (Gaboriaud *et al.* (2003) *J. Biol. Chem.* 278(47):46974-46982).

- C1q initiates the classical pathway of complement in two different ways. First, the classical pathway is activated by the interaction of C1q with immune complexes (*i.e.* antigen-antibody complexes or aggregated IgG or IgM antibody) thus linking the antibody-mediated humoral immune response with complement activation.
- 20 When the Fab portion (the variable region) of IgM or IgG binds antigen, the conformation of the Fc (constant) region is altered, allowing C1q to bind. C1q must bind at least 2 Fc regions to be activated. C1q, however, also is able to activate complement in the absence of antibody thereby functioning in the innate or immediate immune response to infection. Besides initiation by an antibody, complement

activation also is achieved by the interaction of C1q with non-immune molecules such as polyanions (bacterial lipopolysaccharides, DNA, and RNA), certain small polysaccharides, viral membranes, C reactive protein (CRP), serum amyloid P component (SAP), and bacterial, fungal and virus membrane components.

- 5 C1q is part of the C1 complex which contains a single C1q molecule bound to two molecules each of the zymogens C1r and C1s. Binding of more than one of the C1q globular domains to a target surface (such as aggregated antibody or a pathogen), causes a conformational change in the (C1r:C1s)₂ complex which results in the activation of the C1r protease to cleave C1s to generate an active serine protease.
- 10 Active C1s cleaves subsequent complement components C4 and C2 to generate C4b and C2b, which together form the C3 convertase of the classical pathway. The C3 convertase cleaves C3 into C3b, which covalently attaches to the pathogen surface and acts as an opsonin, and C3a, which stimulates inflammation. Some C3b molecules associate with C4b2b complexes yielding C4b2b3b which is the classical
- 15 cascade C5 convertase. Table 6 summarizes the proteins involved in the classical pathway of complement.

Table 6. Proteins of the Classical Pathway		
Native Component	Active Form	Function of the Active Form
C1 (C1q:(C1r:C1s)₂)	C1q	Binds directly to pathogen surfaces or indirectly to antibody bound to pathogens
	C1r	Cleaves C1s to an active protease
	C1s	Cleaves C4 and C2
C4	C4b	Binds to pathogen and acts as an opsonin; binds C2 for cleavage by C1s
	C4a	Peptide mediator of inflammation
C2	C2b	Active enzyme of classical pathway C3/C5 convertase; cleaves C3 and C5
	C2a	Precursor of vasoactive C2 kinin
C3	C3b	Binds to pathogen surfaces and acts as an opsonin; initiates amplification via the alternative pathway; binds C5 for cleavage by C2b
	C3a	Peptide mediator of inflammation

b. Alternative Pathway

The alternative pathway is initiated by foreign pathogens in the absence of antibody. Initiation of complement by the alternative pathway occurs through the spontaneous hydrolysis of C3 into C3b. A small amount of C3b is always present in body fluids, due to serum and tissue protease activity. Host self-cells normally contain high levels of membrane sialic acid which inactivate C3b if it binds, but bacteria contain low external sialic acid levels and thereby bind C3b without inactivating it. C3b on pathogen surfaces is recognized by the protease zymogen Factor B. Factor B is cleaved by Factor D. Factor D is the only activating protease of the complement system that circulates as an active enzyme rather than as a zymogen, but since Factor B is the only substrate for Factor D the presence of low levels of an active protease in normal serum is generally safe for the host. Cleavage of Factor B by Factor D yields the active product Bb which can associate with C3b to form C3bBb, the C3 convertase of the alternative pathway. Similar to the classical pathway, the C3 convertase produces more C3b and C3a from C3. C3b covalently attaches to the pathogen surface and acts as an opsonin and additionally initiates the alternative pathway, while C3a stimulates inflammation. Some C3b joins the complex to form C3bBb3b, the alternative pathway C5 convertase. C3bBb3b is stabilized by the plasma protein properdin or Factor P which binds to microbial surfaces and stabilizes the convertase. Table 7 summarizes the proteins involved in the alternative pathway of complement.

Table 7. Proteins of the Alternative Pathway		
Native Component	Active Form	Function of the Active Form
C3	C3b	Binds to pathogen surface, binds Factor B for cleavage by Factor D
Factor B	Ba	Small fragment of Factor B, unknown function
	Bb	Active enzyme of the C3 convertase and C5 convertase
Factor D	D	Plasma serine protease, cleaves Factor B when it is bound to C3b to Ba and Bb
Factor P (properdin)	P	Plasma proteins with affinity for C3bBb convertase on bacterial cells; stabilizes convertase

c. Lectin Pathway

The lectin pathway (also referred to as the MBL pathway) is initiated following recognition and binding of pathogen-associated molecular patterns (PAMPs; *i.e.*, carbohydrates moieties) by lectin proteins. Examples of lectin proteins that activate the lectin pathway of complement include mannose binding lectin (MBL) and ficolins (*i.e.* L-ficolin, M-ficolin, and H-ficolin). MBL is a member of the collectin family of proteins and thereby exists as an oligomer of subunits composed of identical polypeptide chains each of which contains a cysteine-rich, a collagen-like, a neck, and a carbohydrate-recognition or lectin domain. MBL acts as a pattern recognition molecule to recognize carbohydrate moieties, particularly neutral sugars such as mannose or N-acetylglucosamine (GlcNAc) on the surface of pathogens via its globular lectin domain in a calcium-dependent manner. MBL also acts as an opsonin to facilitate the phagocytosis of bacterial, viral, and fungal pathogens by phagocytic cells. Additional initiators of the lectin pathway include the ficolins including L-ficolin, M-ficolin, and H-ficolin (see *e.g.*, Liu *et al.* (2005) *J Immunol.* 175:3150-3156). Similar to MBL, ficolins recognize carbohydrate moieties such as, for example, N-acetyl glucosamine and mannose structures.

The activation of the alternative pathway by MBL or ficolins is analogous to activation of the classical pathway by C1q whereby a single lectin molecule interacts with two protease zymogens. In the case of the lectin proteins, the zymogens are MBL-associated serine proteases, MASP-1 and MASP-2, which are closely homologous to the C1r and C1s zymogens of the classical pathway. Upon recognition of a PAMP by a lectin protein, such as for example by binding to a pathogen surface, MASP-1 and MASP-2 are activated to cleave C4 and C2 to form the MBL cascade C3 convertase. C3b then joins the complex to form the MBL cascade C5 convertase. MASP activation is implicated not only in responses to microorganisms, but in any response that involves exposing neutral sugars, including but not limited to tissue injury, such as that observed in organ transplants. Like the alternative cascade, the MBL cascade is activated independent of antibody; like the classical cascade, the MBL cascade utilizes C4 and C2 to form C3 convertase. Table 8 summarizes the proteins involved in the lectin pathway of complement.

Table 8. Proteins of the Lectin Pathway

Native Component	Active Form	Function of the Active Form
MBL	MBL	Recognizes PAMPs, such as on pathogen surfaces (<i>e.g.</i> , via recognition of carbohydrates)
Ficolins	L-Ficolin; M-Ficolin, or H-Ficolin	Recognizes PAMPs, such as on pathogen surfaces (<i>e.g.</i> , via recognition of carbohydrates)
MASP-1	MASP-1	Cleaves C4 and C2
MASP-2	MASP-2	Cleaves C4 and C2

d. Complement-Mediated Effector Functions

Regardless of which initiation pathway is used, the end result is the formation of activated fragments of complement proteins (*e.g.* C3a, C4a, and C5a anaphylatoxins and C5b-9 membrane attack complexes), which act as effector molecules to mediate diverse effector functions. The recognition of complement effector molecules by cells for the initiation of effector functions (*e.g.* chemotaxis and opsonization) is mediated by a diverse group of complement receptors. The complement receptors are distributed on a wide range of cell types including erythrocytes, macrophages, B cells, neutrophils, and mast cells. Upon binding of a complement component to the receptor, the receptors initiate an intracellular signaling cascade resulting in cell responses such as stimulating phagocytosis of bacteria and secreting inflammatory molecules from the cell. For example, the complement receptors CR1 and CR2 which recognize C3b, C4b, and their products are important for stimulating chemotaxis. CR3 (CD11b/CD18) and CR4 (CD11c/CD18) are integrins that are similarly important in phagocytic responses but also play a role in leukocyte adhesion and migration in response to iC3b. The C5a and C3a receptors are G protein-coupled receptors that play a role in many of the pro-inflammatory-mediated functions of the C5a and C3a anaphylatoxins. For example, receptors for C3a, C3aR, exist on mast cells, eosinophils, neutrophils, basophils and monocytes and are directly involved in the pro-inflammatory effects of C3a.

Thus, through complement receptors, these complement effector molecule fragments mediate several functions including leukocyte chemotaxis, activation of macrophages, vascular permeability and cellular lysis (Frank, M. and Fries, L. Complement. In Paul, W. (ed.) Fundamental Immunology, Raven Press, 1989). A summary of some effector functions of complement products are listed in Table 9.

Table 9: Complement Effector Molecules and Functions	
Product	Activity
C2b (prokinin)	accumulation of body fluid
C3a (anaphylatoxin)	basophil and mast cell degranulation; enhanced vascular permeability; smooth muscle contraction; Induction of suppressor T cells
C3b and its products	opsonization; phagocyte activation
C4a (anaphylatoxin)	basophil & mast cell activation; smooth muscle contraction; enhanced vascular permeability
C4b	opsonization
C5a (anaphylatoxin; chemotactic factor)	basophil & mast cell activation; enhanced vascular permeability; smooth muscle contraction; chemotaxis; neutrophil aggregation; oxidative metabolism stimulation; stimulation of leukotriene release; induction of helper T-cells
C5b67	chemotaxis; attachment to other cell membranes and lysis of bystander cells
C5b6789 (C5b-9)	lysis of target cells

i. Complement-Mediated Lysis: Membrane Attack Complex

The final step of the complement cascade by all three pathways is the formation of the membrane attack complex (MAC) (Figure 1). C5 can be cleaved by any C5 convertase into C5a and C5b. C5b combines with C6 and C7 in solution, and the C5b67 complex associates with the pathogen lipid membrane via hydrophobic sites on C7. C8 and several molecules of C9, which also have hydrophobic sites, join to form the membrane attack complex, also called C5b6789 or C5b-9. C5b-9 forms a pore in the membrane through which water and solutes can pass, resulting in osmotic lysis and cell death. If complement is activated on an antigen without a lipid membrane to which the C5b67 can attach, the C5b67 complex can bind to nearby cells and initiate bystander lysis. A single MAC can lyse an erythrocyte, but nucleated cells can endocytose MAC and repair the damage unless multiple MACs are present. Gram negative bacteria, with their exposed outer membrane and enveloped viruses, are generally susceptible to complement-mediated lysis. Less susceptible are Gram positive bacteria, whose plasma membrane is protected by their thick peptidoglycan layer, bacteria with a capsule or slime layer around their cell wall, or viruses which have no lipid envelope. Likewise, the MAC can be disrupted by proteins that bind to the complex before membrane insertion such as Streptococcal inhibitor of complement (SIC) and clusterin. Typically, the MAC helps to destroy gram-negative

bacteria as well as human cells displaying foreign antigens (virus-infected cells, tumor cells, etc.) by causing their lysis and also can damage the envelope of enveloped viruses.

ii. Inflammation

- 5 Inflammation is a process in which blood vessels dilate and become more permeable, thus enabling body defense cells and defense chemicals to leave the blood and enter the tissues. Complement activation results in the formation of several proinflammatory mediators such as C3a, C4a and C5a. The intact anaphylatoxins in serum or plasma are quickly converted into the more stable, less active C3a-desArg, C4a-desArg, or C5a-desArg forms, by carboxypeptidase N. C3a, C4a and C5a, and to 10 a lesser extent their desArg derivatives, are potent bioactive polypeptides, termed anaphylatoxins because of their inflammatory activity. Anaphylatoxins bind to receptors on various cell types to stimulate smooth muscle contraction, increase vascular permeability, and activate mast cells to release inflammatory mediators.
- 15 C5a, the most potent anaphylatoxin, primarily acts on white blood cells, particularly neutrophils. C5a stimulates leukocyte adherence to blood vessel walls at the site of infection by stimulating the increased expression of adhesion molecules so that leukocytes can squeeze out of the blood vessels and into the tissues, a process termed diapedesis. C5a also stimulates neutrophils to produce reactive oxygen species for 20 extracellular killing, proteolytic enzymes, and leukotrienes. C5a also can further amplify the inflammatory process indirectly by inducing the production of chemokines, cytokines, and other proinflammatory mediators. C5a also interacts with mast cells to release vasodilators such as histamine so that blood vessels become more permeable. C3a also interacts with white blood cells, with major effects on 25 eosinophils indicating a role for C3a in allergic inflammation. C3a induces smooth muscle contraction, enhances vascular permeability, and causes degranulation of basophils and release of histamine and other vasoactive substances. C2a can be converted to C2 kinin, which regulates blood pressure by causing blood vessels to dilate.
- 30 Although technically not considered an anaphylatoxin, iC3b, an inactive derivative of C3b, functions to induce leukocyte adhesion to the vascular endothelium and induce the production of the pro-inflammatory cytokine IL-1 via binding to its

cell surface integrin receptors. C5b-9 also indirectly stimulates leukocyte adhesion, activation, and chemotaxis by inducing the expression of cell adhesion molecules such as E-selectin, and inducing interleukin-8 secretion (Bhole *et al.* (2003) *Crit Care Med* 31(1):97-104). C5b-9 also stimulates the release of secondary mediators that
5 contribute to inflammation, such as for example, prostaglandin E₂, leukotriene B₄, and thromboxane.

Conversion of the human complement components C3 and C5 to yield their respective anaphylatoxin products has been implicated in certain naturally occurring pathologic states including: autoimmune disorders such as systemic lupus
10 erythematosus, rheumatoid arthritis, malignancy, myocardial infarction, Purtscher's retinopathy, sepsis and adult respiratory distress syndrome. In addition, increased circulating levels of C3a and C5a have been detected in certain conditions associated with iatrogenic complement activation such as: cardiopulmonary bypass surgery, renal dialysis, and nylon fiber leukaphoresis.

15 **iii. Chemotaxis**

Chemotaxis is a process by which cells are directed to migrate in response to chemicals in their environment. In the immune response, a variety of chemokines direct the movement of cells, such as phagocytic cells, to sites of infection. For example, C5a is the main chemotactic factor for circulating neutrophils, but also can
20 induce chemotaxis of monocytes. Phagocytes will move towards increasing concentrations of C5a and subsequently attach, via their CR1 receptors, to the C3b molecules attached to the antigen. The chemotactic effect of C5a, observed with basophils, eosinophils, neutrophils, and mononuclear phagocytes, is active at concentrations as low as 10⁻¹⁰ M.

25 **iv. Opsonization**

An important action of complement is to facilitate the uptake and destruction of pathogens by phagocytic cells. This occurs by a process termed opsonization whereby complement components bound to target bacteria interact with complement receptors on the surface of phagocytic cells such as neutrophils or macrophages. In
30 this instance, the complement effector molecules are termed opsonins. Opsonization of pathogens is a major function of C3b and C4b. iC3b also functions as an opsonin.

C3a and C5a increase the expression of C3b receptors on phagocytes and increase their metabolic activity.

C3b and, to a lesser extent, C4b help to remove harmful immune complexes from the body. C3b and C4b attach the immune complexes to CR1 receptors on erythrocytes. The erythrocytes then deliver the complexes to fixed macrophages within the spleen and liver for destruction. Immune complexes can lead to a harmful Type III hypersensitivity.

v. Activation of the Humoral Immune Response

Activation of B cells requires ligation of the B cell receptor (BCR) by antigen. It has been shown, however, that complement plays a role in lowering the threshold for B cell responses to antigen by up to 1000-fold. This occurs by the binding of C3d or C3dg, complement products generated from the breakdown fragments of C3, to CR2 receptors on B-lymphocytes which can co-ligate with the BCR. Co-ligation occurs when antigenic particles, such as for example immune complexes, opsonized with C3d bind the CR2 receptor via C3d as well as the BCR through antigen. Co-ligation of antigen complexes also can occur when C3d binds to antigens enhancing their uptake by antigen presenting cells, such as dendritic cells, which can then present the antigen to B cells to enhance the antibody response. Mice deficient in CR2 display defects in B cell function that result in reduced levels of natural antibody and impaired humoral immune responses.

2. C3 Structure and Function

The variant MTSP-1 polypeptides provided herein cleave complement protein C3 or its proteolytic fragments thereby inhibiting complement. Human complement protein C3 (Uniprot Accession No. P01024) is a 1663 amino acid single chain pre-proprotein having an amino acid sequence set forth in SEQ ID NO:9. The protein is encoded by a 41 kb gene located on chromosome 19 (nucleotide sequence set forth in SEQ ID NO:10). The pre-proprotein contains a 22 amino acid signal peptide (amino acids 1-22 of SEQ ID NO:9) and a tetra-arginine sequence (amino acids 668-671 of SEQ ID NO:9) that is removed by a furin-like enzyme resulting in formation of a mature two chain protein containing a beta chain (amino acids 23-667 of SEQ ID NO:9) and an alpha chain (amino acids 672-1663 of SEQ ID NO:9), that are linked by

an interchain disulfide bond between amino acid residues Cys559 and Cys816. The mature 2 chain protein has a sequence of amino acids set forth in SEQ ID NO:16.

During the complement cascade, complement protein C3 is further processed by proteolytic cleavage to form various C3 proteolytic fragments. As described above,
 5 all three complement initiation pathways converge on the C3 convertases C4b2b and C3bBb. C3 convertases cleave C3 between residues 748 and 749 of SEQ ID NO:9 (see Table 10 below) generating the anaphylatoxin C3a (amino acids 672-748 of SEQ ID NO: 9) and the opsonin C3b (C3b alpha' chain; amino acids 749-1663 of SEQ ID NO: 9). C3a is involved in inflammation and C3b forms the C5 convertases
 10 ultimately leading to C5a anaphylatoxin and the MAC. The variant MTSP-1 polypeptides provided herein inhibit complement, and as such, do not cleave C3 at this GLAR cleavage site.

C3b has binding sites for various complement components including C5, properdin (P), factors H, B and I, complement receptor 1 (CR1) and the membrane
 15 co-factor protein (MCP) (see Sahu and Lambris (2001) *Immunological Reviews* 180:35-48). Binding of factor I, a plasma protease, in the presence of cofactors H, CR1 and MCP results in inactivation of C3b whereas binding of factors B and P in the presence of factor D results in amplification of C3 convertase and initiation of MAC. Factor I cleaves C3b in the presence of cofactors between residues 1303-1304, 1320-
 20 1321 and 954-955 of SEQ ID NO:9 (see Table 10 below) generating fragments iC3b (amino acids 749-1303 of SEQ ID NO: 9) and C3f (amino acids 1304-1320 of SEQ ID NO: 9). Factor I subsequently cleaves iC3b generating C3c (C3c alpha' chain fragment 1; amino acids 749-954 of SEQ ID NO: 9) and C3dg (amino acids 955-1303 of SEQ ID NO: 9). The end result is that C3b is permanently inactivated (see Sahu
 25 and Lambris (2001) *Immunological Reviews* 180:35-48). Since Factor I inactivates C3b, the factor I cleavage sites are ideal candidates for cleavage by the variant MTSP-1 polypeptides provided herein. Additional C3b proteolytic fragments include C3g (amino acids 955-1001 of SEQ ID NO: 9), C3d (amino acids 1002-1303 of SEQ ID NO: 9), and C3c alpha' chain fragment 2 (amino acids 1321-1663 of SEQ ID NO: 9).
 30 Cleavage sequences in complement protein C3 are set forth in Table 10 below, which lists the P4-P1 residues, the amino acid residues of the cleavage site (P1-P1' site) and

the protease responsible for cleavage. The modified MTSP-1 polypeptides provided herein do not cleave at these sites.

TABLE 10: Complement Protein C3 Cleavage Sequences

P4-P1 Residues	Cleavage Site (in SEQ ID NO:9)	Protease	SEQ ID NO
GLAR	748-749	C3 convertase	17
RLGR	954-955	Factor I	18
LPSR	1303-1304	Factor I	19
SLLR	1320-1321	Factor I	20

a. C3a

5 C3a (amino acids 672-748 of SEQ ID NO:9) is an anaphylatoxin that is involved in inflammation, basophil and mast cell degranulation, enhanced vascular permeability, smooth muscle contraction and induction of suppressor T cells.

b. C3b

10 C3b (amino acids 749-1663 of SEQ ID NO:9) has various roles in the complement cascade. C3b is an opsonin that facilitates the uptake and destruction of pathogens by phagocytic cells. Additionally, C3b combines with the C3 convertases to generate the C5 convertases which activate complement protein C5 thereby generating the C5a anaphylatoxin and C5b, which combines with C6, C7, C8 and C9 to form the membrane attack complex. Furthermore, as described in section 1b above,
15 C3b is involved in the alternative pathway of complement initiation. C3b is regulated by complement regulatory protein Factor I, a plasma protease which degrades C3b into various fragments, including iC3b, C3c, C3d, C3f and C3dg, thereby permanently inactivating C3b.

20 C3b plays a critical role in complement-mediated effector functions by virtue of its ability to bind to the C3 convertases C4b2b and C3bBb thereby generating the C5 convertases C4b2b3b and C3bBb3b. The C5 convertases cleave the zymogen C5 into its active fragments, namely the C5a anaphylatoxin and C5b. C5a is involved in chemotaxis and inflammation and C5b is involved in formation of MAC.

i. Inhibitors of C3b

25 C3b has binding sites for various complement components including C5, properdin (P), factors H, B and I, complement receptor 1 (CR1) and the membrane co-factor protein (MCP) (see Sahu and Lambris (2001) *Immunological Reviews*

180:35-48). Binding of factor I, a plasma protease, in the presence of cofactors H, CR1 and MCP results in inactivation of C3b whereas binding of factors B and P in the presence of factor D results in amplification of C3 convertase and initiation of MAC. Factor I cleaves C3b in the presence of cofactors between residues 1303-1304, 1320-1321 and 954-955 of SEQ ID NO:9 generating fragments iC3b (amino acids 749-1303 of SEQ ID NO:9) and C3f (amino acids 1304-1320 of SEQ ID NO:9). Although technically not considered an anaphylatoxin, iC3b, an inactive derivative of C3b, functions to induce leukocyte adhesion to the vascular endothelium and induce the production of the pro-inflammatory cytokine IL-1 via binding to its cell surface integrin receptors. In addition, iC3b functions as an opsonin. Factor I subsequently cleaves iC3b generating fragments C3c (C3c alpha' chain fragment 1: amino acids 749-954 of SEQ ID NO: 9 and C3c alpha' chain fragment 2: amino acids 1321-1663 of SEQ ID NO: 9) and C3dg (amino acids 955-1303 of SEQ ID NO: 9). The end result is that C3b is permanently inactivated (see Sahu and Lambris (2001) *Immunological Reviews* 180:35-48). C3dg can be further cleaved to generate fragments C3g (amino acids 955-1001 of SEQ ID NO: 9) and C3d (amino acids 1002-1303 of SEQ ID NO: 9).

D. MODIFIED MTSP-1 POLYPEPTIDES THAT CLEAVE C3

Provided herein are modified or variant membrane type-serine protease 1 (MTSP-1) polypeptides. The modified MTSP-1 polypeptides provided herein exhibit altered activities or properties compared to a wild-type, native or reference MTSP-1 polypeptide. For example, the MTSP-1 polypeptides provided herein contain modifications compared to a wild-type, native or reference MTSP-1 polypeptide set forth in any of SEQ ID NOS:1-4, or in a polypeptide that has at least 65%, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, particularly at least 95%, sequence identity to any of SEQ ID NOS: 1-4, such as the reference MTSP-1 protease domain set forth in SEQ ID NO:4. Included among the modified MTSP-1 polypeptides provided herein are MTSP-1 polypeptides that alter (inhibit) complement activation by effecting inhibitory cleavage of complement protein C3. Among the modified MTSP-1 polypeptides provided herein are those that effect inhibitory cleavage of complement protein C3. Included are those that effect inhibitory cleavage of C3 with greater activity or specificity, k_{cat}/K_m ,

compared to a corresponding form of the MTSP-1 that does not contain the modification (the replacement, deletion and/or insertion) or compared to the corresponding form of unmodified MTSP-1 whose sequences are set forth in any of SEQ ID NOs:1-4. The modified MTSP-1 polypeptides also can have decreased
5 specificity and/or selectivity for substrates and targets cleaved or recognized by unmodified MTSP-1 compared to a MTSP-1 polypeptide not containing the amino acid modification(s), such as, for example, proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or hepatocyte growth factor (HGF).

The modified MTSP-1 polypeptides provided herein inhibit or inactivate
10 complement through inhibitory or inactivation cleavage of complement protein C3. The modified MTSP-1 polypeptides provided herein inhibit or inactivate complement by cleaving complement protein C3 at a cleavage site that results in inhibition or inactivation of C3. Inactivation or inhibition cleavage of complement protein C3 can be at any sequence in C3 so long as the resulting cleavage of C3 results in inactivation
15 or inhibition of activation of complement. Since the modified MTSP-1 polypeptides provided herein inhibit complement activation, the modified MTSP-1 polypeptides do not effect cleavage of the zymogen form of C3 to generate the C3a and C3b activated fragments. Thus, modified MTSP-1 polypeptides provided herein do not cleave C3 between residues 748-749 of SEQ ID NO: 9, which would result in generation of C3a
20 and C3b. Inhibition or inactivation cleavage sites of complement protein C3 can be empirically determined or identified. If necessary, a modified MTSP-1 polypeptide provided herein can be tested for its ability to inhibit complement as described in section E below and as exemplified in the Examples.

The modified MTSP-1 polypeptides provided herein are isolated protease
25 domains of MTSP-1. Smaller portions thereof that retain protease activity also are contemplated. The protease domains provided herein are single-chain polypeptides with an N-terminus generated at the cleavage site (generally having the consensus sequence R↓VVG, R↓IVGG, R↓IVNG, R↓ILGG, R↓VG, R↓ILGG or a variation thereof; an N-terminus R↓V or R↓I, where the arrow represents the cleavage point)
30 when the zymogen is activated.

The protease domains generated herein, however, do not result from activation, which produces a two chain activated product, but rather are single chain

polypeptides with the N-terminus include the consensus sequence ↓VVGG, ↓IVGG, ↓VGLL, ↓ILGG or ↓IVNG or other such motif at the N-terminus. As shown herein, such polypeptides, although not the result of activation and not double-chain forms, exhibit proteolytic (catalytic) activity. These protease domain polypeptides are used in assays to screen for agents that modulate the activity of the MT-SP. Such assays are also provided herein. In exemplary assays, the effects of test compounds in the ability of a protease domains to proteolytically cleave a known substrate, typically a fluorescently, chromogenically or otherwise detectably labeled substrate, are assessed. Agents, generally compounds, particularly small molecules, that modulate the activity of the protease domain are candidate compounds for modulating the activity of the MT-SP. The protease domains can also be used to produce single-chain protease-specific antibodies. The protease domains provided herein include, but are not limited to, the single chain region having an N-terminus at the cleavage site for activation of the zymogen, through the C-terminus, or C-terminal truncated portions thereof that exhibit proteolytic activity as a single-chain polypeptide in in vitro proteolysis assays, of any MT-SP family member, preferably from a mammal, including and most preferably human, such as, for example, MTSP-1.

The modified MTSP-1 polypeptides provided herein are mutants of the single chain protease domain of MTSP-1, particularly modified MTSP-1 polypeptides in which the Cys residue in the protease domain that is free (*i.e.*, does not form disulfide linkages with any other Cys residue in the protein) is substituted with another amino acid substitution, preferably with a conservative amino acid substitution or a substitution that does not eliminate the activity, such as, for example, substitution with Serine, and modified MTSP-1 polypeptides in which a glycosylation site(s) is eliminated. Modified MTSP-1 polypeptides in which other conservative amino acid substitutions in which catalytic activity is retained are also contemplated (see, *e.g.*, Table 3, for exemplary amino acid substitutions).

The modified MTSP-1 polypeptides provided herein catalyze inhibitory or inactivation cleavage of complement protein C3. The modified MTSP-1 polypeptides provided herein cleave complement protein C3 at any cleavage sequence as long as the resulting C3 fragments are inactive, or unable to activate a complement-mediated effector function. The modified MTSP-1 polypeptides provided herein include those

that have altered (*i.e.*, decreased) specificity and/or selectivity for natural targets of MTSP-1. In one example, the modified MTSP-1 polypeptides provided herein have reduced selectivity for PAR-2, uPA and/or HGF. In other examples, the modified MTSP-1 polypeptides provided herein have increased specificity for cleavage of complement protein C3, and decreased specificity for PAR-2, uPA and/or HGF.

The modified MTSP-1 polypeptides provided herein contain one or more amino acid modifications such that they cleave complement protein C3 in a manner that results in inactivation or inhibition of complement. The modifications can be a single amino acid modification, such as single amino acid replacements (substitutions), insertions or deletions, or multiple amino acid modifications, such as multiple amino acid replacements, insertions or deletions. Exemplary modifications are amino acid replacements, including single or multiple amino acid replacements. The amino acid replacement can be a conservative substitution, such as set forth in Table 3, or a non-conservative substitution, such as any described herein. Modified MTSP-1 polypeptides provided herein can contain at least or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more modified positions compared to the MTSP-1 polypeptide not containing the modification.

The modifications described herein can be made in any MTSP-1 polypeptide. For example, the modifications are made in a human MTSP-1 polypeptide having a sequence of amino acids including or set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, or SEQ ID NO:4; a mouse MTSP-1 polypeptide having a sequence of amino acids including or set forth in SEQ ID NO:12; or a rat MTSP-1 polypeptide having a sequence of amino acids including or set forth in SEQ ID NO:13; or in sequence variants or catalytically active fragments that exhibit at least 65%, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS:1-4, 12 and 13.

The modified MTSP-1 polypeptides provided herein can be modified in any region or domain of a MTSP-1 polypeptide provided herein, as long as the modified MTSP-1 polypeptide retains its ability to effect inactivation or inhibitory cleavage of complement protein C3. The modified MTSP-1 polypeptides provided herein can be single-chain or two chain polypeptides, species variants, splice variants, allelic variants, isoforms, or catalytically active fragments thereof, such as, for example, the

protease domain thereof. The MTSP-1 polypeptides provided herein can be full length or truncated MTSP-1 polypeptides. The modified MTSP-1 polypeptides provided herein can be the protease domain of MTSP-1 or a modified form of the protease domain of MTSP-1. Also contemplated for use herein are zymogen, precursor or

5 mature forms of modified MTSP-1 polypeptides, provided the MTSP-1 polypeptides retain their ability to effect inhibitory or inactivation cleavage of complement protein C3. Modifications in a MTSP-1 polypeptide also can be made to a MTSP-1 polypeptide that also contains other modifications, including modifications of the primary sequence and modifications not in the primary sequence of the polypeptide.

10 For example, modifications described herein can be in a MTSP-1 polypeptide that is a fusion polypeptide or chimeric polypeptide. The modified MTSP-1 polypeptides provided herein also include polypeptides that are conjugated to a polymer, such as a PEG reagent.

For purposes herein, reference to positions and amino acids for modification,

15 including amino acid replacement or replacements, herein are with reference to the MTSP-1 polypeptide set forth in any of SEQ ID NOs:1-4. It is within the level of one of skill in the art to make any of the modifications provided herein in another MTSP-1 polypeptide by identifying the corresponding amino acid residue in another MTSP-1 polypeptide, such as the MTSP-1 polypeptide set forth in any of SEQ ID NOs:1-4 or a

20 variant thereof that exhibits at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to a MTSP-1 polypeptide set forth in any of SEQ ID NOs:1-4. Corresponding positions in another MTSP-1 polypeptide can be identified by alignment of the MTSP-1 polypeptide with the reference a MTSP-1 polypeptide set forth in any of SEQ ID

25 NOs:1-4. For purposes of modification (*e.g.*, amino acid replacement), the corresponding amino acid residue can be any amino acid residue, and need not be identical to the residue set forth in any of SEQ ID NOs:1-4. Typically, the corresponding amino acid residue identified by alignment with, for example, residues in SEQ ID NO:4 is an amino acid residue that is identical to SEQ ID NO:4, or is a

30 conservative or semi-conservative amino acid residue thereto. It is also understood that the exemplary replacements provided herein can be made at the corresponding residue in a MTSP-1 polypeptide, such as the protease domain of MTSP-1, so long as

the replacement is different than exists in the unmodified or reference form of the MTSP-1 polypeptide, such as the protease domain of MTSP-1. Based on this description and the description elsewhere herein, it is within the level of one of skill in the art to generate a modified MTSP-1 polypeptide containing any one or more of the described mutations, and test each for a property or activity as described herein.

The modified MTSP-1 polypeptides provided herein alter complement activity by proteolysis-mediated inhibition or inactivation of complement protein C3. The modified MTSP-1 provided herein can have decreased specificity for a MTSP-1 substrate, such as, for example, proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or hepatocyte growth factor (HGF). For example, the modified MTSP-1 polypeptides provided herein exhibit less than 100% of the wild type activity of a MTSP-1 polypeptide for cleavage of proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or hepatocyte growth factor (HGF), such as less than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10% or less of the activity for cleavage of proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or hepatocyte growth factor (HGF) of a wild type or reference MTSP-1 polypeptide, such as the corresponding polypeptide not containing the amino acid modification. In another example, the modified MTSP-1 polypeptides provided herein exhibit less than 100% of the wild type binding activity of a MTSP-1 polypeptide for PAR-2, uPA and/or HGF, such as less than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10% or less of the activity for binding to PAR-2, uPA and/or HGF of a wild type or reference MTSP-1 polypeptide, such as the corresponding polypeptide not containing the amino acid modification.

Also provided herein are nucleic acid molecules that encode any of the modified MTSP-1 polypeptides provided herein. Nucleic acid molecules that encode a single-chain protease domain or catalytically active portion thereof also are provided. In some examples, the encoding nucleic acid molecules also can be modified to contain a heterologous signal sequence to alter (*e.g.*, increased) expression and secretion of the polypeptide. The modified MTSP-1 polypeptides and encoding nucleic acid molecules provided herein can be produced or isolated by any method known in the art including isolation from natural sources, isolation of recombinantly produced proteins in cells, tissues and organisms, and by recombinant methods and by

methods including *in silico* steps, synthetic methods and any methods known to those of skill in the art. The modified polypeptides and encoding nucleic acid molecules provided herein can be produced by standard recombinant DNA techniques known to one of skill in the art. Any method known in the art to effect mutation of any one or more amino acids in a target protein can be employed. Methods include standard site-directed or random mutagenesis of encoding nucleic acid molecules, or solid phase polypeptide synthesis methods. For example, nucleic acid molecules encoding a MTSP-1 polypeptide can be subjected to mutagenesis, such as random mutagenesis of the encoding nucleic acid, error-prone PCR, site-directed mutagenesis, overlap PCR, gene shuffling, or other recombinant methods. The nucleic acid encoding the polypeptides can then be introduced into a host cell to be expressed heterologously. Hence, also provided herein are nucleic acid molecules encoding any of the modified polypeptides provided herein. In some examples, the modified MTSP-1 polypeptides are produced synthetically, such as using solid phase or solutions phase peptide synthesis.

The MTSP-1 polypeptides provided herein have been modified to have increased specificity and/or selectivity for cleavage of an inhibitory or inactivation cleavage sequence of complement protein C3. MTSP-1 polypeptides can be modified using any method known in the art for modification of proteins. Such methods include site-directed and random mutagenesis. Assays such as the assays for biological function of complement activation provided herein and known in the art can be used to assess the biological function of a modified MTSP-1 polypeptide to determine if the modified MTSP-1 polypeptide targets complement protein C3 for cleavage and inactivation. Exemplary methods to identify an MTSP-1 polypeptide and the modified MTSP-1 polypeptides are provided herein.

1. Exemplary Modified MTSP-1 Polypeptides

Provided herein are modified MTSP-1 polypeptides that contain one more, including 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and more amino acid modifications in a MTSP-1 polypeptide and that cleave complement protein C3 such that complement is inhibited or inactivated. Modifications are in the primary amino acid sequence, and include replacements, deletions and insertions of amino acid residues. The modification alters the specificity/activity of the MTSP-1 polypeptide.

The modified MTSP-1 polypeptides herein are designed or selected to recognize and cleave a target site in a complement protein, particularly C3 in a site that inactivates C3. They also can be further modified and screened to have reduced specificity/activity on *in vivo* natural substrates and/or to cleave such substrates less than an unmodified wild-type MTSP-1 polypeptide. They can be selected and identified by any suitable protease screening method. The modified MTSP-1 polypeptides herein initially were identified using the screening method described in U.S. Patent No. 8,211,428, in which a library of modified proteases are reacted with a cognate or other inhibitory serpin, such as ATIII that is modified to include a target sequence in the reactive site loop to capture modified proteases that would cleave such target.

Modified MTSP-1 polypeptides provided herein display increased activity or specificity or k_{cat}/K_m for complement protein C3 at a site that inactivates C3, and also can have reduced activity or specificity and/or display increased selectivity, specificity and/or activity for a target site on complement protein C3, whereby the modified MTSP-1 polypeptide inactivates C3. The modified MTSP-1 polypeptides exhibit increased activity for cleaving and inactivating C3 compared to the corresponding form of wild-type or wild-type with the replacement C122S (by chymotrypsin numbering). In particular, the protease domain of the modified polypeptide exhibits increased inactivation cleavage activity of C3 compared to the MTSP-1 protease domain of SEQ ID NO:4 (MTSP-1 protease domain with C122S). The increase in activity can be 10%, 20%, 50%, 100%, 1-fold, 2-fold, 3-fold, 4, 5, 6, 7, 8, 9, 10-fold and more compared to the unmodified MTSP-1.

For example, the modified MTSP-1 polypeptide can exhibit 110-1000 % or more of the MTSP-1 activity of a wild type or reference MTSP-1 polypeptide, such as the MTSP-1 polypeptide set forth in any of SEQ ID NOs: 1-4 for inactivating C3. For example, modified MTSP-1 polypeptides provided herein exhibit 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more of the activity of the unmodified or reference MTSP-1 polypeptide, such as the corresponding polypeptide not containing the amino acid modification (*e.g.* amino acid replacement), for example, a MTSP-1 protease domain set forth in any of SEQ ID NOs: 1-4. For example, exemplary

positions that can be modified, for example by amino acid replacement or substitution, include, but are not limited to, any of positions corresponding to position 637, 640, 658, 661, 664, 666, 705, 706, 707, 708, 731, 759, 783, or 801 with reference to the sequence of amino acids set forth in SEQ ID NO:1 (corresponding to positions 38, 41, 59, 60b, 60e, 60g, 96, 97, ins97a, 98, 99, 122, 151, 175, 192 according to chymotrypsin numbering). For example, the amino acid positions can be replacements at positions corresponding to replacement of glutamine (Q) at position 637, I640, Y658, D661, F664, Y666, D705, F706, T707, F708, C731, G759, Q783, or C801 with reference to amino acid positions set forth in SEQ ID NO:1 (corresponding to Q38, I41, Y59, D60b, F60e, Y60g, D96, F97, T98, F99, C122, G151, Q175, C191 according to chymotrypsin numbering).

Exemplary amino acid replacements at any of the above positions are set forth in Table 11. Reference to corresponding position in Table 11 is with reference to positions set forth in SEQ ID NO:1. It is understood that the replacements can be made in the corresponding position in another MTSP-1 polypeptide by alignment with the sequence set forth in SEQ ID NO:1, whereby the corresponding position is the aligned position. For example, the replacement can be made in the MTSP-1 protease domain with the sequence set forth in SEQ ID NO: 2 or a reference MTSP-1 protease domain with the sequence set forth in SEQ ID NO: 4. In some examples, the amino acid replacement(s) can be at the corresponding position in a MTSP-1 polypeptide as set forth in SEQ ID NO: 4 or a variant thereof having at least or at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 86%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, particularly 95%, or more sequence identity thereto, so long as the resulting modified MTSP-1 polypeptide exhibits altered (*i.e.*, enhanced) specificity towards complement protein C3 compared to a reference MTSP-1 polypeptide. In one example, any one or more of the replacements are in any of SEQ ID NOs: 1- 4, so long as the resulting modified MTSP-1 polypeptide exhibits altered (*i.e.*, enhanced) specificity towards complement protein C3 compared to a reference MTSP-1 polypeptide, such as, for example, a reference MTSP-1 polypeptide set forth in any of SEQ ID NOs: 1-4.

Table 11. Active Variants		
Corresponding Position (in SEQ ID NO:1)	Corresponding Position (chymotrypsin numbering)	Replacement

637	38	H
640	41	S, R, A, D
658	59	F
661	60b	T, V
664	60e	S, R K
666	60g	W
705	96	K, V, Y, L, I, P, E
706	97	G, T, E, D, N, Y, W
	97a	Insertion of V, E, A, G, N
707	98	P, G, N
708	99	L
731	122	S
759	151	H, N
783	175	L
801	192	D, E, T

Exemplary of amino acid modifications in the modified MTSP-1 polypeptides provided herein include, but are not limited to, replacement with histidine (H) at a position corresponding to position 38; S at a position corresponding to position 41; R at a position corresponding to position 41; A at a position corresponding to position 41; D at a position corresponding to position 41; F at a position corresponding to position 59; T at a position corresponding to position 60b; V at a position corresponding to position 60b; S at a position corresponding to position 60e; R at a position corresponding to position 60e; K at a position corresponding to position 60e; W at a position corresponding to position 60g; K at a position corresponding to position 96; V at a position corresponding to position 96; Y at a position corresponding to position 96; L at a position corresponding to position 96; I at a position corresponding to position 96; P at a position corresponding to position 96; E at a position corresponding to position 96; G at a position corresponding to position 97; T at a position corresponding to position 97; E at a position corresponding to position 97; D at a position corresponding to position 97; N at a position corresponding to position 97; Y at a position corresponding to position 97; W at a position corresponding to position 97; V at a position corresponding to position 97a; E at a position corresponding to position 97a; A at a position corresponding to position 97a; G at a position corresponding to position 97a; N at a position corresponding to position 97a; P at a position corresponding to position 98; G at a position corresponding to position 98; N at a position corresponding to position 98; L

at a position corresponding to position 99; S at a position corresponding to position 122; H at a position corresponding to position 151; N at a position corresponding to position 151; L at a position corresponding to position 175; D at a position corresponding to position 192; E at a position corresponding to position 192; T at a position corresponding to position 192, according to chymotrypsin numbering each with reference to the amino acid positions set forth in SEQ ID NOs:1 or 3. S at a position corresponding to position 731 (122 S at a position corresponding to position 731) replaces a free Cys to thereby reduce a tendency for aggregation.

Exemplary modified MTSP-1 polypeptides containing amino acid modifications are set forth in Table 12a below. Table 12b includes mature numbering for exemplary modified MTSP-1 polypeptides. The Sequence ID No. references an exemplary MTSP-1 protease domain that contains the recited replacements, which include the replacement at C122S to reduce or eliminate aggregation. C122 is a free cysteine, which can result in cross-linking among the protease polypeptides; this replacement, while advantageous, is optional. It is understood, that the referenced (by SEQ ID NO.) protease domain is exemplary, and full-length and precursor molecules, as well as other catalytically active portions of the protease domain, full-length and precursor polypeptide can include the recited replacements.

Table 12a. Modified MTSP-1 Polypeptides

Chymotrypsin numbering	SEQ ID NO
I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E	21
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	22
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	23
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	24
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	25
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	26
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192D	27
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	28
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D	29
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D	30
Q38H/I41A/D60bV/F60eR/Y60gW/D96P/F97W/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192E	31

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Chymotrypsin numbering	SEQ ID NO
Q38H/I41A/D60bV/F60eR/Y60gW/D96L/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	32
Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97E/ins97aV/T98G/F99L/C122S/G151H/Q175L/Q192D	33
Q38H/I41S/D60bT/F60eS/Y60gW/D96L/F97D/ins97aG/T98N/F99L/C122S/G151H/Q175L/Q192E	34
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35
Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	36
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D	37
Q38H/I41S/D60bT/F60eS/Y60gW/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	38
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	39
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L	40
I41E/F99L/C122S/G151N/Q192T	41
I41D/C122S/G151N/Q192T	42
I41S/F99L/C122S/G151N/Q192V	43
I41E/F99L/C122S/G151N/Q192T	44
I41D/Y59F/D96E/F99L/C122S/G151N/Q192T	45
I41D/Y59F/C122S/G151N/Q192T	46
I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	47
Q38H/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	48
Q38H/I41S/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	49
Q38H/I41S/D60bT/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	50
Q38H/I41S/D60bT/F60eS/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	51
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D	52
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/F99L/C122S/G151H/Q175L/Q192D	53
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/C122S/G151H/Q175L/Q192D	54
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	55
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q192D	56
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D	57
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	58
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	59
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D	63
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	64
Q38H/I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V	65
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	66
I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V	67
I41S/D96M/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	68
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192V/D217I	69

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Chymotrypsin numbering	SEQ ID NO
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192H	70
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192N/D217V	71
I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	72
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	73
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192V	74
I41S/P49S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	75
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192N/D217V	76
I41T/F97W/F99L/C122S/G151N/Q175M/Q192G/D217L	77
I41G/F97L/F99L/C122S/Q175A/Q192T/D217V	78
I41G/F97V/F99L/C122S/G151Q/Q175M/Q192A/D217L	79
I41G/F97I/F99L/C122S/G151L/Q175M/Q192S/D217V	80
I41G/F97S/F99L/C122S/G151N/Q175L/Q192G/D217I	81
F97E/F99L/C122S/D217I/K224N	154
C122S/G193A	155
C122S/G193E	156
D96_F97delinsWYY/T98P/F99L/C122S	157
F97D/F99L/C122S/Q192G	158
H40R/I41H/F97D/F99L/C122S/Q192G	159
C122S/G151N/G193A	160
H40R/I41H/C122S/G151N	161
H40R/I41H/F97D/C122S/G151N	162
H40R/I41H/F97E/C122S	163
F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E	164
H40R/I41H/Y60gL/F97D/F99L/C122S/G151N/Q175M/D217I/K224S	165
H40R/I41H/F97D/F99L/C122S/G151D/Q192G	166
H40R/I41H/F97D/F99L/Q192G	167
H40R/I41H/Y60gH/F97D/F99L/C122S/G151N/Q175A/Q192H/D217I/K224R	168
H40R/I41H/Y60gF/F97D/F99L/C122S/Q192G/D217M/K224R	169
H40R/I41H/Y60gF/F97D/F99L/C122S/Q192G/D217R/K224A	170
H40R/I41H/F97D/F99L/C122S/Q175L/Q192G/D217K/K224A	171
H40R/I41H/F97D/F99L/C122S/Q175M/Q192G/D217V/K224Y	172
H40R/I41H/F97D/F99L/C122S/Q175K/Q192G/D217I/K224H	173
H40R/I41H/F97D/F99L/C122S/Q175M/Q192G/D217S	174
H40R/I41H/Y60gF/F97D/F99L/C122S/Q175M/Q192G/D217W/K224R	175
H40R/I41H/Y60gN/F97D/F99L/C122S/G151N/Q175K/Q192S/D217S/K224L	176
H40R/I41H/Y60gH/F97D/F99L/C122S/Q175M/Q192G/D217I/K224L	177
H40K/I41L/Y60gF/F97D/F99L/C122S/G151N/Q175R	178
H40R/I41H/Y60gL/F97D/F99L/C122S/G151N	179
H40K/I41M/Y60gG/F97D/F99L/C122S/G151N/Q175R/Q192R/D217V/K224S	180
H40K/I41M/Y60gF/F97D/F99L/C122S/G151N/Q175L/Q192D	181
H40R/I41H/F97D/C122S/G151N/Q175M/Q192A/D217S/K224R	182
H40R/I41H/Y60gH/F97D/F99L/C122S/Q175M/Q192G/D217I/K224R	183
H40R/I41H/F97D/F99L/C122S/G151D/Q175M/Q192G/D217V	184
H40R/I41H/F97D/F99L/C122S/G151N/Q175M/Q192A/D217N/K224R	185
H40R/I41H/F97D/F99L/C122S/G151N/Q175L/Q192A/D217N/K224R	186
H40K/I41M/F97D/F99L/C122S/G151N/Q175M/Q192D/D217N/K224R	187
H40K/I41M/F97D/F99L/C122S/G151N/Q175L/Q192A/D217N/K224R	188
H40R/I41H/F97D/F99L/C122S/Q175M/Q192D/D217N/K224R	189
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H40K/I41M/F97D/F99L/C122S/Q175M/Q192D/D217N/K224R	191
H40K/I41M/F97D/F99L/C122S/G151N/Q175M/Q192A/D217N/K224R	192
H40K/I41M/F97D/F99L/C122S/Q175M/D217N/K224R	193
H40R/I41H/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E	194

Chymotrypsin numbering	SEQ ID NO
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H40R/I41H/F97D/F99L/C122S/G151N/Q192H	197
H40R/I41H/F97D/F99L/C122S/G151N/L153R	198
H40R/I41H/F97D/C122S/G151N/L153R/V202M	199
H40R/I41H/F97D/F99L/C122S/G151N/Q192H/P232S	200
H40R/I41H/F97D/ins97aE/T98G/F99L/C122S/Q175L/Q192G	201
H40R/I41H/F97D/C122S/G151N/L153R	202
H40K/I41M/F99L/C122S/T150A/G151R/Q192G	203
H40R/I41H/F97D/C122S/G133D/G151N	204
I41R/F99L/C122S/Q192G	205
H40R/I41H/F99L/C122S/G151K/Q192G	206
I41R/ins97aE/F97T/T98G/F99L/C122S/G151E/Q175L/Q192E	207
K86R/K110R/C122S/K134R/K157R/K224R/K239R	208
H40R/I41H/K86R/F97D/K110R/C122S/K134R/G151N/K157R/K224R/K239R	209
K86R/F97T/ins97aE/T98G/F99L/K110R/C122S/K134R/K157R/Q175L/Q192E/K224R/K239R	210
H40R/I41H/F97D/F99L/C122S/Q175R/Q192G/D217H/K224S	211
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H40R/I41H/F97D/F99L/C122S/Q192G/D217K/K224A	213
H40R/I41H/F97D/F99L/C122S/Q175R/Q192G/D217E/K224R	214
H40R/I41H/F97D/C122S/Q175R/Q192G/D217I/K224Q	215
H40P/I41R/F99L/C122S/Q192G	216
H40P/I41R/F99L/C122S/G151K/Q192G	217
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I41R/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	229
H40P/I41R/F99L/C122S/G151E/Q192G	230
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I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175S/Q192E	232
I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175I/Q192E	233
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H40R/I41H/F97D/F99L/C122S/G151N/Q192N/D217L/K224R	236
H40R/I41H/F97D/F99L/C122S/G151N/Q192H/D217K/K224A	237
ins97aV/F97D/T98P/F99L/C122S/Q192G	238
F97N/ins97aT/T98Y/F99N/C122S	239
F97M/ins97aD/T98D/F99L/C122S/Q192T	240
ins97aV/F97Q/T98P/F99L/C122S/Q175F/Q192D	241
ins97aD/F97T/T98S/F99L/C122S/Q192E/D217Y/K224R	242
ins97aN/F97H/T98D/F99L/C122S/Q192E/D217Q/K224S	243
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ins97aD/F97Q/T98G/F99L/C122S/Q175L/Q192E/D217F/K224S	245
ins97aD/F97G/T98N/F99L/C122S/Q192E/D217Y/K224R	246

Chymotrypsin numbering	SEQ ID NO
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ins97aA/F97G/T98N/F99L/C122S/Q175M/Q192T/K224A	249
I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175S/Q192D	250
I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175I/Q192D	251
I41R/F97T/ins97aE/T98G/F99L/C122S/G151D/Q175I/Q192E	252
I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175I/Q192D	253
S90T/D96A/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	254
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ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E/Q209L	256
Y59F/D96V/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	257
D96V/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	258
I41R/ins97aE/F97T/T98G/F99L/C122S/G151S/Q175L/Q192E	259
E24K/ins97aE/F97T/T98G/F99L/C122S/A152S/Q175L/Q192D	260
ins97aE/F97T/T98G/F99L/C122S/L153Q/Q175L/Q192D	261
ins97aE/F97T/T98G/F99L/C122S/I136M/L155M/N170D/Q175L/Q192E	262
I41R/ins97aE/F97T/T98G/F99L/A112V/C122S/Q175L/Q192E	263
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I41R/Y59F/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	267
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Q38G/H40R/I41H/D60bK/F97D/F99L/C122S/Q175L/Q192G	284
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ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192G	297
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Q38G/H40R/I41H/D60bK/F60eT/F97D/F99L/C122S/Q175L/Q192G	299

Chymotrypsin numbering	SEQ ID NO
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Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192D	342

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Chymotrypsin numbering	SEQ ID NO
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175A/Q192D	343
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D60bY/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G	346
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Q38E/I41V/D60bF/F60eK/Y60gF/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G	357
Q38H/H40P/I41A/F60eQ/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192D	358
Q38R/I41V/D60bV/F60eV/Y60gF/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192G	359
Q38L/H40P/I41T/D60bV/F60eH/Y60gL/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192A	360
Q38H/I41A/D60bV/F60eH/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	361
Q38H/I41S/D60bA/F60eV/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192V	362
Q38R/I41T/D60bH/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192G	363
Q38H/I41S/D60bT/F60eR/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	364
Q38K/I41T/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192A	365
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ins97aA/F97G/T98L/C122S/Q175M/Q192A/D217I/K224R	368
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ins97aL/F97Q/T98G/F99L/C122S/Q175M/Q192S/D217I	371
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Q38Y/I41S/D60bR/F60eE/Y60gF/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192V	373
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Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192V	375
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Q38E/I41A/D60bH/ins97aV/F97D/T98P/F99L/C122S/Q192G/Q209L/D217H	383
I41S/D60bT/F93L/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217H	384

Chymotrypsin numbering	SEQ ID NO
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Q38R/I41T/D60bT/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217N/L233Q	387
Q38H/I41A/D60bW/ins97aV/F97D/T98P/F99L/C122S/I136M/Q192G/D217N	388
Q38H/I41S/P49Q/D60bS/F93L/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217Q	389
Q38H/I41S/D60bT/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217S	390
Q38H/I41S/D60bS/F93L/D96Y/ins97aV/F97D/T98P/F99L/C122S/I136F/Q192G/D217V	391
Q38H/I41T/D60bH/ins97aV/F97D/T98P/F99L/C122S/I136F/L153P/Q192G/D217Y	392
Q38H/I41S/D60bT/F93L/ins97aV/F97D/T98P/F99L/S115N/C122S/Q192V/F208L/D217Q	393
Q38K/I41T/D60bY/ins97aV/F97D/T98P/F99L/C122S/I136T/Q192G/F208V/D217R	394
Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217V	395
Q38H/I41S/D60bG/ins97aV/F97D/T98P/F99L/M117T/C122S/N164D/Q192G/D217E	396
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Q38H/I41S/L52M/D60bH/D96V/ins97aV/F97D/T98P/F99L/C122S/T150A/Q192G/Q209L/D217T	401
I41S/D60bS/D96V/ins97aV/F97D/T98P/F99L/C122S/Q192G/F208L/D217N	402
Q38H/I41S/D60bT/S90T/F97D/ins97aV/T98P/F99L/C122S/S127N/I136F/Q192G/D217Q	403
Q38H/I41S/D60bT/F93S/ins97aV/F97D/T98P/F99L/C122S/I136L/Q192G/D217A	404
I41S/D60bH/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217N	405
L33M/Q38H/I41A/D60bA/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217N	406
Q38H/I41S/D60bY/D96Y/ins97aV/F97D/T98P/F99L/L106M/C122S/I136M/Q192G/Q209L/D217T	407
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Q38H/I41S/D60bS/F60eQ/Y60gF/ins97aV/F97D/T98P/F99L/C122S/H143R/G151N/Q175L/Q192T	418
Q38H/I41S/D60bF/F60eT/ins97aV/F97D/T98P/F99L/C122S/H143Q/G151N/Q175L/Q192G	419

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Chymotrypsin numbering	SEQ ID NO
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Q38H/I41A/D60bV/F60eR/Y60gW/D96Q/F97E/ins97aD/T98S/F99L/C122S/G151N/Q175L/Q192R	424
Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97D/ins97aE/T98S/F99L/C122S/G151H/Q175L/Q192A	425
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Q38H/I41S/D60bT/F60eG/D96Y/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	453
Q38V/I41G/F60eG/Y60gW/D96P/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	454

Chymotrypsin numbering	SEQ ID NO
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Q38Y/I41S/D60bT/F60eR/Y60gW/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	486
Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/T98G/F99L/C122S/G151N/Q175L/Q192D	487

Chymotrypsin numbering	SEQ ID NO
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Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/M117K/C122S/G151H/Q175L/Q192D	493
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I41R/F97A/F99L/C122S/G151N/Q175R/Q192G/D217Q	499
I41S/F97E/F99L/C122S/G151N/Q175G/Q192R/D217A	500
I41G/F97S/F99L/C122S/G151T/Q175R/Q192A/D217Y	501
I41G/F97L/F99L/C122S/G151N/Q175A/Q192V/D217R	502
I41G/F97T/F99M/C122S/G151D/Q175T/Q192T/D217V	503
I41G/F97L/F99L/C122S/G151T/Q175M/Q192D/D217M	504
F97S/F99L/C122S/G151N/Q175I/Q192T/D217T	505
I41G/F99L/C122S/G151N/Q175I/Q192T/D217T	506
I41G/F97S/C122S/G151N/Q175I/Q192T/D217T	507
I41G/F97S/F99L/C122S/Q175I/Q192T/D217T	508
I41G/F97S/F99L/C122S/G151N/Q192T/D217T	509
I41G/F97S/F99L/C122S/G151N/Q175I/D217T	510
I41G/F97S/F99L/C122S/G151N/Q175I/Q192T	511
F97R/ins97aT/T98V/C122S/Q175M/Q192T/D217S	512
F97V/ins97aH/T98R/F99L/C122S/Q175R/Q192G/D217S	513
F97Q/F99L/C122S/Q175N/Q192V/D217G	514
F97L/ins97aM/T98N/F99L/C122S/Q175T/Q192T/D217S	515
F97S/ins97aH/T98G/F99M/C122S/Q175T/Q192T/D217S	516
I41T/F97H/F99L/C122S/G151N/Q175H/Q192V/D217L	517
I41R/F97T/F99L/C122S/G151N/Q175T/Q192T/D217I	518
I41E/F97V/F99L/C122S/G151N/Q175L/Q192S/D217H	519
I41D/F97R/F99L/C122S/G151Q/Q175R/Q192V/D217L	520
I41E/F97R/F99L/C122S/G151Q/Q175G/Q192T/D217V	521
I41D/F97T/F99L/C122S/G151N/Q175S/Q192T/D217A	522
I41E/F97A/F99M/C122S/G151N/Q175R/Q192S/D217E	523
I41G/F99L/C122S/Q175I/Q192T/D217T	524
I41G/F99L/C122S/G151N/Q192T/D217T	525
I41G/F99L/C122S/G151N/Q175I/Q192T	526
F97V/F99L/C122S/G151N/Q175L/Q192S/D217H	527
I41E/F99L/C122S/G151N/Q175L/Q192S/D217H	528
I41E/F97V/F99L/C122S/Q175L/Q192S/D217H	529
I41E/F97V/F99L/C122S/G151N/Q192S/D217H	530
I41E/F97V/F99L/C122S/G151N/Q175L/D217H	531
I41E/F97V/F99L/C122S/G151N/Q175L/Q192S	532
F97R/F99L/C122S/G151Q/Q175R/Q192V/D217L	533
I41D/F99L/C122S/G151Q/Q175R/Q192V/D217L	534
I41D/F97R/F99L/C122S/Q175R/Q192V/D217L	535
I41D/F97R/F99L/C122S/G151Q/Q192V/D217L	536

Chymotrypsin numbering	SEQ ID NO
I41D/F97R/F99L/C122S/G151Q/Q175R/D217L	537
I41D/F97R/F99L/C122S/G151Q/Q175R/Q192V	538
I41E/F97R/F99L/C122S/G151Q/Q175G/Q192T	539
I41D/F99L/C122S/G151N/Q175S/Q192T/D217A	540
I41D/F97T/F99L/C122S/Q175S/Q192T/D217A	541
I41D/F97T/F99L/C122S/G151N/Q192T/D217A	542
I41D/F97T/F99L/C122S/G151N/Q175S/D217A	543
I41D/F97T/F99L/C122S/G151N/Q175S/Q192T	544
F97T/F99L/C122S/G151N/Q175S/Q192T/D217A	545
I41S/F97Q/F99L/C122S/Q175W/Q192V/D217R	546
I41G/F97L/F99L/C122S/G151N/Q192V/D217L	547
I41G/F97A/F99L/C122S/G151N/Q175M/Q192S	548
I41G/F97V/F99L/C122S/G151N/Q192T/D217V	549
I41D/F97R/F99L/C122S/Q175L/Q192T/D217I	550
I41E/F97S/F99L/C122S/Q175L/Q192V/D217A	551
F97L/F99L/C122S/Q175K/Q192V/D217M	552
F97E/F99L/C122S/G151A/Q192V	553
F97E/F99L/C122S/Q175H/Q192V/D217P	554
F97R/ins97aI/T98P/C122S/Q175M/Q192V/D217I	555
I41D/F99L/C122S/G151N/Q192T/D217A	556
I41D/F99L/C122S/G151N/Q175S/Q192T	557
I41D/F97T/F99L/C122S/G151N/Q192T	558
I41D/F99L/C122S/G151N/Q192T	559
I41D/F99L/C122S/Q175S/Q192T	560
I41D/F99L/C122S/Q192T	561
Q38R/I41G/Y60gG/F99M/C122S/G151N/Q192R	562
Q38K/I41G/Y60gG/F99L/C122S/G151N/Q192H	563
Q38L/I41R/Y60gF/F99L/C122S/G151N/Q192A	564
Q38K/I41D/Y60gG/F99L/C122S/G151N	565
Q38R/I41R/Y60gF/F99L/C122S/G151N/Q192G	566
Q38S/I41S/Y60gW/F99L/C122S/G151D/Q192T	567
Q38K/I41G/Y60gW/F99L/C122S/G151N/Q192A	568
Q38H/I41S/Y60gW/C122S/G151H/Q192A	569
Q38K/I41S/Y60gW/F99L/C122S/G151N/Q192G	570
Q38F/I41S/Y60gA/C122S/G151N/Q192R	571
Q38R/I41S/Y60gW/F99L/C122S/G151N/Q192E	572
Q38K/I41R/Y60gG/F99L/C122S/G151N/Q192G	573
Q38R/I41R/F99L/C122S/G151N/Q192G	574
Q38R/I41R/Y60gL/F99L/C122S/G151N/Q192G	575
I41E/C122S/G151N/Q175L/Q192A	576
I41S/F99M/C122S/G151N/Q175L/Q192G	577
I41E/F99L/C122S/G151N/Q175L/Q192A	578
I41S/F99L/C122S/G151H/Q175L/Q192V	579
I41G/F99L/C122S/G151N/Q192A	580
I41S/F99M/C122S/G151N/Q175G/Q192R	581
I41E/F99L/C122S/G151N/Q175R/Q192H	582
I41S/F99M/C122S/G151N/Q175E/Q192R	583
I41E/F99L/C122S/G151N/Q192V	584
I41E/F99L/C122S/G151N/Q192S	585
I41S/F99L/C122S/G151N/Q175P/Q192V	586
I41E/F99L/C122S/G151N/Q175G/Q192T	587
I41S/C122S/G151N/Q175R/Q192R	588
I41S/F99M/C122S/G151N/Q175P/Q192S	589

Chymotrypsin numbering	SEQ ID NO
I41S/C122S/G151N/Q175D/Q192R	590
I41E/F99L/C122S/G151N/Q175R/Q192T	591
I41G/F99L/C122S/G151N/Q175R/Q192A	592
F99L/C122S/G151N/Q192T	593
I41D/F99L/C122S/G151N	594
I41S/F99L/C122S/Q175P/Q192V	595
I41S/F99L/C122S/G151N/Q175P	596
I41E/F99L/C122S/Q175G/Q192T	597
I41E/F99L/C122S/G151N/Q175G	598
I41D/Y59F/F99L/C122S/G151N/Q192T/V213A	599
I41D/G43A/F99L/C122S/G151N/Q192T/P232S/K239R	600
I41D/G43A/D96E/F99L/C122S/G151N/Q192T	601
I41D/D96E/F99L/C122S/G151N/Q192T	602
I41D/D96E/C122S/G151N/Q192T	603
I41D/D96E/F99L/C122S/G151N/Q192T/D217E	604
I41D/F99L/M117T/C122S/G151N/Q192T/A204D/D217E	605
I41D/F99L/C122S/G151N/Q192T/D217E	606
I41D/F99L/C122S/I136M/G151N/Q192T/D217L/K224R	607
I41D/F60eI/D96E/F99L/C122S/G151N/Q192T	608
I41D/C122S/G151N/Q192T/D217E	609
D96E/C122S/G151N/Q192T	610
Y59F/C122S/G151N/Q192T	611
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/F99L/C122S/G151H/Q175L/Q192D	612
I41S/ins97aV/C122S/Q192D	613
I41S/F97L/F99L/C122S/Q192S	614
I41T/F97R/ins97aV/T98L/C122S/Q192S	615
I41S/F97V/T98N/F99L/C122S/Q192S	616
I41S/F97G/ins97aA/T98L/C122S/Q192A	617
I41S/F97D/F99L/C122S/Q192V	618
I41E/F97L/F99L/C122S/Q192A	619
I41S/F97A/ins97aV/T98L/C122S/Q192A	620
I41S/F97del/T98S/F99L/C122S/Q192S	621
I41A/Y60gW/D96F/F97G/F99M/C122S/Q175W/Q192A	622
I41G/Y60gW/F99L/C122S/Q175R/Q192S	623
I41A/Y60gW/ins97aE/F99L/C122S/Q175M/Q192T	624
I41T/ins97aA/F99Y/C122S/Q175L/Q192A	625
I41A/ins97aY/F99L/C122S/Q175R/Q192H	626
I41S/ins97aT/F99L/C122S/Q175R/Q192H	627
I41S/Y60gW/ins97aN/F99L/C122S/Q175R/Q192T	628
Q38H/I41S/D96S/ins97aK/C122S/G151N/Q192A	629
Q38H/I41A/D96A/ins97aA/C122S/G151D/Q192T	630
Q38H/I41S/D96Q/ins97aT/C122S/G151N/Q192A	631
Q38H/I41T/D96M/ins97aA/C122S/G151D	632
Q38Y/I41A/D96I/ins97aQ/C122S	633
Q38H/I41S/D96K/ins97aT/C122S/G151K/Q192A	634
Q38W/I41S/D96R/ins97aA/C122S/G151N/Q192A	635
Q38H/I41A/D96R/ins97aQ/C122S	636
Q38F/I41V/D96Q/ins97aT/C122S/G151D	637
L33M/Q38F/I41S/D96A/ins97aW/C122S/G151N/Q192S	638
Q38H/I41S/D96V/ins97aA/C122S/G151N/Q192A	639
Q38H/I41T/D96K/ins97aL/C122S/G151N/Q192A	640
Q38H/I41S/D96Q/ins97aA/C122S/Q192T	641
Q38W/I41V/D96R/ins97aA/C122S/G151N	642

Chymotrypsin numbering	SEQ ID NO
Q38Y/I41T/D96M/ins97aS/C122S/G151N	643
Q38H/I41S/D96K/ins97aS/C122S/G151P/Q192S	644
Q38H/I41S/D96G/ins97aG/C122S/G151N/Q192A	645
Q38H/I41S/D96K/ins97aD/C122S/G151N/Q192S	646
I41S/D96E/ins97aG/C122S/G151Q/Q192A	647
I41S/Y59F/ins97aV/C122S/G187D/Q192V/D217V	648
A35V/I41S/Y59F/C122S/Q192D/D217V	649
I41S/F93L/ins97aV/C122S/Q192V/D217V	650
I41S/S90P/ins97aV/C122S/Y146E/Q192N/D217V	651
I41S/S90T/ins97aV/C122S/Q192N/D217V	652
I41S/S90T/ins97aV/C122S/Q192V/D217V	653
I41S/Y59F/ins97aV/C122S/Q192G	654
I41S/Y59F/F97S/ins97aV/S116Y/C122S/Q192G/D217V	655
I41S/ins97aV/C122S/Q192G/Q209L	656
Q38H/I41S/ins97aV/A112V/C122S/Q192A/Q209L	657
I41S/ins97aV/C122S/Q192V/D217V	658
I41S/Y59F/ins97aV/C122S/Q192A	659
I41A/F97G/ins97aM/T98L/C122S	660
I41G/F97E/F99L/C122S/Q192A	661
I41S/F97V/ins97aV/T98P/C122S	662
I41S/T98S/F99L/C122S/Q192A	663
I41S/F97Q/F99L/C122S/Q192S	664
I41G/F97L/F99L/C122S/Q192S	665
I41S/F97G/ins97aA/T98P/C122S/Q192A	666
I41A/F97G/ins97aV/T98E/C122S	667
I41A/F97S/ins97aA/C122S	668
I41A/F97W/T98S/F99L/C122S/Q192A	669
I41L/N95D/D96T/F97W/F99L/C122S/Q192A	670
I41T/Y60gL/N95D/D96F/F97S/F99L/C122S/Q175S/Q192A	671
I41A/Y60gW/N95D/D96F/F97G/F99L/C122S/Q175H/Q192A	672
I41A/Y60gW/F99L/C122S/Q175T/Q192A	673
Q38M/I41T/D96M/ins97aH/C122S/G151E	674
Q38H/I41T/D96R/ins97aG/C122S/G151S	675
I41S/D60bY/ins97aV/T98N/C122S/Q192H	676
I41S/Y59F/D60bY/ins97aV/C122S/Q192G	677
I41S/D60bY/ins97aV/A112V/C122S/Q192G/Q209L	678
A35T/I41S/Y59F/ins97aV/C122S/Y146F/V183A/Q192G/R235H	679
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175H/Q192D	680
I41S/ins97aV/C122S/N164D/Q192G/R235H	681
I41S/Y59F/ins97aV/C122S/Q192G/N223D	682
I41S/ins97aV/C122S/N164D/Q192G/R235L	683
I41S/Y59F/F97Y/ins97aV/C122S/Q192G	684
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192V	685
I41S/F99L/C122S/G151N/Q175M/Q192G/D217V	686
I41S/F97L/F99L/C122S/G151N/Q192G/D217V	687
I41S/F97S/F99L/C122S/G151N/Q175L/Q192A/D217L	688
I41G/F97R/F99L/C122S/G151N/Q175L/Q192S/D217V	689
I41T/F97L/F99L/C122S/G151N/Q175S/Q192S/D217W	690
I41D/F97T/F99M/C122S/Q192V/D217M	691

Table 12b. Modified MTSP-1 Polypeptides		
Mature MTSP-1 numbering	Chymotrypsin numbering	SEQ ID NO
I640R/F706T/InsE/T707G/F708L/C731S/G759N/Q783L/Q802E	I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E	21
Q637H/I640A/D661V/F664R/Y666W/F706T/InsE/T707G/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	22
Q637H/I640A/D661T/F664K/Y666W/F706T/InsE/T707G/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	23
Q637H/I640S/D661T/F664S/Y666W/F706D/InsV/T707P/F708L/C731S/G759H/Q783L/Q802E	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	24
Q637H/I640S/D661T/F664S/Y666W/F706D/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	25
Q637H/I640A/D661T/F664K/Y666W/F706T/InsE/T707G/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	26
Q637H/I640S/D661T/F664S/Y666W/F706D/InsV/T707P/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192D	27
Q637H/I640A/D661V/F664R/Y666W/F706T/InsE/T707G/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	28
Q637H/I640A/D661V/F664R/Y666W/D705I/F706Y/InsN/T707G/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D	29
Q637H/I640S/D661T/F664S/Y666W/D705K/F706D/InsA/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D	30
Q637H/I640A/D661V/F664R/Y666W/D705P/F706W/InsN/T707G/F708L/C731S/G759N/Q783L/Q802E	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/F97W/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192E	31
Q637H/I640A/D661V/F664R/Y666W/D705I/F706N/T707G/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	32
Q637H/I640S/D661T/F664S/Y666W/D705Y/F706E/InsV/T707G/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97E/ins97aV/T98G/F99L/C122S/G151H/Q175L/Q192D	33
Q637H/I640S/D661T/F664S/Y666W/D705L/F706D/InsG/T707N/F708L/C731S/G759H/Q783L/Q802E	Q38H/I41S/D60bT/F60eS/Y60gW/D96L/F97D/ins97aG/T98N/F99L/C122S/G151H/Q175L/Q192E	34
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35
Q637H/I640S/D661T/F664S/Y666W/D705V/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	36
Q637H/I640S/D661T/F664S/Y666W/D705K/F706D/InsA/T707P/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D	37
Q637H/I640S/D661T/F664S/Y666W/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	38

Table 12b. Modified MTSP-1 Polypeptides		
Mature MTSP-1 numbering	Chymotrypsin numbering	SEQ ID NO
Q637H/I640S/D661T/F664S/Y666W/D705K/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	39
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L	40
I640E/F708L/C731S/G759N/Q802T	I41E/F99L/C122S/G151N/Q192T	41
I640D/C731S/G759N/Q802T	I41D/C122S/G151N/Q192T	42
I640S/F708L/C731S/G759N/Q802V	I41S/F99L/C122S/G151N/Q192V	43
I640E/F708L/C731S/G759N/Q802T	I41E/F99L/C122S/G151N/Q192T	44
I640D/Y658F/D705E/F708L/C731S/G759N/Q802T	I41D/Y59F/D96E/F99L/C122S/G151N/Q192T	45
I640D/Y658F/C731S/G759N/Q802T	I41D/Y59F/C122S/G151N/Q192T	46
I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	47
Q637H/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	48
Q637H/I640S/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	49
Q637H/I640S/D661T/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	50
Q637H/I640S/D661T/F664S/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	51
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D	52
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/F99L/C122S/G151H/Q175L/Q192D	53
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/C122S/G151H/Q175L/Q192D	54
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	55
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q192D	56
Q637H/I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802D	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D	57
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	58
Q637H/I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	59
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802D	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D	63
Q637H/I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	64
Q637H/I640S/D661Y/D705K/F706G/InsV/T707P/F708L/C731S/Q802D/D828V	Q38H/I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V	65

Table 12b. Modified MTSP-1 Polypeptides		
Mature MTSP-1 numbering	Chymotrypsin numbering	SEQ ID NO
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802G/D828V	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	66
I640S/D661Y/D705K/F706G/InsV/T707P/F708L/C731S/Q802D/D828V	I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V	67
I640S/D705M/F706G/InsV/T707P/F708L/C731S/Q802G/D828V	I41S/D96M/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	68
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802V/D828I	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192V/D217I	69
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802H	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192H	70
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802N/D828V	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192N/D217V	71
I640S/D661Y/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	72
Q637H/I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802G/D828V	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	73
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802V	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192V	74
I640S/P648S/D705K/F706G/InsV/T707P/F708L/C731S/Q802G/D828V	I41S/P49S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	75
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802N/D828V	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192N/D217V	76
I640T/F706W/F708L/C731S/G759N/Q783M/Q802G/D828L	I41T/F97W/F99L/C122S/G151N/Q175M/Q192G/D217L	77
I640G/F706L/F708L/C731S/Q783A/Q802T/D828V	I41G/F97L/F99L/C122S/Q175A/Q192T/D217V	78
I640G/F706V/F708L/C731S/G759Q/Q783M/Q802A/D828L	I41G/F97V/F99L/C122S/G151Q/Q175M/Q192A/D217L	79
I640G/F706I/F708L/C731S/G759L/Q783M/Q802S/D828V	I41G/F97I/F99L/C122S/G151L/Q175M/Q192S/D217V	80
I640G/F706S/F708L/C731S/G759N/Q783L/Q802G/D828I	I41G/F97S/F99L/C122S/G151N/Q175L/Q192G/D217I	81

2. Additional Modifications

Any of the modified MTSP-1 polypeptides provided herein can contain any one or more additional modifications. The additional modifications can include, for example, any amino acid substitution, deletion or insertion known in the art, typically any that increase specificity of a modified MTSP-1 polypeptide for inactivation cleavage of complement protein C3 compared to an unmodified or reference MTSP-1 polypeptide, such as the protease domain. Any modified MTSP-1 polypeptide provided herein can contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more additional amino acid modifications. Also, contemplated are

modifications that alter any other activity of interest. It is long known in the art that amino acid modifications of the primary sequence are additive (see, *e.g.*, Wells (1990) *Biochem* 29:8509-8517). Examples of additional modifications that can be included in the modified MTSP-1 polypeptides provided herein include, but are not limited to,

5 those described in U.S. Patent Nos. 7,939,304; 8,211,428; 8,445,245; 9,290,757; 9,359,598; 8,663,633; U.S. Patent Publication Nos. 2003/0119168; 2007/0093443; 2010/0189652; 2010/0105121; 2012/0244139; 2014/0242062; 2004/0146938; and 2009/0136477; Miyake *et al.* (2010) *Biochim BioPhys Acta* 1804(1):156-165; List *et al.* (2007) *J. Biol. Chem.* 282(50):36714-23; Desilets *et al.* (2008) *J. Biol. Chem.* 283(16):10535-10542; Szabo (2009) *Am J Pathol.* 174(6):2015; Vanagaite *et al.* (2007) *Am J Hum Genet.* 80(3):467; Alef *et al.* (2009) *J Invest Dermatol.* 129(4):862; Ge *et al.* (2006) *J. Biol. Chem.* 281:7406; Takeuchi *et al.* (1999) *PNAS* 96(20):11054-61; Oberst *et al.* (2003) *J. Biol. Chem.* 279(18):26773; and International Patent Publication Nos. WO 2015/166427 and WO 2015/085395. Non-limiting examples of

15 exemplary amino acid modifications described in the art include any one or more of R85H, N109Q, G149N, D251E, N302Q, Q348H, G349Y, R381S, P452R, D482Y, N485Q, D519Y, S524M, D555Y, C574R, D598Y, K600R, C602S, C604S, V615I, V616L, V616G, G617N, G617L, G618L, D622E, Q637D, I640T, I640A, I640L, I640F, I640D, I640E, C641S, L651M, H656A, C657S, D661I, D661F, D661R, D661A, R662F, R662D, R662A, R662W, Y666S, T673K, A674V, H679R, S685R, F702L, N704K, D705A, D705V, D705F, D705S, D705T, F706N, F706D, F706E, F706A, F706W, F706R, F706Y, F706L, T707P, F708Y, F708W, F708N, F708D, F708E, F708A, F708V, F708R, F708I, F708L, F708T, F708S, F708G, D711A, C731S, A735T, V738D, P740S, I745T, I745V, H752R, T753I, T755F, T755N, T755D, T755E, T755A, T755W, T755R, G756E, G759L, I762V, N772Q, N772D, T774A, T775P, C776S, L779F, L780N, L780D, L780E, L780A, L780V, L780F, L780R, P781S, Q780N, Q780D, Q780E, Q780A, Q780V, Q780F, Q780R, P781S, Q782H, Q782A, Q782V, Q782F, Q782R, Q782K, Q782L, Q782Y, Q783D, Q783E, Q783A, Q783V, Q783H, Q783I, Q783L, Q783F, Q783W, Q783Y, Q783R, Q783K, M788E, M788Y, M788R, M788A, C790S, F793L, C801S, Q802A, Q802V, Q802D, Q802R, Q802F, Q802X, Q802L, Q802I, Q802E, Q802K, Q802Y, Q802H, S805A, S811I, Q820L, W826F, W826Y, W826I, W826D, W826R, W826X, G827R, D828A,

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D828V, D828F, D828E, D828R, D828Q, D828N, D828H, C830S, Q832D, Q832L, Q832E, K835A, K835F, K835V, K835D, K835L, K835R, K835N, K835T, K835Y, K835S, K835F, R841W, F845L, and V855G, according to the sequence of amino acids set forth in SEQ ID NO:1. Additional modifications includes amino acid
5 replacements that introduce a glycosylation site.

The modified MTSP-1 polypeptides include those that contain chemical or post-translational modifications. In some examples, modified MTSP-1 polypeptides provided herein do not contain chemical or post-translational modifications. Chemical and post-translational modifications include, but are not limited to, PEGylation,
10 sialylation, albumination, glycosylation, farnesylation, carboxylation, hydroxylation, phosphorylation, and other polypeptide modifications known in the art. Also, in addition to any one or more amino acid modifications, such as amino acid replacements, provided herein, modified MTSP-1 polypeptides provided herein can be conjugated or fused to any moiety using any method known in the art, including
15 chemical and recombinant methods, providing the resulting polypeptide retains the ability to effect inhibitory or inactivation cleavage of complement protein C3.

For example, in addition to any one or more amino acid modifications, such as amino acid replacements, provided herein, modified MTSP-1 polypeptides provided herein also can contain other modifications that are or are not in the primary sequence
20 of the polypeptide, including, but not limited to, modification with a carbohydrate moiety, a polyethylene glycol (PEG) moiety, a sialylation moiety, an Fc domain from immunoglobulin G, or any other domain or moiety. For example, such additional modifications can be made to increase the stability or serum half-life of the protein.

a. Decreased Immunogenicity

25 The modified MTSP-1 polypeptides provided herein can be modified to have decreased immunogenicity. Decreased immunogenicity can be effected by sequence changes that eliminate antigenic epitopes from the polypeptide or by altering post-translational modifications. One of skill in the art is familiar with methods of identifying antigenic epitopes in a polypeptide (*see, e.g., Liang et al. (2009) BMC*
30 *Bioinformatics*, 10:302; Yang et al. (2009) *Rev. Med. Virol.*, 19:77-96). In some examples, one or more amino acids can be modified in order to remove or alter an antigenic epitope. In another example, altering the glycosylation of a protein also can

affect immunogenicity. For example, altering the glycosylation of the peptide is contemplated, so long as the polypeptides retain the ability to effect inhibitory or inactivation cleavage of complement protein C3. Glycosylation sites can be removed by single mutations. Glycosylation sites can be added by introducing a canonical
5 sequence, such as by insertion or single or a plurality of mutations, such as NXS(T), where X is not a proline. Glycosylation sites also can increase serum half-life.

b. Fc Domains

The modified MTSP-1 polypeptides can be linked to the Fc region of an immunoglobulin polypeptide. Typically, such a fusion retains at least a functionally
10 active hinge, C_H2 and C_H3 domains of the constant region of an immunoglobulin heavy chain. For example, a full-length Fc sequence of IgG1 includes amino acids 99-330 of the sequence set forth in the SEQ ID NO: 100. An exemplary Fc sequence for hIgG1 is set forth in SEQ ID NO: 101. It contains almost all of the hinge sequence corresponding to amino acids 100-110 of SEQ ID NO:100; the complete sequence for
15 the C_H2 and C_H3 domain as set forth in SEQ ID NO:100.

Another exemplary Fc polypeptide is set forth in International Patent Publication No. WO 93/10151, and is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody (SEQ ID NO:100). The precise site at which the linkage is made is not
20 critical: particular sites are well known and can be selected in order to optimize the biological activity, secretion, or binding characteristics of the HABP polypeptide. For example, other exemplary Fc polypeptide sequences begin at amino acid C109 or P113 of the sequence set forth in SEQ ID NO: 101 (see *e.g.*, U.S. Pub. No. 2006/0024298).

25 In addition to hIgG1 Fc, other Fc regions also can be used. For example, where effector functions mediated by Fc/FcγR interactions are to be minimized, fusion with IgG isotypes that poorly recruit complement or effector cells, such as for example, the Fc of IgG2 or IgG4, is contemplated. Additionally, the Fc fusions can contain immunoglobulin sequences that are substantially encoded by immunoglobulin
30 genes belonging to any of the antibody classes, including, but not limited to IgG (including human subclasses IgG1, IgG2, IgG3, or IgG4), IgA (including human

subclasses IgA1 and IgA2), IgD, IgE, and IgM classes of antibodies. Linkers can be used to covalently link Fc to another polypeptide to generate a Fc chimera.

Modified Fc domains also are well known. In some examples, the Fc region is modified such that it exhibits altered binding to an FcR resulting in altered (*i.e.* more or less) effector function than the effector function of an Fc region of a wild-type immunoglobulin heavy chain. Thus, a modified Fc domain can have altered affinity, including but not limited to, increased or low or no affinity for the Fc receptor. For example, the different IgG subclasses have different affinities for the FcγRs, with IgG1 and IgG3 typically binding substantially better to the receptors than IgG2 and IgG4. In addition, different FcγRs mediate different effector functions. FcγR1, FcγRIIa/c, and FcγRIIIa are positive regulators of immune complex triggered activation, characterized by having an intracellular domain that has an immunoreceptor tyrosine-based activation motif (ITAM). FcγRIIb, however, has an immunoreceptor tyrosine-based inhibition motif (ITIM) and is therefore inhibitory. Altering the affinity of an Fc region for a receptor can modulate the effector functions and/or pharmacokinetic properties associated by the Fc domain. Modified Fc domains are known to one of skill in the art and described in the literature, see *e.g.*, U.S. Patent No. 5,457,035; U.S. Patent Publication No. US 2006/0024298; and International Patent Publication No. WO 2005/063816 for exemplary modifications.

The resulting chimeric polypeptides containing Fc moieties, and multimers formed therefrom, can be easily purified by affinity chromatography over Protein A or Protein G columns.

c. Conjugation to Polymers

In some examples, the modified MTSP-1 polypeptides provided herein are conjugated to polymers. Polymers can increase the size of the polypeptide to reduce kidney clearance and thereby increase half-life or to modify the structure of the polypeptide to increase half-life or reduce immunogenicity. Exemplary polymers that can be conjugated to the MTSP-1 polypeptides, include natural and synthetic homopolymers, such as polyols (*i.e.*, poly-OH), polyamines (*i.e.*, poly-NH₂) and polycarboxylic acids (*i.e.*, poly-COOH), and other heteropolymers *i.e.* polymers comprising one or more different coupling groups *e.g.* a hydroxyl group and amine groups. Examples of suitable polymeric molecules include polymeric molecules

selected from among polyalkylene oxides (PAO), such as polyalkylene glycols (PAG), including polyethylene glycols (PEG), methoxypolyethylene glycols (mPEG) and polypropylene glycols, PEG-glycidyl ethers (Epox-PEG), PEG-oxycarbonylimidazole (CDI-PEG), branched polyethylene glycols (PEGs), polyvinyl alcohol (PVA), polycarboxylates, polyvinylpyrrolidone, poly-D,L-amino acids, polyethylene-co-maleic acid anhydride, polystyrene-co-maleic acid anhydride, dextrans including carboxymethyl-dextrans, heparin, homologous albumin, celluloses, including methylcellulose, carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, carboxyethylcellulose and hydroxypropylcellulose, hydrolysates of chitosan, starches such as hydroxyethyl-starches and hydroxypropyl-starches, glycogen, agaroses and derivatives thereof, guar gum, pullulan, inulin, xanthan gum, carrageenan, pectin, alginic acid hydrolysates and bio-polymers.

Typically, the polymers are polyalkylene oxides (PAO), such as polyethylene oxides, such as PEG, typically mPEG, which have few reactive groups capable of cross-linking. Typically, the polymers are non-toxic polymeric molecules such as (methoxy)polyethylene glycol (mPEG) which can be covalently conjugated to the MTSP-1 polypeptides (*e.g.*, to attachment groups on the protein surface) using a relatively simple chemistry.

Suitable polymeric molecules for attachment to the MTSP-1 polypeptides include, but are not limited to, polyethylene glycol (PEG) and PEG derivatives such as methoxy-polyethylene glycols (mPEG), PEG-glycidyl ethers (Epox-PEG), PEG-oxycarbonylimidazole (CDI-PEG), branched PEGs, and polyethylene oxide (PEO) (*see e.g.*, Roberts *et al.* (2002) *Advanced Drug Delivery Review* 54: 459-476; Harris and Zalipsky (eds.) "Poly(ethylene glycol), Chemistry and Biological Applications" ACS Symposium Series 680, 1997; Mehvar *et al.* (2000) *J. Pharm. Pharmaceut. Sci.*, 3(1):-136; Harris and Chess (2003) *Nat Rev Drug Discov.* 2(3):214-21; and Tsubery (2004), *J Biol. Chem* 279(37):38118-24). The polymeric molecule can be of a molecular weight typically ranging from about 3 kDa to about 60 kDa. In some embodiments the polymeric molecule that is conjugated to a MTSP-1 polypeptide provided herein has a molecular weight of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 or more than 60 kDa.

Methods of modifying polypeptides by covalently attaching (conjugating) a PEG or PEG derivative (*i.e.*, “PEGylation”) are well known in the art (*see e.g.*, U.S. 2006/0104968; U.S. 5,672,662; U.S. 6,737,505; and U.S. 2004/0235734). Techniques for PEGylation include, but are not limited to, specialized linkers and coupling chemistries (*see e.g.*, Harris (2002) *Adv. Drug Deliv. Rev.* 54:459-476), attachment of multiple PEG moieties to a single conjugation site (such as via use of branched PEGs; *see e.g.*, Veronese *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12:177-180), site-specific PEGylation and/or mono-PEGylation (*see e.g.*, Chapman *et al.* (1999) *Nature Biotech.* 17:780-783), and site-directed enzymatic PEGylation (*see e.g.*, Sato, *Adv. Drug Deliv. Rev.*, 54:487-504, 2002) (see, also, for example, Lu and Felix (1994) *Int. J. Peptide Protein Res.* 43:127-138; Lu and Felix (1993) *Peptide Res.* 6:142-6, 1993; Felix *et al.* (1995) *Int. J. Peptide Res.* 46:253-64; Benhar *et al.* (1994) *J. Biol. Chem.* 269:13398-404; Brumeanu *et al.* (1995) *J Immunol.* 154:3088-95; see also, Caliceti *et al.* (2003) *Adv. Drug Deliv. Rev.* 55(10):1261-77 and Molineux (2003) *Pharmacotherapy* 23 (8 Pt 2):3S-8S). Methods and techniques described in the art can produce proteins having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 PEG or PEG derivatives attached to a single protein molecule (*see e.g.*, U.S. 2006/0104968).

Numerous reagents for PEGylation have been described in the art. Such reagents include, but are not limited to, N-hydroxysuccinimidyl (NHS) activated PEG, succinimidyl mPEG, mPEG2-N-hydroxysuccinimide, mPEG succinimidyl alpha-methylbutanoate, mPEG succinimidyl propionate, mPEG succinimidyl butanoate, mPEG carboxymethyl 3-hydroxybutanoic acid succinimidyl ester, homobifunctional PEG-succinimidyl propionate, homobifunctional PEG propionaldehyde, homobifunctional PEG butyraldehyde, PEG maleimide, PEG hydrazide, p-nitrophenyl-carbonate PEG, mPEG-benzotriazole carbonate, propionaldehyde PEG, mPEG butyraldehyde, branched mPEG2 butyraldehyde, mPEG acetyl, mPEG piperidone, mPEG methylketone, mPEG “linkerless” maleimide, mPEG vinyl sulfone, mPEG thiol, mPEG orthopyridylthioester, mPEG orthopyridyl disulfide, Fmoc-PEG-NHS, Boc-PEG-NHS, vinylsulfone PEG-NHS, acrylate PEG-NHS, fluorescein PEG-NHS, and biotin PEG-NHS (*see e.g.*, Monfardini *et al.*, (1995) *Bioconjugate Chem.* 6:62-69; Veronese *et al.* (1997), *J. Bioactive Compatible Polymers* 12:197-207; U.S. Patent Nos. 5,672,662; U.S.

5,932,462; U.S. 6,495,659; U.S. 6,737,505; U.S. 4,002,531; U.S. 4,179,337; U.S. 5,122,614; U.S. 5,183,550; U.S. 5,324, 844; U.S. 5,446,090; U.S. 5,612,460; U.S. 5,643,575; U.S. 5,766,581; U.S. 5,795, 569; U.S. 5,808,096; U.S. 5,900,461; U.S. 5,919,455; U.S. 5,985,263; U.S. 5,990, 237; U.S. 6,113,906; U.S. 6,214,966; U.S. 6,258,351; U.S. 6,340,742; U.S. 6,413,507; U.S. 6,420,339; U.S. 6,437,025; U.S. 6,448,369; U.S. 6,461,802; U.S. 6,828,401; and U.S. 6,858,736; U.S. Patent Publication Nos. 2001/0021763; U.S. 2001/0044526; U.S. 2001/0046481; U.S. 2002/0052430; U.S. 2002/0072573; U.S. 2002/0156047; U.S. 2003/0114647; U.S. 2003/0143596; U.S. 2003/0158333; U.S. 2003/0220447; U.S. 2004/0013637; U.S. 2004/0235734; U.S. 2005/000360; U.S. 2005/0114037; U.S. 2005/0171328; and U.S. 2005/0209416; European Patent Nos. EP 01064951 and EP 0822199; and International Patent Publication Nos. WO 00/176640; WO 00/02017; WO 02/49673; WO 94/28024; and WO 01/87925).

d. Protein Transduction Domains

15 The modified MTSP-1 polypeptides provided herein can be linked, such as a fusion protein containing an antibody, or antigen binding fragment thereof, conjugated to a protein transduction domain (PTD) that increases the retention of the antibody at a target site for therapy, such as a mucosal site, such as the eye. Any PTD can be employed so long as the PTD promotes the binding to target cell surfaces at the therapeutic site (*e.g.* mucosal site) and/or uptake of the modified MTSP-1 polypeptide by target cells at the therapeutic site (*e.g.* mucosal site, such as the eye).

20 Generally, PTDs include short cationic peptides that can bind to the cell surface through electrostatic attachment to the cell membrane and can be uptaken by the cell by membrane translocation (Kabouridis (2003) *TRENDS Biotech* 21(11) 498-503). The PTDs provided generally interact with a target cell via binding to glycosaminoglycans (GAGs), such as for example, hyaluronic acid, heparin, heparan sulfate, dermatan sulfate, keratin sulfate or chondroitin sulfate and their derivatives.

25 The protein transduction domain can be of any length. Generally the length of the PTD ranges from 5 or about 5 to 100 or about 100 amino acids in length. For example, the length of the PTD can range from 5 or about 5 to 25 or about 25 amino acids in length. In some examples, the PTD is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 amino acids in length.

A single PTD or a plurality thereof can be conjugated to a modified MTSP-1 polypeptide. These are advantageously employed for treatment of ocular or ophthalmic disorders, such as diabetic retinopathies or macular degeneration, including AMD. For example, multiple copies of the same PTD (*e.g.*, dimer, trimer, 5 tetramer, pentamer, hexamer, heptamer, octamer, nonamer, decamer or larger multimer) or different PTDs can be conjugated to the modified MTSP-1 polypeptide.

Several proteins and their peptide derivatives possess cell internalization properties. Exemplary PTDs are known in the art and include, but are not limited to, PTDs listed in Table 13 below, including, for example, PTDs derived from human 10 immunodeficiency virus 1 (HIV-1) TAT (SEQ ID NOS:-135; Ruben *et al.* (1989) *J. Virol.* 63:1-8), the herpes virus tegument protein VP22 (SEQ ID NO: 140; Elliott and O'Hare (1997) *Cell* 88:223-233), the homeotic protein of *Drosophila melanogaster* Antennapedia (Antp) protein (Penetratin PTD; SEQ ID NO: 112; Derossi *et al.* (1996) *J. Biol. Chem.* 271:18188-18193), the protegrin 1 (PG-1) anti-microbial peptide SynB 15 (*e.g.*, SynB1 (SEQ ID NO: 121), SynB3 (SEQ ID NO: 122), and Syn B4 (SEQ ID NO: 123); Kokryakov *et al.* (1993) *FEBS Lett.* 327:231-236) and the Kaposi fibroblast growth factor (SEQ ID NO: 105; Lin *et al.* (1995) *J. Biol. Chem.* 270-14255-14258). Other proteins and their peptide derivatives have been found to possess similar cell internalization properties. The carrier peptides that have been 20 derived from these proteins show little sequence homology with each other, but are all highly cationic and arginine or lysine rich. Indeed, synthetic poly-arginine peptides have been shown to be internalized with a high level of efficiency and can be selected for conjugation to an antibody provided (Futaki *et al.* (2003) *J. Mol. Recognit.* 16:260-264; Suzuki *et al.* (2001) *J. Biol. Chem.* 276:5836-5840). The PTD also can be 25 selected from among one or more synthetic PTDs, including but not limited to, transportan (SEQ ID NO: 136; Pooga *et al.* (1988) *FASEB J.* 12:67-77; Pooga *et al.* (2001) *FASEB J.* 15:1451-1453), MAP (SEQ ID NO: 103; Oehlke *et al.* (1998) *Biochim. Biophys. Acta.* 1414:127-139), KALA (SEQ ID NO: 101; Wyman *et al.* (1997) *Biochemistry* 36:3008-3017) and other cationic peptides, such as, for example, 30 various β -cationic peptides (Akkarawongsa *et al.* (2008) *Antimicrob. Agents and Chemother.* 52(6):2120-2129). Additional PTD peptides and variant PTDs also are provided in, for example, U.S. Patent Publication Nos. US 2005/0260756, US

2006/0178297, US 2006/0100134, US 2006/0222657, US 2007/0161595, US 2007/0129305, European Patent Publication No. EP 1867661, PCT Publication Nos. WO 2000/062067, WO 2003/035892, WO 2007/097561, WO 2007/053512 and Table 13 herein (below). Any such PTDs provided herein or known in the art can be

5 conjugated to a provided therapeutic antibody.

Table 13: Known Protein Transduction Domains		
Protein Transduction Domain (PTD)	Source Protein	SEQ ID NO
TRSSRAGLQFPVGRVHRLLRK	Buforin II	82
RKKRRRESRKKRRRES	DPV3	83
GRPRESGKKRKRRLKP	DPV6	84
GKRKKKGKLGKKRDP	DPV7	85
GKRKKKGKLGKKRPRSR	DPV7b	86
RKKRRRESRRARRSPRHL	DPV3/10	87
SRARRSPRESGKKRKRKR	DPV10/6	88
VKRGLKLRHVPRVTRMDV	DPV1047	89
VKRGLKLRHVPRVTRDV	DPV1048	90
SRARRSPRHLGSG	DPV10	91
LRRERQSRLRRERQSR	DPV15	92
GAYDLRRERQSRLRRERQSR	DPV15b	93
WEAALAEALAEALAEHLAEALAEALAEALAA	GALA	94
KGSWYSMRKMSMKIRPFFPQQ	Fibrinogen beta chain	95
KTRYYSMKKTTMKIIPFNRL	Fibrinogen gamma chain precursor	96
RGADYSLRAVRMKIRPLVTQ	Fibrinogen alpha chain	97
LGTYTQDFNKFHTFPQTAIGVGAP	hCT(9-32)	98
TSPLNIHNGQKL	HN-1	99
NSAAFEDLRVLS	Influenza virus nucleoprotein (NLS)	100
WEAKLAKALAKALAKHLAKALAKALKACEA	KALA	101
VPMLKPMLKE	Ku70	102
KLALKLALKALKAAALKLA	MAP	103
GALFLGFLGAAGSTMGAWSQPKKKRKV	MPG	104
AAVALLPAVLLALLAP	Human Fibroblast growth factor 4 (Kaposi Fibroblast growth factor)	105
VQRKRQKLM	N50 (NLS of NF-kB P50)	106
KETWWETWWTEWSQPKKKRKV	Pep-1	107
SDLWEMMMVSLACQY	Pep-7	108
RQIKIWFQNRMRKWKK	Penetratin	109
GRQIKIWFQNRMRKWKK	Penetratin variant	110
RRMKWKK	Short Penetratin	111

Table 13: Known Protein Transduction Domains		
Protein Transduction Domain (PTD)	Source Protein	SEQ ID NO
ERQIKIWFQNRRMKWKK	Penetratin 42-58	112
RRRRRRR	Poly Arginine - R7	113
RRRRRRRRR	Poly Arginine - R9	114
RVIRVWFQNKRCDDK	pISL	115
MANLGWLLALFVTMWTDVGLCKKRPKP	Prion mouse PrPc1-28	116
LLIILRRRIRKQAHAAHSK	pVEC	117
LLIILRRRIRKQAHAAH	pVEC variant	118
VRLPPPVRLLPPPVRLLPPP	SAP	119
PKKKRKV	SV-40 (NLS)	120
RGGRLSYSSRRRFSTSTGR	SynB1	121
RRLSYSSRRF	SynB3	122
AWSFVSYRGISYRRSR	SynB4	123
YGRKKRRQRRRPPQ	Tat 47-60	124
YGRKKRRQRRR	Tat 47-57	
YGRKKRRQRR	Tat 47-56	126
GRKKRRQRR	Tat 48-56	127
GRKKRRQRRR	Tat 48-57	128
RKKRRQRRR	Tat 49-57	129
RKKRRQRR	Tat 49-56	130
GRKKRRQRRRPPQ	Tat 48-60	131
GRKKR	Tat 48-52	132
CFITKALGISYGRKKRRQRRRPPQFSQTHQVSLSKQ	Tat 37-72	133
FITKALGISYGRKKRRQRRRPPQFSQTHQVSLSKQ	Tat 38-72	134
YGRKKRRQRRRPP	Tat 47-59	135
GWTLSAGYLLGKINLKALAALAKKIL	Transportan	136
AGYLLGKINLKALAALAKKIL	Transportan 10	137
GWTLSAGYLLG	Transportan derivative	138
INLKALAALAKKIL	Transportan derivative	139
DAATATGRSAASRPTERPRAPARSASRRRPVD	VP22	140
DPKGDPKGVTVTVTVTVTGKDPKPD	VT5	141
GALFLGWLGAAGSTMGAWSQPKKKRKV	Signal Sequence-based peptide	142
KLALKLALKALKAALKLA	Amphiphilic model peptide	143
KFFKFFKFFK	Bacterial cell wall permeating	144
LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES	LL- 37	145
SWLSKTAKKLENSAKKRRISEGAIAIAIQGGPR	Cecropin P1	146
ACYCRIPACIAGERRYGTCTIYQGRWAFCC	alpha defensin	147
DHNCVSSGGQCLYSACPIFTKIQTCTYRGKAKCCK	beta defensin	148
RKCRIWIRVCR	Bactenecin	149
RRRPRPPYLPRPRPPPPFFPPRLPPRIPPGFPPRFPPRF PGKR	PR- 39	150

Table 13: Known Protein Transduction Domains		
Protein Transduction Domain (PTD)	Source Protein	SEQ ID NO
ILPWKWPWWPWRR	Indolicidin	151
GALFLGWLGAAGSTMGAWSQPKKKRKV	MPS	152
PVIRRVWFQNKRCCKDKK	pIsI	153

In some examples, the PTDs can be modified by replacement of a lysine or arginine with another basic amino acid, such as replacement of a lysine with an arginine or by replacement of an arginine with a lysine.

E. ASSAYS TO ASSESS AND/OR MONITOR MTSP-1 ACTIVITY ON

5 COMPLEMENT-MEDIATED FUNCTIONS

The modified MTSP-1 polypeptides provided herein exhibit altered specificity and/or selectivity for complement protein C3. Exemplary modified MTSP-1 polypeptides specifically cleave complement protein C3 and thereby alter complement activation. Further, exemplary modified MTSP-1 polypeptides provided herein can have altered, or reduced, specificity and/or selectivity for cleavage of substrates of MTSP-1, such as, for example, proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or hepatocyte growth factor (HGF).

Various *in vitro* and *in vivo* assays can be used to monitor or screen MTSP-1 polypeptides for their ability to cleave complement protein C3 and for their effects on complement activation and complement-mediated diseases and disorders. Such assays are well known to those of skill in the art. One of skill in the art can test a particular MTSP-1 polypeptide for cleavage of complement protein C3 and/or test to assess any change in the effects of a MTSP-1 on a complement-mediated activity compared to the absence of a protease. Some such assays are exemplified herein.

Exemplary *in vitro* and *in vivo* assays are provided herein for comparison of an activity of a modified MTSP-1 polypeptide on the function of complement protein C3. In addition, numerous assays, such as assays for measuring complement activation, are known to one of skill in the art. Assays for activities of complement include, but are not limited to, assays that measure activation products of complement activation, such as for example the C5b-9 MAC complex, and generation of any one or more of the complement cleavage products such as C5a, C3b, and C3d. Assays to measure complement activation also include functional assays that measure the functional activity of specific components of the complement pathways, such as for

example hemolytic assays used to measure activation of any one of the classical, lectin or alternative pathways. Assays to assess effects of MTSP-1 polypeptides on complement proteins and/or complement-mediated functions include, but are not limited to, SDS-PAGE analysis followed by Western Blot or Coomassie Brilliant Blue staining, enzyme immunoassays, and hemolytic assays. In one example, *in vitro* assays can be performed using purified complement protein C3, as exemplified in Example 2. In another example, *in vivo* assays can be performed by testing the serum of a species, including mammalian or human species, for functional activation of complement, as exemplified in Examples 8 and 10. In another example, *in vitro* assays can be performed by testing the serum of a species, including mammalian or human species, for functional activation of complement, as exemplified in Examples 4-6. In another example, *in vitro* assays can be performed using peptide libraries, as exemplified in Examples 5-7. Various disease models known to one of skill in the art can be used to test the efficacy of MTSP-1 polypeptides provided herein on various complement-mediated diseases and disorders.

Also provided herein are exemplary assays for determining the activity of the modified MTSP-1 polypeptides for wild type MTSP-1 activities, such as cleavage of proteinase-activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or hepatocyte growth factor (HGF). Also provided are assays for determining the specificity of the modified MTSP-1 polypeptides for complement protein C3. Exemplary assays are described below.

1. Methods for Assessing MTSP-1 Activity and Specificity for Cleaving Complement Protein C3 to Inactivate it

A modified MTSP-1 protease can exhibit alterations in specificity and/or selectivity for inactivating C3, compared to the corresponding full-length wildtype or protease domain or corresponding form of the unmodified MTSP-1 protease (*i.e.*, the MTSP-1 polypeptides of SEQ ID NOs.: 1-4). Modified MTSP-1 proteases provided herein can retain protease activity, but exhibit an increased specificity and/or selectivity or activity for cleaving C3 to thereby inhibit complement activation. All such modified MTSP-1 proteases with increased specificity and/or selectivity to any one or more complement protein are candidate therapeutics for treating any disorder in which complement activation plays a role or is involved.

Where the modified MTSP-1 protease exhibits an increased specificity and/or selectivity to any one or more complement protein, *in vitro* and *in vivo* assays can be used to monitor or screen proteases for effects on complement-mediated functions. Such assays are well known to those of skill in the art. One of skill in the art can test a modified MTSP-1 protease for cleavage of C3 and/or test to assess any change in the effects of a modified MTSP-1 protease on a complement-mediated activity compared to the absence of a modified MTSP-1 protease. Some such assays are exemplified herein.

Exemplary *in vitro* and *in vivo* assays are provided herein for comparison of an activity of a modified MTSP-1 protease on the function of any one or more targeted complement proteins. Many of the assays are applicable to other proteases and modified proteases. In addition, numerous assays, such as assays for measuring complement activation, are known to one of skill in the art. Assays for activities of complement include, but are not limited to, assays that measure activation products of complement activation, such as for example the C5b-9 MAC complex, and generation of any one or more of the complement cleavage products such as C4a, C5a, C3b, and C3d. Assays to measure complement activation also include functional assays that measure the functional activity of specific components of the complement pathways, such as for example hemolytic assays used to measure activation of any one of the classical, lectin or alternative pathways. Assays to assess effects of proteases and modified proteases on complement proteins and/or complement-mediated functions include, but are not limited to, SDS-analysis followed by Western Blot or Coomassie Brilliant Blue staining, enzyme immunoassays, and hemolytic assays. In one example, *in vitro* assays can be performed using purified complement proteins. In another example, *in vivo* assays can be performed by testing the serum of a species, including mammalian or human species, for functional activation of complement. Exemplary assays are described below.

a. Protein Detection

Protein detection is a means to measure individual complement components in a sample. Complement proteins can be detected to assess directly the effects of a MTSP-1 polypeptide on cleavage of complement protein C3, or alternatively, complement proteins can be measured as a means to assess complement activation.

Complement protein C3, treated in the presence or absence of a MTSP-1 polypeptide, can be analyzed by any one or more assays including SDS-PAGE followed by Coomassie staining or Western Blot, enzyme immunoassay, immunohistochemistry, flow cytometry, nephelometry, agar gel diffusion, or radial immunodiffusion.

5 Exemplary assays for protein detection are described below.

i. SDS-PAGE Analysis

Analysis of complement proteins in the presence or absence of increasing concentrations of MTSP-1 polypeptide can be performed by analysis of proteins on SDS-PAGE followed by detection of those proteins. In such examples, complement
10 proteins can be detected by staining for total protein, such as by Coomassie Brilliant Blue stain, Silver stain, or by any other method known to one of skill in the art, or by Western Blot using polyclonal or monoclonal antibodies specific for a specified protein. Typically, a purified complement protein, such as for example complement protein C3, can be incubated in the presence or absence of a MTSP-1 polypeptide.
15 The treated complement protein can be resolved on an SDS-PAGE gel followed by a method to detect protein in the gel, for example, by staining with Coomassie Brilliant blue. The treated protein can be compared to its cognate full length protein and the degradation products formed by protease cleavage of the protein can be determined.

In another embodiment, a sample, such as for example human serum or
20 plasma or breast milk, can be treated in the presence or absence of a MTSP-1 polypeptide or can be collected after treatment of an animal or a human with or without a MTSP-1 polypeptide. The MTSP-1 -treated sample can be analyzed on SDS-PAGE and a specific complement protein can be detected, such as for example C3, C5, or Factor B, by Western Blot using monoclonal or polyclonal antibodies
25 against the protein. The cleavage of the complement protein can be compared to a sample that was not treated with a MTSP-1 polypeptide. Additionally, the sample can be stimulated to initiate complement activation such as by incubation with IgG which stimulates activation of the classical pathway or by LPS which stimulates activation of the alternative pathway. The sample can be resolved by SDS-PAGE for detection
30 of any one or more of the native complement proteins to determine the presence or absence of cleavage products of a specified protein compared to a sample of the protein not treated with a MTSP-1 polypeptide. In such examples, cleavage effector

molecules of native complement proteins also can be analyzed by Western Blot using monoclonal and polyclonal antibodies to assess the activation of one or more of the complement pathways. Examples of complement effector molecules can include, but are not limited to, C3a, C3d, iC3b, Bb, and C5-b9. For example, decreased expression
5 in a sample of Bb can indicate that a MTSP-1 polypeptide inhibited the activation of the alternative pathway of complement. The cleavage products of the effector molecules also can be determined to assess the effects of increasing concentrations of a MTSP-1 polypeptide on the cleavage of complement effector molecules themselves.

10

ii. Enzyme Immunoassay

Enzyme immunoassay (EIA; also called enzyme-linked immunosorbent assay; ELISA) is an assay used to measure the presence of a protein in a sample. Typically, measurement of the protein is an indirect measurement of the binding of the protein to an antibody, which itself is chemically labeled with a detectable substrate such as an
15 enzyme or fluorescent compound. EIA assays can be used to measure the effects of MTSP-1 polypeptides on complement activation by measuring for the presence of a complement effector molecule generated following complement activation. In such examples, a sample, such as for example human serum or plasma, can be pretreated in the presence or absence of increasing concentrations of a MTSP-1 polypeptide and
20 subsequently activated to induce complement activation by incubation with initiating molecules, or can be collected following treatment of an animal or a human with a MTSP-1 polypeptide. For example, the classical pathway can be activated by incubation with IgG and the alternative pathway can be activated by incubation of the sample with LPS. A complement activation assay specific for the lectin pathway
25 requires that the classical pathway of complement is inhibited since the C4/C2 cleaving activity of the lectin pathway is shared with the classical pathway of complement. Inhibition of the classical pathway can be achieved using a high ionic strength buffer which inhibits the binding of C1q to immune complexes and disrupts the C1 complex, whereas a high ionic strength buffer does not affect the carbohydrate
30 binding activity of MBL. Consequently, activation of the lectin pathway can be induced by incubation of a sample, such as human serum or plasma, with a mannan-coated surface in the presence of 1 M NaCl.

Following activation, the sample can be quenched with the addition of Pefabloc (Roche) and EDTA to minimize continued activation of the pathways. Samples can be analyzed for the presence of complement effector molecules by an EIA or ELISA assay. EIA and ELISA assays for measuring complement proteins are well known to one skilled in the art. Any complement activation product can be assessed. Exemplary complement activation products for measurement of complement activation include iC3b, Bb, C5b-9, C3a, C3a-desArg and C5a-desArg. The complement pathway activated can be determined depending on the complement activation product measured. For example, measurement of Bb cleavage product is a unique marker of the alternative pathway.

In some examples, the EIA can be paired with detection of the cleaved complement proteins by analysis of the protease-treated, complement-stimulated sample by SDS-PAGE followed by Western blot analysis for identification of specific complement components. Using densitometry software, the cleavage of the complement product can be compared to the full length complement component cleaved throughout the assay and the appearance of all major degradation products and the percent cleavage can be determined.

iii. Radial Immunodiffusion (RID)

Radial immunodiffusion (RID) is a technique that relies on the precipitation of immune complexes formed between antibodies incorporated into agarose gels when it is poured, and antigen present in a test sample resulting in a circular precipitin line around the sample well. The diameter of the precipitin ring is proportional to the concentration of the antibody (or antigen) present in the test sample. By comparing the diameter of the test specimen precipitin ring to known standards, a relatively insensitive estimation of the concentration of specific antibody or antigen can be achieved. RID can be used to measure the amount of a complement protein in a sample. For example, a sample such as for example human serum or plasma, can be treated in the presence or absence of increasing concentrations of a MTSP-1 polypeptide. The protease-treated sample can be added to a well of an agarose gel that has been made to incorporate a polyclonal or monoclonal antibody against any one of the complement proteins such as including, but not limited to, C3, C5, C6, C7, C9, or Factor B. After removal of unprecipitated proteins by exposure to 0.15 M NaCl, the

precipitated protein rings can be assessed by staining with a protein dye, such as for example Coomassie Brilliant blue or Crowles double stain.

b. Hemolytic Assays

Functional hemolytic assays provide information on complement function as a whole. This type of assay uses antibody-sensitized or unsensitized sheep erythrocytes. Hemolytic assays include the total hemolytic complement assay (CH50), which measures the ability of the classical pathway and the MAC to lyse a sheep RBC. It depends on the sequential activation of the classical pathway components (C1 through C9) to lyse sheep erythrocytes that have been sensitized with optimal amounts of rabbit anti-sheep erythrocyte antibodies to make cellular antigen-antibody complexes. Hemolytic assays also can include an alternative pathway CH50 assay (rabbit CH50 or APCH50), which measures the ability of the alternative pathway and the MAC to lyse a rabbit RBC. One CH50 and/or APCH50 unit is defined as the quantity or dilution of serum required to lyse 50% of the red cells in the test. Typically, to assess complement activation, a sample, such as for example human serum or human plasma, can be treated in the presence or absence of increasing concentrations of a MTSP-1 polypeptide, or can be collected following treatment of an animal or human in the presence or absence of a MTSP-1 polypeptide. The protease-treated sample can be subsequently mixed with sheep's red blood cells that have been activated or sensitized with IgG. A water only sample mixed with sheep red blood cells can act as a total lysis control in order to accurately assess percent lysis of the samples analyzed. The addition of 0.15M NaCl to the sample can be added to stop the lysing reaction. Lysis of the red blood cells, induced by the activation of the terminal components of the complement pathway, can be assessed by measuring the release of hemoglobin. Measurement can be by optical density (OD) readings of the samples using a spectrophotometer at an OD of 415 nm.

In one embodiment, limiting dilution hemolytic assays can be used to measure functional activity of specific components of either pathway. In such an assay, a serum source is used that has an excess of all complement components, but is deficient for the one being measured in the sample, *i.e.*, a media or serum source is complement-depleted for a specific protein. The extent of hemolysis is therefore dependent on the presence of the measured component in the test sample. In such an

assay, a purified complement protein, such as for example any one of the native complement proteins including, but not limited to C3, can be incubated in the presence or absence of increasing concentrations of a MTSP-1 polypeptide. The protease-treated purified complement protein can then be mixed with complement-
5 depleted media or plasma and IgG-activated sheep red blood cells and hemolysis of the sample can be assessed as described above. In another embodiment, protease cleavage can be correlated with complement activation by assaying for hemolytic activity of a protease-treated sample, and subsequently analyzing the sample on SDS-PAGE gel followed by staining with a protein stain, such as for example Coomassie
10 Blue. The purified complement protein treated with the proteases can be assessed for cleavage and the percentage of the full length complement component cleaved throughout the assay and the appearance of all major degradation products can be calculated. Alternatively, analysis of the protease-treated complement protein can be by Western blot.

15 An alternative to the hemolytic assay, called the liposome immunoassay (LIA), can be used to assess activation of the classical pathway. The LIA (Waco Chemicals USA, Richmond, Va.) utilizes dinitrophenyl (DNP)-coated liposomes that contain the enzyme glucose-6-phosphate dehydrogenase. When serum is mixed with the liposomes and a substrate containing anti-DNP antibody, glucose-6-phosphate,
20 and nicotinamide adenine dinucleotide, activated liposomes lyse, and an enzymatic colorimetric reaction occurs which is proportional to total classical complement activity.

c. Methods for Determining Cleavage Sites

Cleavage sequences in complement protein C3 can be identified by any
25 method known in the art (see *e.g.*, published U.S. Publication No. US 2004/0146938). In one example, a cleavage sequence is determined by incubating complement protein C3 with any modified MTSP-1 polypeptide provided herein. Following incubation with the MTSP-1 polypeptide, the C3 protein can be separated by SDS-PAGE and degradative products can be identified by staining with a protein dye such as
30 Coomassie Brilliant Blue. Proteolytic fragments can be sequenced to determine the identity of the cleavage sequences. After identification, fluorogenic peptide substrates

designed based on the cleavage sequence of a desired target substrate can be used to assess activity, as described below.

2. Methods for Assessing Wild Type MTSP-1 Activity

The modified MTSP-1 polypeptides provided herein can have altered, or
5 reduced, specificity for their normal substrates, such as, for example, proteinase-
activated receptor-2 (PAR-2), urokinase-type plasminogen activator (uPA), and/or
hepatocyte growth factor (HGF). Modified MTSP-1 polypeptides can be tested to
determine whether they retain catalytic efficiency and/or substrate specificity for their
native substrate. For example, cleavage of PAR-2 can be assessed by incubation of a
10 MTSP-1 polypeptide with PAR-2 and detecting protein cleavage products. In another
example, cleavage of PAR-2 can be determined *in vitro* by measuring cleavage of a
fluorogenically tagged tetrapeptide of the peptide substrate, for example, a
fluorogenic substrate, such as fluorophores ACC (7-amino-4-carbamoyl-methy-
coumarin)- or AMC- (7-amino-4-methylcoumarin) linked to a tetrapeptide. In some
15 examples, PAR-2 activation assays are used to determine the specificity of the MTSP-
1 polypeptides provided herein.

In another example, cleavage of C3 can be assessed by incubation of a MTSP-
1 polypeptide with C3 and detecting protein cleavage products. In another example,
cleavage of C3 can be determined *in vitro* by measuring cleavage of a fluorogenically
20 tagged tetrapeptide of the peptide substrate, for example, an ACC- or AMC-
tetrapeptide. In some examples, C3 activation assays are used to determine the
specificity of the modified MTSP-1 polypeptides provided herein. In another
example, cleavage of HGF can be assessed by incubation of a modified MTSP-1
polypeptide with HGF and detecting protein cleavage products. In another example,
25 cleavage of HGF can be determined *in vitro* by measuring cleavage of a
fluorogenically tagged tetrapeptide of the peptide substrate, for example, an ACC- or
AMC- tetrapeptide. In some examples, HGF activation assays are used to determine
the specificity of the MTSP-1 polypeptides provided herein. In other examples, the
ability of the MTSP-1 polypeptides provided herein to form a complex with the
30 Kunitz-type serine protease inhibitor, hepatocyte growth factor activator inhibitor-1
(HAI-1) is determined.

a. Cleavage of MTSP-1 Substrates

In one example, modified MTSP-1 polypeptides can be assayed using individual fluorogenic peptide substrates corresponding to the desired cleavage sequence. For example, a method of assaying for a modified MTSP-1 protease that
5 can cleave any one or more of the desired cleavage sequences includes: (a) contacting a peptide fluorogenic sample (containing a desired target cleavage sequence) with a protease, in such a manner whereby a fluorogenic moiety is released from a peptide substrate sequence upon action of the protease, thereby producing a fluorescent moiety; and (b) observing whether the sample undergoes a detectable change in
10 fluorescence, the detectable change being an indication of the presence of the enzymatically active protease in the sample. In such an example, the desired cleavage sequence is made into a fluorogenic peptide by methods known in the art. In one embodiment, the individual peptide cleavage sequences can be attached to a fluorogenically tagged substrate, such as for example an ACC or AMC fluorogenic
15 leaving group, and the release of the fluorogenic moiety can be determined as a measure of specificity of a protease for a peptide cleavage sequence. The rate of increase in fluorescence of the target cleavage sequence can be measured such as by using a fluorescence spectrophotometer. The rate of increase in fluorescence can be measured over time. Michaelis-Menton kinetic constants can be determined by the
20 standard kinetic methods. The kinetic constants k_{cat} , K_m and k_{cat}/K_m can be calculated by graphing the inverse of the substrate concentration versus the inverse of the velocity of substrate cleavage, and fitting to the Lineweaver-Burk equation ($1/\text{velocity} = (K_m/V_{max})(1/[S]) + 1/V_{max}$; where $V_{max} = [ET]k_{cat}$). The second order rate constant or specificity constant (k_{cat}/K_m) is a measure of how well a substrate is cut by
25 a particular protease. For example, an ACC- or AMC- tetrapeptide such as Ac-CPGR-AMC or can be made and incubated with a modified MTSP-1 polypeptide provided herein and activity of the MTSP-1 polypeptide can be assessed by assaying for release of the fluorogenic moiety. The choice of the tetrapeptide depends on the desired cleavage sequence to be assayed for and can be empirically determined.

30 In other embodiments, MTSP-1 polypeptides also can be assayed to ascertain that they will cleave the desired sequence when presented in the context of the full-length protein. In one example, a purified target protein, *i.e.*, PAR-2, uPA or HGF,

can be incubated in the presence or absence of a selected MTSP-1 polypeptide and the cleavage event can be monitored by SDS-PAGE followed by Coomassie Brilliant Blue staining for protein and analysis of cleavage products using densitometry.

b. MTSP-1-Substrate Binding Assays

5 Binding of the MTSP-1 polypeptides to an MTSP-1 substrate can be assessed by any assay known to one of skill in the art to detect protein-protein binding interactions, including but not limited to solid phase binding assays, ELISA, surface plasmon resonance and FACS. In one example, ELISA can be used. The recombinant substrate protein is immobilized on a microtiter plate and MTSP-1 polypeptide
10 binding is measured by addition of a reagent that specifically binds to MTSP-1, such as, for example, an MTSP-1 binding antibody. In another example, binding can be determined in a cell based assay using a cell line that expresses substrate. The MTSP-1 polypeptides can be labeled, for example, with a chromogenic, fluorogenic or radioactive substrate to effect detection of binding.

15 **c. C3 Cleavage Assays**

The activity of the modified MTSP-1 polypeptides can be assessed by cleavage of the substrate complement protein human C3 by measuring the amount of intact human C3 remaining after incubation with various concentrations of the modified MTSP-1 protease. In accord with this assay, signal is generated in the
20 presence of intact human C3, and is lost as the C3 is cleaved.

Purified C3 protein can be incubated with the modified MTSP-1 polypeptides and the residual levels of undigested human C3 can be quantified by any assay known in the art to assess protein concentration, such as, for example using an Amplified Luminescent Proximity Homogeneous Assay Screen (AlphaScreen; Perkin Elmer).
25 The C3/ MTSP-1 polypeptide mixture is incubated with α -mouse IgG-coated acceptor beads, and following incubation the α -hC3 mAb/acceptor beads mixture is incubated with a biotinylated α -hC3 pAb. Streptavidin-coated donor beads are added to the mixture and the 'alphascreen' signal (Excitation = 680 nm, Emission = 570 nm) is then measured. This signal corresponds to the concentration of remaining C3 protein. The
30 concentration of MTSP-1 polypeptide required to cleave through 50% of the available hC3 (EC_{50}) can be calculated.

3. Specificity

The specificity constant of cleavage of target substrate, *e.g.*, complement protein C3 or an MTSP-1 substrate, such as, for example, PAR-2, uPA or HGF, by a modified MTSP-1 polypeptide can be determined by using gel densitometry to assess changes in densitometry over time of a full-length target substrate incubated in the presence of a MTSP-1 polypeptide. In specific embodiments, comparison of the specificities of a modified MTSP-1 polypeptide can be used to determine if the modified MTSP-1 polypeptide exhibits altered, for example, increased, specificity for C3 compared to the wild-type or reference MTSP-1 polypeptide. The specificity of a MTSP-1 polypeptide for a target substrate, *e.g.* complement protein C3, can be determined from the specificity constant of cleavage of a target substrate compared to a non-target substrate (*e.g.* the native wild type substrate of MTSP-1). A ratio of the specificity constants of a modified MTSP-1 polypeptide for the target substrate C3 versus a non-target substrate, such as, for example, PAR-2, uPA or HGF, can be made to determine a ratio of the efficiency of cleavage of the modified MTSP-1 polypeptide. Comparison of the ratio of the efficiency of cleavage between a modified MTSP-1 polypeptide and a wild-type or reference MTSP-1 polypeptide can be used to assess the fold change in specificity for a target substrate. Specificity can be at least 2-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 times or more when compared to the specificity of a wild-type MTSP-1 polypeptide for a target substrate versus a non-target substrate.

Kinetic analysis of cleavage of native substrates of a MTSP-1 polypeptide can be compared to analysis of cleavage of desired target substrates in complement protein C3 to assess specificity of the modified MTSP-1 polypeptide for complement protein C3. In addition, second order rate constants of inhibition (k_i) can be assessed to monitor the efficiency and reactivity of a modified MTSP-1 polypeptide for complement protein C3. For purposes herein, the modified MTSP-1 polypeptides cleave C3 so that complement activation is inhibited, and, as shown in the Examples, they do so with significantly greater activity, such as at least 5-fold more activity, than unmodified modified MTSP-1 polypeptide (or modified MTSP-1 polypeptide with the C122S replacement, which eliminates a free cysteine to thereby reduce aggregation.

For example, the modified MTSP-1 polypeptide of SEQ ID NO:35, cleaves human C3 in the assay described herein with an ED_{50} of 2 nM, compared to 11 nM for the wild-type protease domain of SEQ ID NO:4.

4. Disease Models

5 The modified MTSP-1 polypeptides provided herein can be used in any clinically relevant disease model known to one of skill in the art to determine their effects on complement-mediated diseases or disorders. Exemplary assays include, but are not limited to, assays for transplantation, including *in vitro* assays with human islet cells (Tjernberg *et al.* (2008) *Transplantation* 85:1193-1199) and *ex vivo* assays
10 with pig kidneys (Fiane *et al.* (1999) *Xenotransplantation* 6:52-65); bioincompatibility, including *in vitro* artificial surface-induced inflammation (Lappegard *et al.* (2008) *J Biomed Mater Res A* 87:129-135; Lappegard *et al.* (2005) *Ann Thorac Surg* 79:917-923; Nilsson *et al.* (1998) *Blood* 92:1661-1667; Schmidt *et al.* (2003) *J Biomed Mater Res A* 66:491-499); inflammation, including *in vitro* *E.*
15 *coli*-induced inflammation (Mollnes *et al.* (2002) *Blood* 100:1867-1877) and heparin/protamine complex-induced inflammation in baboons (Soulika *et al.* (2000) *Clin Immunol* 96:212-221); age-related macular degeneration in rabbits and monkeys and rodents (Chi *et al.* (2010) *Adv Exp Med Biol* 703:127-135; Pennesi *et al.* (2012) *Mol. Aspects Med.* 33(4):487-509; Fletcher *et al.* (2014) *Optm. Vis. Sci.* 91(8):878-
20 886; Forest *et al.* (2015) *Disease Models and Mechanisms* 8:421-427); and delayed graft function in pigs (Hanto *et al.*, (2010) *Am J Transplant* 10(11):2421-2430) and dogs (Petrinec *et al.* (1996) *Surgery* 61:1331-1337).

F. METHODS OF PRODUCING NUCLEIC ACIDS ENCODING MODIFIED MTSP-1 POLYPEPTIDES

25 Polypeptides of a modified MTSP-1 polypeptide set forth herein can be obtained by methods well known in the art for protein purification and recombinant protein expression. Polypeptides also can be synthesized chemically. Modified or variant, including truncated forms, can be engineered from a wild type polypeptide using standard recombinant DNA methods. For example, modified MTSP-1
30 polypeptides can be engineered from a wild type polypeptide, such as by site-directed mutagenesis.

1. Isolation or Preparation of Nucleic Acids Encoding MTSP-1

Polypeptides

Polypeptides can be cloned or isolated using any available methods known in the art for cloning and isolating nucleic acid molecules. Such methods include PCR
5 amplification of nucleic acids and screening of libraries, including nucleic acid hybridization screening, antibody-based screening and activity-based screening. For example, when the polypeptides are produced by recombinant means, any method known to those of skill in the art for identification of nucleic acids that encode desired genes can be used. Any method available in the art can be used to obtain a full length
10 or partial (*i.e.*, encompassing the entire coding region) cDNA or genomic DNA clone encoding a MTSP-1, such as from a cell or tissue source.

Methods for amplification of nucleic acids can be used to isolate nucleic acid molecules encoding a desired polypeptide, including for example, polymerase chain reaction (PCR) methods. Exemplary of such methods include use of a Perkin-Elmer
15 Cetus thermal cycler and Taq polymerase (Gene Amp). A nucleic acid containing material can be used as a starting material from which a desired polypeptide-encoding nucleic acid molecule can be isolated. For example, DNA and mRNA preparations, cell extracts, tissue extracts, fluid samples (*e.g.*, blood, serum, saliva, breast milk), samples from healthy and/or diseased subjects can be used in amplification methods.
20 The source can be from any eukaryotic species including, but not limited to, vertebrate, mammalian, human, porcine, bovine, feline, avian, equine, canine, and other primate sources. Nucleic acid libraries also can be used as a source of starting material. Primers can be designed to amplify a desired polypeptide. For example, primers can be designed based on expressed sequences from which a desired
25 polypeptide is generated. Primers can be designed based on back-translation of a polypeptide amino acid sequence. If desired, degenerate primers can be used for amplification. Oligonucleotide primers that hybridize to sequences at the 3' and 5' termini of the desired sequence can be used as primers to amplify by PCR sequences from a nucleic acid sample. Primers can be used to amplify the entire full-length
30 MTSP-1, or a truncated sequence thereof, such as a nucleic acid encoding any of the soluble MTSP-1 polypeptides provided herein. Nucleic acid molecules generated by amplification can be sequenced and confirmed to encode a desired polypeptide.

Additional nucleotide sequences can be joined to a polypeptide-encoding nucleic acid molecule, including linker sequences containing restriction endonuclease sites for the purpose of cloning the synthetic gene into a vector, for example, a protein expression vector or a vector designed for the amplification of the core protein coding DNA sequences. Furthermore, additional nucleotide sequences specifying functional DNA elements can be operatively linked to a polypeptide-encoding nucleic acid molecule. Examples of such sequences include, but are not limited to, promoter sequences designed to facilitate intracellular protein expression, and secretion sequences, for example heterologous signal sequences, designed to facilitate protein secretion. Such sequences are known to those of skill in the art. Additional nucleotide residues sequences such as sequences of bases specifying protein binding regions also can be linked to enzyme-encoding nucleic acid molecules. Such regions include, but are not limited to, sequences of residues that facilitate or encode proteins that facilitate uptake of an enzyme into specific target cells, or otherwise alter pharmacokinetics of a product of a synthetic gene.

In addition, tags or other moieties can be added, for example, to aid in detection or affinity purification of the polypeptide. For example, additional nucleotide residues sequences such as sequences of bases specifying an epitope tag or other detectable marker also can be linked to enzyme-encoding nucleic acid molecules. Exemplary of such sequences include nucleic acid sequences encoding a SUMO tag or His tag or Flag Tag.

The identified and isolated nucleic acids can then be inserted into an appropriate cloning vector. A large number of vector-host systems known in the art can be used. Possible vectors include, but are not limited to, plasmids or modified viruses, but the vector system must be compatible with the host cell used. Such vectors include, but are not limited to, bacteriophages such as lambda derivatives, or plasmids such as pCMV4, pBR322 or pUC plasmid derivatives or the Bluescript vector (Stratagene, La Jolla, CA). The insertion into a cloning vector can, for example, be accomplished by ligating the DNA fragment into a cloning vector which has complementary cohesive termini. Insertion can be effected using TOPO cloning vectors (Invitrogen, Carlsbad, CA).

If the complementary restriction sites used to fragment the DNA are not present in the cloning vector, the ends of the DNA molecules can be enzymatically modified. Alternatively, any site desired can be produced by ligating nucleotide sequences (linkers) onto the DNA termini; these ligated linkers can contain specific
5 chemically synthesized oligonucleotides encoding restriction endonuclease recognition sequences. In an alternative method, the cleaved vector and protein gene can be modified by homopolymeric tailing.

Recombinant molecules can be introduced into host cells via, for example, transformation, transfection, infection, electroporation and sonoporation, so that many
10 copies of the gene sequence are generated. In specific embodiments, transformation of host cells with recombinant DNA molecules that incorporate the isolated protein gene, cDNA, or synthesized DNA sequence enables generation of multiple copies of the gene. Thus, the gene can be obtained in large quantities by growing transformants, isolating the recombinant DNA molecules from the transformants and, when
15 necessary, retrieving the inserted gene from the isolated recombinant DNA.

In addition to recombinant production, modified MTSP-1 polypeptides provided herein, can be produced by direct peptide synthesis using solid-phase techniques (*see e.g.*, Stewart *et al.* (1969) Solid-Phase Peptide Synthesis, WH Freeman Co., San Francisco; Merrifield J (1963) *J Am Chem Soc.*, 85:2149-2154). *In*
20 *vitro* protein synthesis can be performed using manual techniques or by automation. Automated synthesis can be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer, Foster City CA) in accordance with the instructions provided by the manufacturer. Various fragments of a polypeptide can be chemically synthesized separately and combined using chemical methods.

25 **2. Generation of Mutant or Modified Nucleic Acids and Encoding Polypeptides**

The modifications provided herein can be made by standard recombinant DNA techniques such as are routine to one of skill in the art. Any method known in the art to effect mutation of any one or more amino acids in a target protein can be
30 employed. Methods include standard site-directed mutagenesis (using *e.g.*, a kit, such as QuikChange available from Stratagene) of encoding nucleic acid molecules, or by solid phase polypeptide synthesis methods.

3. Vectors and Cells

For recombinant expression of one or more of the desired proteins, such as any modified MTSP-1 polypeptide described herein, the nucleic acid containing all or a portion of the nucleotide sequence encoding the protein can be inserted into an appropriate expression vector, *i.e.*, a vector that contains the necessary elements for the transcription and translation of the inserted protein coding sequence. The necessary transcriptional and translational signals also can be supplied by the native promoter for enzyme genes, and/or their flanking regions.

Also provided are vectors that contain a nucleic acid encoding the enzyme. Cells containing the vectors also are provided. The cells include eukaryotic and prokaryotic cells, and the vectors are any suitable for use therein. Generally, the cell is a cell that is capable of effecting glycosylation of the encoded protein.

Prokaryotic and eukaryotic cells containing the vectors are provided. Such cells include bacterial cells, yeast cells, fungal cells, Archea, plant cells, insect cells and animal cells. The cells are used to produce a protein thereof by growing the above-described cells under conditions whereby the encoded protein is expressed by the cell, and recovering the expressed protein. For purposes herein, for example, the enzyme can be secreted into the medium.

A host cell strain can be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation. Post-translational processing can impact the folding and/or function of the polypeptide. Different host cells, such as, but not limited to, CHO (DG44, DXB11, CHO-K1), HeLa, MCDK, 293 and WI38 have specific cellular machinery and characteristic mechanisms for such post-translational activities and can be chosen to ensure the correct modification and processing of the introduced protein. Generally, the choice of cell is one that is capable of introducing N-linked glycosylation into the expressed polypeptide. Hence, eukaryotic cells containing the vectors are provided. Exemplary of eukaryotic cells are mammalian Chinese Hamster Ovary (CHO) cells. For example, CHO cells deficient in dihydrofolate reductase (*e.g.*, DG44 cells) are used to produce polypeptides provided herein.

Provided are vectors that contain a sequence of nucleotides that encodes the modified MTSP-1 polypeptide, such as the modified MTSP-1 protease domain, coupled to the native or heterologous signal sequence, as well as multiple copies thereof. The vectors can be selected for expression of the enzyme protein in the cell or
5 such that the enzyme protein is expressed as a secreted protein.

In one embodiment, vectors containing a sequence of nucleotides that encodes a polypeptide that has protease activity and contains all or a portion of the protease domain, or multiple copies thereof, are provided. Also provided are vectors that contain a sequence of nucleotides that encodes the protease domain and additional
10 portions of a protease protein up to and including a full length protease protein, as well as multiple copies thereof. The vectors can be selected for expression of the scaffold or modified protease protein or protease domain thereof in the cell or such that the protease protein is expressed as a secreted protein. When the protease domain is expressed the nucleic acid is linked to nucleic acid encoding a secretion signal, such
15 as the *Saccharomyces cerevisiae* α -mating factor signal sequence or a portion thereof, or the native signal sequence.

A variety of host-vector systems can be used to express the protein coding sequence. These include but are not limited to mammalian cell systems infected with virus (*e.g.*, vaccinia virus, adenovirus and other viruses); insect cell systems infected
20 with virus (*e.g.*, baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system used, any one of a number of suitable transcription and translation elements can be used.

25 Any methods known to those of skill in the art for the insertion of DNA fragments into a vector can be used to construct expression vectors containing a chimeric gene containing appropriate transcriptional/translational control signals and protein coding sequences. These methods can include *in vitro* recombinant DNA and synthetic techniques and *in vivo* recombinants (genetic recombination). Expression of
30 nucleic acid sequences encoding protein, or domains, derivatives, fragments or homologs thereof, can be regulated by a second nucleic acid sequence so that the genes or fragments thereof are expressed in a host transformed with the recombinant

DNA molecule(s). For example, expression of the proteins can be controlled by any promoter/enhancer known in the art. In a specific embodiment, the promoter is not native to the genes for a desired protein. Promoters which can be used include but are not limited to the SV40 early promoter (Benoist and Chambon (1981) *Nature* 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.* (1980) *Cell* 22:787-797), the herpes thymidine kinase promoter (Wagner *et al.* (1981) *Proc. Natl. Acad. Sci. USA* 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster *et al.* (1982) *Nature* 296:39-42); prokaryotic expression vectors such as the β -lactamase promoter (Jay *et al.*, (1981) *Proc. Natl. Acad. Sci. USA* 78:5543) or the *tac* promoter (DeBoer *et al.* (1983) *Proc. Natl. Acad. Sci. USA* 80:21-25); see also "Useful Proteins from Recombinant Bacteria": in *Scientific American* 242:79-94 (1980); plant expression vectors containing the nopaline synthetase promoter (Herrera-Estrella *et al.* (1984) *Nature* 303:209-213) or the cauliflower mosaic virus 35S RNA promoter (Gardner *et al.* (1981) *Nucleic Acids Res.* 9:2871), and the promoter of the photosynthetic enzyme ribulose biphosphate carboxylase (Herrera-Estrella *et al.* (1984) *Nature* 310:115-120); promoter elements from yeast and other fungi such as the Gal4 promoter, the alcohol dehydrogenase promoter, the phosphoglycerol kinase promoter, the alkaline phosphatase promoter, and the following animal transcriptional control regions that exhibit tissue specificity and have been used in transgenic animals: elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.* (1984) *Cell* 38:639-646; Ornitz *et al.* (1986) *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409; MacDonald (1987) *Hepatology* 7:425-515); insulin gene control region which is active in pancreatic beta cells (Hanahan *et al.* (1985) *Nature* 315:115-122), immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.* (1984) *Cell* 38:647-658; Adams *et al.* (1985) *Nature* 318:533-538; Alexander *et al.* (1987) *Mol. Cell Biol.* 7:1436-1444), mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells (Leder *et al.* (1986) *Cell* 45:485-495), albumin gene control region which is active in liver (Pinckert *et al.* (1987) *Genes and Devel.* 1:268-276), alpha-fetoprotein gene control region which is active in liver (Krumlauf *et al.* (1985) *Mol. Cell. Biol.* 5:1639-1648; Hammer *et al.* (1987) *Science* 235:53-58), alpha-1 antitrypsin gene control region which is active in

liver (Kelsey *et al.* (1987) *Genes and Devel.* 1:161-171), beta globin gene control region which is active in myeloid cells (Magram *et al.*, (1985) *Nature* 315:338-340; Kollias *et al.* (1986) *Cell* 46:89-94), myelin basic protein gene control region which is active in oligodendrocyte cells of the brain (Readhead *et al.* (1987) *Cell* 48:703-712),
5 myosin light chain-2 gene control region which is active in skeletal muscle (Shani (1985), *Nature* 314:283-286), and gonadotrophic releasing hormone gene control region which is active in gonadotrophs of the hypothalamus (Mason *et al.* (1986) *Science* 234:1372-1378).

In a specific embodiment, a vector is used that contains a promoter operably
10 linked to nucleic acids encoding a desired protein, or a domain, fragment, derivative or homolog, thereof, one or more origins of replication, and optionally, one or more selectable markers (*e.g.*, an antibiotic resistance gene). Depending on the expression system, specific initiation signals also are required for efficient translation of a MTSP-1 sequence. These signals include the ATG initiation codon and adjacent
15 sequences. In cases where the initiation codon and upstream sequences of MTSP-1 or catalytically active fragments thereof are inserted into the appropriate expression vector, no additional translational control signals are needed. In cases where only coding sequence, or a portion thereof, is inserted, exogenous transcriptional control signals including the ATG initiation codon must be provided. Furthermore, the
20 initiation codon must be in the correct reading frame to ensure transcription of the entire insert. Exogenous transcriptional elements and initiation codons can be of various origins, both natural and synthetic. The efficiency of expression can be enhanced by the inclusion of enhancers appropriate to the cell system in use (Scharf *et al.* (1994) *Results Probl Cell Differ* 20:-62; Bittner *et al.* (1987) *Methods in Enzymol*
25 153:516-544).

Exemplary plasmid vectors for transformation of *E. coli* cells, include, for example, the pQE expression vectors (available from Qiagen, Valencia, CA; see also literature published by Qiagen describing the system). pQE vectors have a phage T5 promoter (recognized by *E. coli* RNA polymerase) and a double lac operator
30 repression module to provide tightly regulated, high-level expression of recombinant proteins in *E. coli*, a synthetic ribosomal binding site (RBS II) for efficient translation, a 6XHis tag coding sequence, t₀ and T1 transcriptional terminators, ColE1 origin of

replication, and a beta-lactamase gene for conferring ampicillin resistance. The pQE vectors enable placement of a 6xHis tag at either the N- or C-terminus of the recombinant protein. Such plasmids include pQE 32, pQE 30, and pQE 31 which provide multiple cloning sites for all three reading frames and provide for the
5 expression of N-terminally 6xHis-tagged proteins. Other exemplary plasmid vectors for transformation of *E. coli* cells, include, for example, the pET expression vectors (see, U.S. Patent No. 4,952,496; available from Novagen, Madison, WI; see, also literature published by Novagen describing the system). Such plasmids include pET 11a, which contains the T7lac promoter, T7 terminator, the inducible *E. coli* lac
10 operator, and the lac repressor gene; pET 12a-c, which contains the T7 promoter, T7 terminator, and the *E. coli* ompT secretion signal; and pET 15b and pET19b (Novagen, Madison, WI), which contain a His-TagTM leader sequence for use in purification with a His column and a thrombin cleavage site that permits cleavage following purification over the column, the T7-lac promoter region and the T7
15 terminator.

Typically, vectors can be plasmid, viral, or others known in the art, used for expression of the modified MTSP-1 polypeptide *in vivo* or *in vitro*. For example, the modified MTSP-1 polypeptide is expressed in mammalian cells, including, for example, Chinese Hamster Ovary (CHO) cells.

20 Viral vectors, such as adenovirus, retrovirus or vaccinia virus vectors, can be employed. In some examples, the vector is a defective or attenuated retroviral or other viral vector (see U. S. Patent No. 4,980,286). For example, a retroviral vector can be used (see, Miller *et al.* (1993) *Meth. Enzymol.* 217: 581-599). These retroviral vectors have been modified to delete retroviral sequences that are not necessary for
25 packaging of the viral genome and integration into host cell DNA. In some examples, viruses armed with a nucleic acid encoding a modified MTSP-1 polypeptide can facilitate their replication and spread within a target tissue. The virus can also be a lytic virus or a non-lytic virus wherein the virus selectively replicates under a tissue specific promoter. As the viruses replicate, the coexpression of the MTSP-1
30 polypeptide with viral genes will facilitate the spread of the virus *in vivo*.

4. Expression

Modified MTSP-1 polypeptides can be produced by any method known to those of skill in the art including *in vivo* and *in vitro* methods. The modified MTSP-1 polypeptides can be expressed in any organism suitable to produce the required amounts and forms of the proteins, such as for example, needed for administration and treatment. Expression hosts include prokaryotic and eukaryotic organisms such as *E. coli*, yeast, plants, insect cells, mammalian cells, including human cell lines and transgenic animals. Expression hosts can differ in their protein production levels as well as the types of post-translational modifications that are present on the expressed proteins. The choice of expression host can be made based on these and other factors, such as regulatory and safety considerations, production costs and the need and methods for purification. The skilled person is well-equipped to select appropriate hosts and vectors.

Many expression vectors are available and known to those of skill in the art and can be used for expression of proteins. The choice of expression vector will be influenced by the choice of host expression system. In general, expression vectors can include transcriptional promoters and optionally enhancers, translational signals, and transcriptional and translational termination signals. Expression vectors that are used for stable transformation typically have a selectable marker which allows selection and maintenance of the transformed cells. In some cases, an origin of replication can be used to amplify the copy number of the vector.

Modified MTSP-1 polypeptides also can be utilized or expressed as protein fusions. For example, an enzyme fusion can be generated to add additional functionality to an enzyme. Examples of enzyme fusion proteins include, but are not limited to, fusions of a signal sequence, a tag such as for localization, *e.g.*, a his₆ tag or a myc tag, or a tag for purification, for example, a GST fusion, and a sequence for directing protein secretion and/or membrane association.

For example, a modified MTSP-1 polypeptide described herein is one that is generated by expression of a nucleic acid molecule encoding the protease domain set forth in any one of SEQ ID NOS: 1-4, 11-13 and 21-59 or a sequence of amino acids that exhibits at least 65%, 70%, 75%, 80%, 84%, 90%, 91%, 92%, 93%, 94%, 95%,

96%, 97%, 98%, or 99% sequence identity to a sequence set forth in any of SEQ ID NOS: 1-4, 11-13 and 21-59.

For long-term, high-yield production of recombinant proteins, stable expression is desired. For example, cell lines that stably express a modified MTSP-1 polypeptide can be transformed using expression vectors that contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following the introduction of the vector, cells can be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells that successfully express the introduced sequences. Resistant cells of stably transformed cells can be proliferated using tissue culture techniques appropriate to the cell types.

Any number of selection systems can be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler *et al.*, (1977) *Cell* 11:223-232) and adenine phosphoribosyltransferase (Lowy I *et al.* (1980) *Cell* 22:817-23) genes, which can be employed in TK- or APRT- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection. For example, DHFR, which confers resistance to methotrexate (Wigler M *et al.* (1980) *Proc. Natl. Acad. Sci.*, 77:3567-70); npt, which confers resistance to the aminoglycosides neomycin and G-418 (Colbere-Garapin F *et al.* (1981) *J. Mol. Biol.*, 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively, can be used. Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan or hisD, which allows cells to utilize histinol in place of histidine (Hartman SC and RC Mulligan (1988) *Proc. Natl. Acad. Sci.*, 85:8047-8051). Visible markers, such as but not limited to, anthocyanins, beta glucuronidase and its substrate, GUS, and luciferase and its substrate luciferin, also can be used to identify transformants and also to quantify the amount of transient or stable protein expression attributable to a particular vector system (Rhodes CA *et al.* (1995) *Methods Mol. Biol.* 55:121-131).

The presence and expression of MTSP-1 polypeptides can be monitored. For example, detection of a functional polypeptide can be determined by testing the

conditioned media for hyaluronidase enzyme activity under appropriate conditions. Exemplary assays to assess the solubility and activity of expressed proteins is provided herein.

a. Prokaryotic Cells

5 Prokaryotes, especially *E. coli*, provide a system for producing large amounts of proteins. Transformation of *E. coli* is a simple and rapid technique well known to those of skill in the art. Expression vectors for *E. coli* can contain inducible promoters, such promoters are useful for inducing high levels of protein expression and for expressing proteins that exhibit some toxicity to the host cells. Examples of
10 inducible promoters include the lac promoter, the trp promoter, the hybrid tac promoter, the T7 and SP6 RNA promoters and the temperature regulated λ PL promoter.

Proteins, such as any provided herein, can be expressed in the cytoplasmic environment of *E. coli*. The cytoplasm is a reducing environment and for some
15 molecules, this can result in the formation of insoluble inclusion bodies. Reducing agents such as dithiothreitol and β -mercaptoethanol and denaturants, such as guanidine-HCl and urea can be used to resolubilize the proteins. An alternative approach is the expression of proteins in the periplasmic space of bacteria which provides an oxidizing environment and chaperonin-like and disulfide isomerases and
20 can lead to the production of soluble protein. Typically, a leader sequence is fused to the protein to be expressed which directs the protein to the periplasm. The leader is then removed by signal peptidases inside the periplasm. Examples of periplasmic-targeting leader sequences include the pelB leader from the pectate lyase gene and the leader derived from the alkaline phosphatase gene. In some cases, periplasmic
25 expression allows leakage of the expressed protein into the culture medium. The secretion of proteins allows quick and simple purification from the culture supernatant. Proteins that are not secreted can be obtained from the periplasm by osmotic lysis. Similar to cytoplasmic expression, in some cases proteins can become insoluble and denaturants and reducing agents can be used to facilitate solubilization
30 and refolding. Temperature of induction and growth also can influence expression levels and solubility, typically temperatures between 25 °C and 37 °C are used. Typically, bacteria produce aglycosylated proteins. Thus, if proteins require

glycosylation for function, glycosylation can be added *in vitro* after purification from host cells.

b. Yeast Cells

Yeasts such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*,
5 *Yarrowia lipolytica*, *Kluyveromyces lactis* and *Pichia pastoris* are well known yeast expression hosts that can be used for production of proteins, such as any described herein. Yeast can be transformed with episomal replicating vectors or by stable chromosomal integration by homologous recombination. Typically, inducible promoters are used to regulate gene expression. Examples of such promoters include
10 GAL1, GAL7 and GAL5 and metallothionein promoters, such as CUP1, AOX1 or other *Pichia* or other yeast promoter. Expression vectors often include a selectable marker such as LEU2, TRP1, HIS3 and URA3 for selection and maintenance of the transformed DNA. Proteins expressed in yeast are often soluble. Co-expression with chaperonins such as BiP and protein disulfide isomerase can improve expression
15 levels and solubility. Additionally, proteins expressed in yeast can be directed for secretion using secretion signal peptide fusions such as the yeast mating type alpha-factor secretion signal from *Saccharomyces cerevisiae* and fusions with yeast cell surface proteins such as the Aga2p mating adhesion receptor or the *Arxula adenivorans* glucoamylase. A protease cleavage site such as for the Kex-2 protease,
20 can be engineered to remove the fused sequences from the expressed polypeptides as they exit the secretion pathway. Yeast also is capable of glycosylation at Asn-X-Ser/Thr motifs.

c. Insects and Insect Cells

Insect cells, particularly using baculovirus expression, are useful for
25 expressing polypeptides such as MTSP-1 polypeptides. Insect cells express high levels of protein and are capable of most of the post-translational modifications used by higher eukaryotes. Baculovirus have a restrictive host range which improves the safety and reduces regulatory concerns of eukaryotic expression. Typical expression vectors use a promoter for high level expression such as the polyhedrin promoter of
30 baculovirus. Commonly used baculovirus systems include the baculoviruses such as Autographa californica nuclear polyhedrosis virus (AcNPV), and the bombyx mori nuclear polyhedrosis virus (BmNPV) and an insect cell line such as Sf9 derived from

Spodoptera frugiperda, Pseudaletia unipuncta (A7S) and Danaus plexippus (DpN1). For high-level expression, the nucleotide sequence of the molecule to be expressed is fused immediately downstream of the polyhedrin initiation codon of the virus.

Mammalian secretion signals are accurately processed in insect cells and can be used to secrete the expressed protein into the culture medium. In addition, the cell lines Pseudaletia unipuncta (A7S) and Danaus plexippus (DpN1) produce proteins with glycosylation patterns similar to mammalian cell systems. Exemplary insect cells are those that have been altered to reduce immunogenicity, including those with “mammalianized” baculovirus expression vectors and those lacking the enzyme FT3.

An alternative expression system in insect cells is the use of stably transformed cells. Cell lines such as the Schneider 2 (S2) and Kc cells (Drosophila melanogaster) and C7 cells (Aedes albopictus) can be used for expression. The Drosophila metallothionein promoter can be used to induce high levels of expression in the presence of heavy metal induction with cadmium or copper. Expression vectors are typically maintained by the use of selectable markers such as neomycin and hygromycin.

d. Mammalian Expression

Mammalian expression systems can be used to express proteins including MTSP-1 polypeptides. Expression constructs can be transferred to mammalian cells by viral infection such as adenovirus or by direct DNA transfer such as liposomes, calcium phosphate, DEAE-dextran and by physical means such as electroporation and microinjection. Expression vectors for mammalian cells typically include an mRNA cap site, a TATA box, a translational initiation sequence (Kozak consensus sequence) and polyadenylation elements. IRES elements also can be added to permit bicistronic expression with another gene, such as a selectable marker. Such vectors often include transcriptional promoter-enhancers for high-level expression, for example the SV40 promoter-enhancer, the human cytomegalovirus (CMV) promoter and the long terminal repeat of Rous sarcoma virus (RSV). These promoter-enhancers are active in many cell types. Tissue and cell-type promoters and enhancer regions also can be used for expression. Exemplary promoter/enhancer regions include, but are not limited to, those from genes such as elastase I, insulin, immunoglobulin, mouse mammary tumor virus, albumin, alpha fetoprotein, alpha 1 antitrypsin, beta globin,

myelin basic protein, myosin light chain 2, and gonadotropic releasing hormone gene control. Selectable markers can be used to select for and maintain cells with the expression construct. Examples of selectable marker genes include, but are not limited to, hygromycin B phosphotransferase, adenosine deaminase, xanthine-guanine phosphoribosyl transferase, aminoglycoside phosphotransferase, dihydrofolate reductase (DHFR) and thymidine kinase. For example, expression can be performed in the presence of methotrexate to select for only those cells expressing the DHFR gene. Fusion with cell surface signaling molecules such as TCR- ζ and Fc ϵ RI- γ can direct expression of the proteins in an active state on the cell surface.

Many cell lines are available for mammalian expression including mouse, rat human, monkey, chicken and hamster cells. Exemplary cell lines include but are not limited to CHO, Balb/3T3, HeLa, MT2, mouse NS0 (nonsecreting) and other myeloma cell lines, hybridoma and heterohybridoma cell lines, lymphocytes, fibroblasts, Sp2/0, COS, NIH3T3, HEK293, 293S, 2B8, and HKB cells. Cell lines also are available adapted to serum-free media which facilitates purification of secreted proteins from the cell culture media. Examples include CHO-S cells (Invitrogen, Carlsbad, CA, Catalog number 11619-012) and the serum free EBNA-1 cell line (Pham *et al.* (2003) *Biotechnol. Bioeng.* 84:332-42.). Cell lines also are available that are adapted to grow in special mediums optimized for maximal expression. For example, DG44 CHO cells are adapted to grow in suspension culture in a chemically defined, animal product-free medium.

e. Plants

Transgenic plant cells and plants can be used to express proteins such as any described herein. Expression constructs are typically transferred to plants using direct DNA transfer such as microprojectile bombardment and PEG-mediated transfer into protoplasts, and with agrobacterium-mediated transformation. Expression vectors can include promoter and enhancer sequences, transcriptional termination elements and translational control elements. Expression vectors and transformation techniques are usually divided between dicot hosts, such as *Arabidopsis* and tobacco, and monocot hosts, such as corn and rice. Examples of plant promoters used for expression include the cauliflower mosaic virus promoter, the nopaline synthase promoter, the ribose biphosphate carboxylase promoter and the ubiquitin and UBQ3 promoters.

Selectable markers such as hygromycin, phosphomannose isomerase and neomycin phosphotransferase are often used to facilitate selection and maintenance of transformed cells. Transformed plant cells can be maintained in culture as cells, aggregates (callus tissue) or regenerated into whole plants. Transgenic plant cells also
5 can include algae engineered to produce hyaluronidase polypeptides. Because plants have different glycosylation patterns than mammalian cells, this can influence the choice of protein produced in these hosts.

5. Purification

Host cells transformed with a nucleic acid sequence encoding a modified
10 MTSP-1 polypeptide can be cultured under conditions suitable for the expression and recovery of the encoded protein from cell culture. The protein produced by a recombinant cell generally is designed so that it is secreted, but it can be contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing nucleic acid
15 encoding MTSP-1 can be designed with signal sequences that facilitate direct secretion of MTSP-1 through prokaryotic or eukaryotic cell membrane.

Thus, method for purification of polypeptides from host cells depend on the chosen host cells and expression systems. For secreted molecules, proteins are generally purified from the culture media after removing the cells. For intracellular
20 expression, cells can be lysed and the proteins purified from the extract. When transgenic organisms such as transgenic plants and animals are used for expression, tissues or organs can be used as starting material to make a lysed cell extract. Additionally, transgenic animal production can include the production of polypeptides in milk or eggs, which can be collected, and if necessary, the proteins can be extracted
25 and further purified using standard methods in the art.

Proteins, such as modified MTSP-1 polypeptides, can be purified using standard protein purification techniques known in the art including but not limited to, SDS-PAGE, size fractionation and size exclusion chromatography, ammonium sulfate precipitation and ionic exchange chromatography, such as anion exchange. Affinity
30 purification techniques also can be utilized to improve the efficiency and purity of the preparations. For example, antibodies, receptors and other molecules that bind MTSP-1 proteins can be used in affinity purification.

Expression constructs also can be engineered to add an affinity tag to a protein such as a Small Ubiquitin-like Modifier (SUMO) tag, myc epitope, GST fusion or His₆ and affinity purified with SUMO or myc antibody, glutathione resin and Ni-resin, respectively. Such tags can be joined to the nucleotide sequence encoding a
5 MTSP-1 as described elsewhere herein, which can facilitate purification of soluble proteins. For example, a modified MTSP-1 polypeptide can be expressed as a recombinant protein with one or more additional polypeptide domains added to facilitate protein purification. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that
10 allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle Wash.). The inclusion of a cleavable linker sequence such as Factor XA or enterokinase (Invitrogen, San Diego, CA) between the purification domain and the expressed MTSP-1 polypeptide
15 is useful to facilitate purification. One such expression vector provides for expression of a fusion protein containing a MTSP-1 polypeptide in and an enterokinase cleavage site. The Small Ubiquitin-like Modifier (SUMO) tag facilitates purification on IMIAC (immobilized metal ion affinity chromatography), while the enterokinase cleavage site provides a means for purifying the polypeptide from the fusion protein.

20 Purity can be assessed by any method known in the art including gel electrophoresis, orthogonal HPLC methods, staining and spectrophotometric techniques. The expressed and purified protein can be analyzed using any assay or method known to one of skill in the art, for example, any described in Section 5. These include assays based on the physical and/or functional properties of the protein,
25 including, but not limited to, analysis by gel electrophoresis, immunoassay and assays of MTSP-1 activity.

6. Additional Modifications

The modified MTSP-1 polypeptides provided herein can be modified to improve or alter pharmacokinetic and pharmacological properties. In particular, the
30 modified MTSP-1 polypeptides can be conjugated to a polymer, such as a PEG moiety or dextran or sialylation to reduce immunogenicity and/or increase half-life in serum and other body fluids including vitreous humor.

a. PEGylation

Polyethylene glycol (PEG) is used in biomaterials, biotechnology and medicine primarily because PEG is a biocompatible, nontoxic, water-soluble polymer that is typically nonimmunogenic (Zhao and Harris, *ACS Symposium Series* 680: 458-72, 1997). In the area of drug delivery, PEG derivatives have been widely used in covalent attachment (*i.e.*, "PEGylation") to proteins to reduce immunogenicity, proteolysis and kidney clearance to increase serum half-life and to enhance solubility (Zalipsky (1995) *Adv. Drug Del. Rev.* 16:157-82). Similarly, PEG has been attached to low molecular weight, relatively hydrophobic drugs to enhance solubility, reduce toxicity and alter biodistribution. Typically, PEGylated drugs are injected as solutions.

A related application is synthesis of crosslinked degradable PEG networks or formulations for use in drug delivery since much of the same chemistry used in design of degradable, soluble drug carriers also can be used in design of degradable gels (Sawhney *et al.* (1993) *Macromolecules* 26: 581-87). It also is known that intermacromolecular complexes can be formed by mixing solutions of two complementary polymers. Such complexes are generally stabilized by electrostatic interactions (polyanion-polycation) and/or hydrogen bonds (polyacid-polybase) between the polymers involved, and/or by hydrophobic interactions between the polymers in an aqueous surrounding (Krupers *et al.* (1996) *Eur. Polym J.* 32:785-790). For example, mixing solutions of polyacrylic acid (PAAc) and polyethylene oxide (PEO) under the proper conditions results in the formation of complexes based mostly on hydrogen bonding. Dissociation of these complexes at physiologic conditions has been used for delivery of free drugs (*i.e.*, non-PEGylated). In addition, complexes of complementary polymers have been formed from homopolymers and copolymers.

Numerous reagents for PEGylation are known as are PEG moieties for therapeutic proteins. Reagents and PEG moieties are commercially available. Such reagents include, but are not limited to, reaction of the polypeptide with N-hydroxysuccinimidyl (NHS) activated PEG, succinimidyl mPEG, mPEG₂-N-hydroxysuccinimide, mPEG succinimidyl alpha-methylbutanoate, mPEG succinimidyl propionate, mPEG succinimidyl butanoate, mPEG carboxymethyl 3-

hydroxybutanoic acid succinimidyl ester, homobifunctional PEG-succinimidyl propionate, homobifunctional PEG propionaldehyde, homobifunctional PEG butyraldehyde, PEG maleimide, PEG hydrazide, p-nitrophenyl-carbonate PEG, mPEG-benzotriazole carbonate, propionaldehyde PEG, mPEG butyraldehyde, 5 branched mPEG₂ butyraldehyde, mPEG acetyl, mPEG piperidone, mPEG methylketone, mPEG "linkerless" maleimide, mPEG vinyl sulfone, mPEG thiol, mPEG orthopyridylthioester, mPEG orthopyridyl disulfide, Fmoc-PEG-NHS, Boc-PEG-NHS, vinylsulfone PEG-NHS, acrylate PEG-NHS, fluorescein PEG-NHS, and biotin PEG-NHS (*see e.g.*, Monfardini *et al.* (1995) *Bioconjugate Chem.* 6:62-69; 10 Veronese *et al.* (1997) *J. Bioactive Compatible Polymers* 12:197-207; U.S. 5,672,662; U.S. 5,932,462; U.S. 6,495,659; U.S. 6,737,505; U.S. 4,002,531; U.S. 4,179,337; U.S. 5,122,614; U.S. 5,324,844; U.S. 5,446,090; U.S. 5,612,460; U.S. 5,643,575; U.S. 5,766,581; U.S. 5,795,569; U.S. 5,808,096; U.S. 5,900,461; U.S. 5,919,455; U.S. 5,985,263; U.S. 5,990, 237; U.S. 6,113,906; U.S. 6,214,966; U.S. 6,258,351; U.S. 15 6,340,742; U.S. 6,413,507; U.S. 6,420,339; U.S. 6,437,025; U.S. 6,448,369; U.S. 6,461,802; U.S. 6,828,401; U.S. 6,858,736; U.S. 2001/0021763; U.S. 2001/0044526; U.S. 2001/0046481; U.S. 2002/0052430; U.S. 2002/0072573; U.S. 2002/0156047; U.S. 2003/0114647; U.S. 2003/0143596; U.S. 2003/0158333; U.S. 2003/0220447; U.S. 2004/0013637; US 2004/0235734; WO 05/00360; U.S. 2005/0114037; U.S. 20 2005/0171328; U.S. 2005/0209416; EP 01064951; EP 0822199; WO 00176640; WO 00/02017; WO 02/49673; WO 94/28024; and WO 01/87925).

In one example, the polyethylene glycol has a molecular weight ranging from about 3 kD to about 50 kD, and typically from about 5 kD to about 30 kD. Covalent attachment of the PEG to the drug (known as "PEGylation") can be accomplished by 25 known chemical synthesis techniques. For example, the PEGylation of protein can be accomplished by reacting NHS-activated PEG with the protein under suitable reaction conditions.

While numerous reactions have been described for PEGylation, those that are most generally applicable confer directionality, use mild reaction conditions, and do 30 not necessitate extensive downstream processing to remove toxic catalysts or bi-products. For instance, monomethoxy PEG (mPEG) has only one reactive terminal hydroxyl, and thus its use limits some of the heterogeneity of the resulting PEG-

protein product mixture. Activation of the hydroxyl group at the end of the polymer opposite to the terminal methoxy group is generally necessary to accomplish efficient protein PEGylation, with the aim being to make the derivatized PEG more susceptible to nucleophilic attack. The attacking nucleophile is usually the epsilon-amino group of a lysyl residue, but other amines also can react (*e.g.*, the N-terminal alpha-amine or the ring amines of histidine) if local conditions are favorable. A more directed attachment is possible in proteins containing a single lysine or cysteine. The latter residue can be targeted by PEG-maleimide for thiol-specific modification. Alternatively, PEG hydrazide can be reacted with a periodate oxidized hyaluronan-degrading enzyme and reduced in the presence of NaCNBH₃. More specifically, PEGylated CMP sugars can be reacted with a hyaluronan-degrading enzyme in the presence of appropriate glycosyl-transferases. One technique is the "PEGylation" technique where a number of polymeric molecules are coupled to the polypeptide in question. When using this technique the immune system has difficulties in recognizing the epitopes on the polypeptide's surface responsible for the formation of antibodies, thereby reducing the immune response. For polypeptides introduced directly into the circulatory system of the human body to give a particular physiological effect (*i.e.*, pharmaceuticals) the typical potential immune response is an IgG and/or IgM response, while polypeptides which are inhaled through the respiratory system (*i.e.*, industrial polypeptide) potentially can cause an IgE response (*i.e.*, allergic response). One of the theories explaining the reduced immune response is that the polymeric molecule(s) shield(s) epitope(s) on the surface of the polypeptide responsible for the immune response leading to antibody formation. Another theory or at least a partial factor is that the heavier the conjugate is, the more reduced immune response is obtained.

Typically, to make the PEGylated modified MTSP-1 polypeptide provided herein, PEG moieties are conjugated, via covalent attachment, to the polypeptides. Techniques for PEGylation include, but are not limited to, specialized linkers and coupling chemistries (*see e.g.*, Harris (2002) *Adv. Drug Deliv. Rev.* 54:459-476), attachment of multiple PEG moieties to a single conjugation site (such as via use of branched PEGs; *see e.g.*, Veronese *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12:177-180), site-specific PEGylation and/or mono-PEGylation (*see e.g.*, Chapman *et al.*

(1999) *Nature Biotech.* 17:780-783), and site-directed enzymatic PEGylation (*see e.g., Sato (2002), Adv. Drug Deliv. Rev., 54:487-504*). Methods and techniques described in the art can produce proteins having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 PEG or PEG derivatives attached to a single protein molecule (*see e.g., U.S. Patent Publication No. 2006/0104968*).

b. Fusion Proteins

Preparation of fusions of therapeutic proteins to other moieties, such as PEGylation, conjugation to albumin, targeting moieties, such as antibodies and antigen binding fragments thereof, immunoglobulins, fc fusions, fusion with albumin (HSA), XTEN fusion proteins, modification of glycosylation patterns are known (*see, Strohl (2015) BioDrugs 29:215-239* for a review of a variety of fusion proteins for improving pharmacokinetic properties of therapeutic proteins). Any of these known modalities for improving pharmacological properties of therapeutics can be applied to the modified MTSP-1 polypeptides provided herein.

Fusion proteins containing a modified MTSP-1 polypeptide provided herein and one or more other polypeptides also are provided. Pharmaceutical compositions containing such fusion proteins formulated for administration by a suitable route are provided. Fusion proteins are formed by linking in any order the modified MTSP-1 polypeptide and another polypeptide, such as an antibody or fragment thereof, growth factor, receptor, ligand and other such agent for the purposes of facilitating the purification of a protease, altering the pharmacodynamic properties of a MTSP-1 polypeptide by directing the modified MTSP-1 polypeptide to a targeted cell or tissue, and/or increasing the expression or secretion of a modified MTSP-1 polypeptide. Within a modified MTSP-1 polypeptide fusion protein, the modified MTSP-1 polypeptide can correspond to all or a catalytically active portion thereof of a MTSP-1 polypeptide. In some embodiments, the MTSP-1 polypeptide or catalytically active portion thereof is a modified MTSP-1 polypeptide provided herein. Fusion proteins provided herein retain substantially all of their specificity and/or selectivity for complement protein C3. Generally, MTSP-1 fusion polypeptides retain at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90% or 95% substrate specificity and/or selectivity compared with a non-fusion MTSP-1 polypeptide, including 96%, 97%,

98%, 99% or greater substrate specificity compared with a non-fusion MTSP-1 polypeptide.

Linkage of a modified MTSP-1 polypeptide and another polypeptide can be effected directly or indirectly via a linker. In one example, linkage can be by chemical
5 linkage, such as via heterobifunctional agents or thiol linkages or other such linkages. Fusion of a MTSP-1 polypeptide to another polypeptide can be to the N- or C-terminus of the MTSP-1 polypeptide. Non-limiting examples of polypeptides that can be used in fusion proteins with a modified MTSP-1 polypeptide provided herein include, for example, a GST (glutathione S-transferase) polypeptide, Fc domain from
10 immunoglobulin G, or a heterologous signal sequence. The fusion proteins can contain additional components, such as *E. coli* maltose binding protein (MBP) that aid in uptake of the protein by cells (*see*, International Patent Publication No. WO 01/32711).

A MTSP-1 polypeptide fusion protein can be produced by standard
15 recombinant techniques. For example, DNA fragments encoding the different polypeptide sequences can be ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable
20 joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric
25 gene sequence (*see, e.g.*, Ausubel *et al.* (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A MTSP-1-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the MTSP-1 polypeptide.

30 Fc fusion proteins, fusion to human serum albumin, fusion to carboxy-terminal peptide are known modifications for improving pharmacokinetics of peptide or biologic drugs. Among these is conjugation to either linear or branched-chain

monomethoxy poly-ethylene glycol (PEG), resulting in increases in the molecular mass and hydrodynamic radius, and a decrease in the rate of glomerular filtration by the kidney.

Another approach to for improving pharmacokinetic parameters includes
5 modification of glycosylation patterns, resulting in reduced clearance and extension of half-life.

7. Nucleic Acid Molecules

Nucleic acid molecules encoding MTSP-1 polypeptides are provided herein. Nucleic acid molecules include allelic variants or splice variants of any encoded
10 MTSP-1 polypeptide, or catalytically active portion thereof. In one embodiment, nucleic acid molecules provided herein have at least 50, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, or 99% sequence identity or hybridize under conditions of medium or high stringency along at least 70% of the full-length of any nucleic acid encoded MTSP-1 polypeptide, or catalytically active portion thereof. In another embodiment, a
15 nucleic acid molecule can include those with degenerate codon sequences of any of the MTSP-1 polypeptides or catalytically active portions thereof such as those provided herein. Exemplary nucleic acid molecules, encoding scaffold or modified proteases, or catalytically active portions thereof, have a sequence of nucleotides as set forth in any of SEQ ID NOS: 60-98.

20 Nucleic acid molecules, or fusion proteins containing a catalytically active portion of a nucleic acid molecule, operably-linked to a promoter, such as an inducible promoter for expression in mammalian cells also are provided. Such promoters include, but are not limited to, CMV and SV40 promoters; adenovirus promoters, such as the E2 gene promoter, which is responsive to the HPV E7
25 oncoprotein; a PV promoter, such as the PBV p89 promoter that is responsive to the PV E2 protein; and other promoters that are activated by the HIV or PV or oncogenes.

A MTSP-1 protease provided herein, also can be delivered to the cells in gene transfer vectors. The transfer vectors also can encode additional other therapeutic agent(s) for treatment of the disease or disorder, such as Rheumatoid Arthritis or
30 cardiovascular disease or AMD or DGF, for which the protease is administered. Transfer vectors encoding a protease can be used systemically, by administering the nucleic acid to a subject. For example, the transfer vector can be a viral vector, such

as an adenovirus vector. Vectors encoding a protease also can be incorporated into stem cells and such stem cells administered to a subject such as by transplanting or engrafting the stem cells at sites for therapy. For example, mesenchymal stem cells (MSCs) can be engineered to express a protease and such MSCs engrafted at a transplant site for therapy.

G. COMPOSITIONS, FORMULATIONS AND DOSAGES

Pharmaceutical compositions containing modified MTSP-1 polypeptides, modified MTSP-1 fusion proteins or encoding nucleic acid molecules, can be formulated in any conventional manner by mixing a selected amount of the

polypeptide with one or more physiologically acceptable carriers or excipients.

Selection of the carrier or excipient is within the skill of the administering profession and can depend upon a number of parameters. These include, for example, the mode of administration (*i.e.*, systemic, oral, nasal, pulmonary, local, topical or any other mode) and disorder treated. The pharmaceutical compositions provided herein can be

formulated for single dosage (direct) administration or for dilution or other modification. The concentrations of the compounds in the formulations are effective for delivery of an amount, upon administration, that is effective for the intended treatment. Typically, the compositions are formulated for single dosage

administration. To formulate a composition, the weight fraction of a compound or mixture thereof is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

1. Administration of Modified MTSP-1 Polypeptides

The polypeptides can be formulated as the sole pharmaceutically active ingredient in the composition or can be combined with other active ingredients. The polypeptides can be targeted for delivery, such as by conjugation to a targeting agent, such as an antibody. Liposomal suspensions, including tissue-targeted liposomes, also can be suitable as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art. For example, liposome formulations can be prepared as described in U.S. Patent No. 4,522,811. Liposomal

delivery also can include slow release formulations, including pharmaceutical matrices such as collagen gels and liposomes modified with fibronectin (*see, for example, Weiner et al. (1985) J Pharm Sci. 74(9): 922-5).*

5 The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the subject treated. The therapeutically effective concentration can be determined empirically by testing the compounds in known *in vitro* and *in vivo* systems, such as the assays provided herein.

10 The MTSP-1 polypeptides provided herein (*i.e.*, active compounds) can be administered *in vitro*, *ex vivo*, or *in vivo* by contacting a mixture, such as a body fluid, such as the vitreous, or other tissue sample, with a MTSP-1 polypeptide provided herein, including any of the modified MTSP-1 polypeptides provided herein. For example, when administering a compound *ex vivo*, a body fluid or tissue sample from a subject can be contacted with the MTSP-1 polypeptides that are coated on a tube or
15 filter, such as for example, a tube or filter in a bypass machine. When administering *in vivo*, the active compounds can be administered by any appropriate route, for example, orally, nasally, pulmonary, parenterally, intravenously, intradermally, intravitreally, periocularly, subcutaneously, or topically, in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration.
20 Determination of dosage is within the skill of the physician, and can be a function of the particular disorder, route of administration and subject. Exemplary dosages will be dosed at 0.1 - 1 mg.

The modified MTSP-1 polypeptide and physiologically acceptable salts and solvates can be formulated for administration by inhalation (either through the mouth
25 or the nose), oral, transdermal, pulmonary, parenteral or rectal administration. For administration by inhalation, the modified MTSP-1 polypeptide can be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable
30 gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin

for use in an inhaler or insufflator, can be formulated containing a powder mix of a therapeutic compound and a suitable powder base such as lactose or starch.

For pulmonary administration to the lungs, the modified MTSP-1 polypeptide can be delivered in the form of an aerosol spray presentation from a nebulizer, 5 turbonebulizer, or microprocessor-controlled metered dose oral inhaler with the use of a suitable propellant. Generally, particle size of the aerosol is small, such as in the range of 0.5 to 5 microns. In the case of a pharmaceutical composition formulated for pulmonary administration, detergent surfactants are not typically used. Pulmonary drug delivery is a promising non-invasive method of systemic administration. The 10 lungs represent an attractive route for drug delivery, mainly due to the high surface area for absorption, thin alveolar epithelium, extensive vascularization, lack of hepatic first-pass metabolism, and relatively low metabolic activity.

For oral administration, the pharmaceutical compositions can take the form of, for example, tablets, pills, liquid suspensions, or capsules prepared by conventional 15 means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets 20 can be coated by methods well known in the art. Liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol 25 syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations also can contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

30 Preparations for oral administration can be formulated for controlled release of the active compound. For buccal administration the compositions can take the form of tablets or lozenges formulated in conventional manner.

The modified MTSP-1 polypeptides can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the therapeutic compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The modified MTSP-1 polypeptide can be formulated for parenteral administration by injection (*e.g.*, by bolus injection or continuous infusion). Formulations for injection can be presented in unit dosage form (*e.g.*, in ampoules or in multi-dose containers) with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder-lyophilized form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The modified MTSP-1 polypeptides can be formulated for ocular or ophthalmic delivery. Ocular drug delivery includes, for example, topical, oral or systemic, and/or injected. For example, a modified MTSP-1 polypeptide(s) or pharmaceutical composition containing a modified MTSP-1 polypeptide(s) can be administered topically, such as in the form of eye drops. In another example, a modified MTSP-1 polypeptide(s) or pharmaceutical composition containing a modified MTSP-1 polypeptide(s) can be administered by periocular and/or intravitreal administration, such as, for example, by periocular or intravitreal injection(s).

The modified MTSP-1 polypeptides or pharmaceutical composition containing modified MTSP-1 polypeptides or nucleic acids encoding modified MTSP-1 polypeptides can be formulated for systemic administration for treatment of DGF. In another example, the modified MTSP-1 polypeptides or pharmaceutical composition containing modified MTSP-1 polypeptides or nucleic acids encoding modified MTSP-1 polypeptides are directly infused or injected into the kidney or into the tissues or organs adjacent or surrounding the transplanted kidney. The modified MTSP-1 polypeptides or pharmaceutical composition containing modified MTSP-1 polypeptides can be administered before the time of allograft transplantation or at the

time of transplantation with administration continuing in a chronic fashion, and/or can be administered during a rejection episode in the event such an episode does occur.

The pharmaceutical compositions can be formulated for local or topical application, such as for topical application to the skin (transdermal) and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Such solutions, particularly those intended for ophthalmic use, can be formulated as 0.01% - 10% isotonic solutions and pH about 5-7 with appropriate salts. The compounds can be formulated as aerosols for topical application, such as by inhalation (*see*, for example, U.S. Patent Nos. 4,044,126, 4,414,209 and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment inflammatory diseases, particularly asthma).

The concentration of active compound in the drug composition depends on absorption, inactivation and excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. As described further herein, dosages can be determined empirically using comparisons of properties and activities (*e.g.*, cleavage of one or more complement proteins) of the modified MTSP-1 polypeptide compared to the unmodified and/or wild type and/or reference MTSP-1 polypeptide.

The compositions, if desired, can be presented in a package, in a kit or dispenser device, that can contain one or more unit dosage forms containing the active ingredient. In some examples, the composition can be coated on a device, such as for example on a tube or filter in, for example, a bypass machine. The package, for example, contains metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration. The compositions containing the active agents can be packaged as articles of manufacture containing packaging material, an agent provided herein, and a label that indicates the disorder for which the agent is provided.

Also provided are compositions containing nucleic acid molecules, including expression vectors, encoding the MTSP-1 polypeptides. In some embodiments, the compositions of nucleic acid molecules encoding the MTSP-1 polypeptides and expression vectors encoding them are suitable for gene therapy. Rather than deliver the protein, nucleic acid can be administered *in vivo*, such as systemically or by other

route, or *ex vivo*, such as by removal of cells, including lymphocytes, introduction of the nucleic therein, and reintroduction into the host or a compatible recipient.

2. Administration of Nucleic Acids Encoding Modified MTSP-1 Polypeptides (Gene Therapy)

5 MTSP-1 polypeptides can be delivered to cells and tissues by expression of nucleic acid molecules. MTSP-1 polypeptides can be administered as nucleic acid molecules encoding MTSP-1 polypeptides, including *ex vivo* techniques and direct *in vivo* expression. Nucleic acids can be delivered to cells and tissues by any method known to those of skill in the art. The isolated nucleic acid can be incorporated into
10 vectors for further manipulation. Exemplary nucleic acids are any that encode or that hybridize under medium to high stringency to a nucleic acid that encodes a MTSP-1 polypeptide, or catalytically active portion thereof having a sequence of amino acids set forth in any of SEQ ID NOS: 21-59. Exemplary nucleic acid molecules, encoding modified MTSP-1 polypeptides, or catalytically active portions thereof, have a
15 sequence of nucleotides as set forth in any of SEQ ID NOS:60-98.

Methods for administering MTSP-1 polypeptides by expression of encoding nucleic acid molecules include administration of recombinant vectors. The vector can be designed to remain episomal, such as by inclusion of an origin of replication or can be designed to integrate into a chromosome in the cell. MTSP-1 polypeptides also can
20 be used in *ex vivo* gene expression therapy using vectors. Suitable gene therapy vectors and methods of delivery are known to those of skill in the art. For example, cells can be engineered to express a modified MTSP-1 polypeptide, such as by integrating MTSP-1 polypeptide encoding nucleic acid into a genomic location, either operatively linked to regulatory sequences or such that it is placed operatively linked
25 to regulatory sequences in a genomic location. Such cells then can be administered locally or systemically to a subject, such as a patient in need of treatment. Exemplary vectors for *in vivo* and *ex vivo* gene therapy include viral vectors, and non-viral vectors such as for example, liposomes or artificial chromosomes.

Viral vectors, including, for example adenoviruses, herpes viruses, adeno-associated viruses (AAV), retroviruses, such as lentiviruses, EBV, SV40,
30 cytomegalovirus vectors, vaccinia virus vectors, and others designed for gene therapy can be employed. The vectors can be those that remain episomal or those that can

integrate into chromosomes of the treated subject. A modified MTSP-1 polypeptide can be expressed by a virus, which is administered to a subject in need of treatment. Virus vectors suitable for gene therapy include adenovirus, adeno-associated virus, retroviruses, lentiviruses and others noted above. For example, adenovirus expression technology is well-known in the art and adenovirus production and administration methods also are well known. Adenovirus serotypes are available, for example, from the American Type Culture Collection (ATCC, Rockville, MD). Adenovirus can be used *ex vivo*, for example, cells are isolated from a patient in need of treatment, and transduced with a modified MTSP-1 polypeptide-expressing adenovirus vector. After a suitable culturing period, the transduced cells are administered to a subject, locally and/or systemically. Alternatively, MTSP-1 polypeptide-expressing adenovirus particles are isolated and formulated in a pharmaceutically-acceptable carrier for delivery of a therapeutically effective amount to prevent, treat or ameliorate a disease or condition of a subject. In one embodiment, the disease to be treated is caused by complement activation. Typically, adenovirus particles are delivered at a dose ranging from 1 particle to 10¹⁴ particles per kilogram subject weight, generally between 10⁶ or 10⁸ particles to 10¹² particles per kilogram subject weight.

The nucleic acid molecules can be introduced into artificial chromosomes and other non-viral vectors. Artificial chromosomes, such as *ACES* (see, Lindenbaum *et al.* (2004) *Nucleic Acids Res.* 32(21):e172) can be engineered to encode and express the MTSP-1 polypeptide. Briefly, mammalian artificial chromosomes (MACs) provide a means to introduce large payloads of genetic information into the cell in an autonomously replicating, non-integrating format. Unique among MACs, the mammalian satellite DNA-based Artificial Chromosome Expression System (*ACES*) can be reproducibly generated *de novo* in cell lines of different species and readily purified from the host cells' chromosomes. Purified mammalian *ACES* can then be re-introduced into a variety of recipient cell lines where they have been stably maintained for extended periods in the absence of selective pressure using an *ACE* System. Using this approach, specific loading of one or two gene targets has been achieved in LMTK(-) and CHO cells.

Another method for introducing nucleic acids encoding the modified MTSP-1 polypeptides is a two-step gene replacement technique in yeast, starting with a

complete adenovirus genome (Ad2; Ketner *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91: 6186-6190) cloned in a Yeast Artificial Chromosome (YAC) and a plasmid containing adenovirus sequences to target a specific region in the YAC clone, an expression cassette for the gene of interest and a positive and negative selectable
5 marker. YACs are of particular interest because they permit incorporation of larger genes. This approach can be used for construction of adenovirus-based vectors bearing nucleic acids encoding any of the described modified MTSP-1 polypeptides for gene transfer to mammalian cells or whole animals.

The nucleic acids can be encapsulated in a vehicle, such as a liposome, or
10 introduced into a cells, such as a bacterial cell, particularly an attenuated bacterium or introduced into a viral vector. For example, when liposomes are employed, proteins that bind to a cell surface membrane protein associated with endocytosis can be used for targeting and/or to facilitate uptake, *e.g.*, capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization
15 in cycling, and proteins that target intracellular localization and enhance intracellular half-life.

In some embodiments, it is desirable to provide a nucleic acid source with an agent that targets cells, such as an antibody specific for a cell surface membrane protein or a target cell, or a ligand for a receptor on a target cell. Polynucleotides and
20 expression vectors provided herein can be made by any suitable method. Further provided are nucleic acid vectors containing nucleic acid molecules as described above. Further provided are nucleic acid vectors containing nucleic acid molecules as described above and cells containing these vectors.

For *ex vivo* and *in vivo* methods, nucleic acid molecules encoding the MTSP-1
25 polypeptide are introduced into cells that are from a suitable donor or the subject to be treated. Cells into which a nucleic acid can be introduced for purposes of therapy include, for example, any desired, available cell type appropriate for the disease or condition to be treated including, but not limited to, epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T
30 lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, including hemo-

poietic stem or progenitor cells, *e.g.*, such as stem cells obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, and other sources thereof.

For *ex vivo* treatment, cells from a donor compatible with the subject to be treated or cells from a subject to be treated are removed, the nucleic acid is introduced
5 into these isolated cells and the modified cells are administered to the subject. Treatment includes direct administration, such as, for example, encapsulated within porous membranes, which are implanted into the patient (see, *e.g.*, U.S. Pat. Nos. 4,892,538 and 5,283,187). Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes and cationic lipids (*e.g.*,
10 DOTMA, DOPE and DC-Chol) electroporation, microinjection, cell fusion, DEAE-dextran, and calcium phosphate precipitation methods. Methods of DNA delivery can be used to express MTSP-1 polypeptides *in vivo*. Such methods include liposome delivery of nucleic acids and naked DNA delivery, including local and systemic delivery such as using electroporation, ultrasound and calcium-phosphate delivery.
15 Other techniques include microinjection, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer and spheroplast fusion.

In vivo expression of a MTSP-1 polypeptide can be linked to expression of additional molecules. For example, expression of a MTSP-1 polypeptide can be linked with expression of a cytotoxic product such as in an engineered virus or
20 expressed in a cytotoxic virus. Such viruses can be targeted to a particular cell type that is a target for a therapeutic effect. The expressed MTSP-1 polypeptide can be used to enhance the cytotoxicity of the virus.

In vivo expression of a MTSP-1 polypeptide can include operatively linking a MTSP-1 polypeptide encoding nucleic acid molecule to specific regulatory sequences
25 such as a cell-specific or tissue-specific promoter. MTSP-1 polypeptides also can be expressed from vectors that specifically infect and/or replicate in target cell types and/or tissues. Inducible promoters can be used to selectively regulate MTSP-1 polypeptide expression.

Nucleic acid molecules, as naked nucleic acids or in vectors, artificial
30 chromosomes, liposomes and other vehicles can be administered to the subject by systemic administration, topical, local and other routes of administration. When

systemic and *in vivo*, the nucleic acid molecule or vehicle containing the nucleic acid molecule can be targeted to a cell.

Administration also can be direct, such as by administration of a vector or cells that typically targets a cell or tissue. For example, tumor cells and proliferating
5 can be targeted cells for *in vivo* expression of MTSP-1 polypeptides. Cells used for *in vivo* expression of a MTSP-1 polypeptide also include cells autologous to the patient. Such cells can be removed from a patient, nucleic acids for expression of a MTSP-1 polypeptide introduced, and then administered to a patient such as by injection or engraftment.

10 H. THERAPEUTIC USES AND METHODS OF TREATMENT

The modified MTSP-1 polypeptides provided herein target complement protein C3 and permit modulation of complement-mediated diseases and disorders. Therapeutic proteases, such as the modified MTSP-1 polypeptides provided herein, have many potential advantages over traditional therapeutic approaches. Chief among
15 them is the ability to inactivate disease targets in a catalytic manner (*i.e.* a one to many stoichiometry). Thus, proteases can maintain effective regulation at concentrations significantly below the target concentration. Additional differentiating advantages include (1) irreversible inactivation; (2) low dosing; (3) decreased dosing frequency; (4) small molecular size; (5) the ability to target post-translational
20 modifications; (6) the ability to neutralize high target concentrations; and (7) the ability to target *away* from the active site. As a therapeutic, a protease must still exhibit the following characteristics: (1) access to the molecular target (extracellular), and (2) possess sufficiently stringent specificity for a target critical to a disease state. The modified MTSP-1 polypeptides provided herein can be used in the treatment of
25 complement-mediated diseases and disorders.

The skilled artisan understands the role of the complement system in disease processes and is aware of a variety of such diseases. Provided is a brief discussion of exemplary diseases and the role of the complement protein C3 in their etiology and pathology. The modified MTSP-1 polypeptides and nucleic acid molecules provided
30 herein can be used for treatment of any condition for which activation of the complement pathway is implicated, particularly inflammatory conditions including acute inflammatory conditions, such as septic shock, and chronic inflammatory

conditions, such as Rheumatoid Arthritis (RA). Acute and inflammatory conditions can be manifested as an immune-mediated disease such as for example autoimmune disease or tissue injury caused by immune-complex-mediated inflammation. A complement-mediated inflammatory condition also can be manifested as a

5 neurodegenerative or cardiovascular disease that have inflammatory components. This section provides exemplary uses of, and administration methods for, modified MTSP-1 polypeptides provided herein. These described therapies are exemplary and do not limit the applications of the modified MTSP-1 polypeptides provided herein. Such methods include, but are not limited to, methods of treatment of physiological

10 and medical conditions described and listed below. Such methods include, but are not limited to, methods of treatment of age-related macular degeneration (AMD), geographic atrophy (GA), aroxysmal nocturnal hemoglobinuria (PNH), renal delayed graft function (DGF), sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), lupus erythematosus, Multiple Sclerosis (MS),

15 Myasthenia gravis (MG), asthma, inflammatory bowel disease, respiratory distress syndrome, immune complex (IC)-mediated acute inflammatory tissue injury, multi-organ failure, Alzheimer's Disease (AD), Ischemia-reperfusion injuries caused by events or treatments such as myocardial infarct (MI), stroke, cardiopulmonary bypass (CPB) or coronary artery bypass graft, angioplasty, or hemodialysis, chronic

20 obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and/or Guillain Barre syndrome.

Treatment of diseases and conditions with modified MTSP-1 polypeptides provided herein can be effected by any suitable route of administration using suitable formulations as described herein including, but not limited to, subcutaneous injection,

25 oral, intravitreal, periocular and transdermal administration. If necessary, a particular dosage and duration and treatment protocol can be empirically determined or extrapolated. For example, exemplary doses of wild type or reference MTSP-1 polypeptides can be used as a starting point to determine appropriate dosages. Modified MTSP-1 polypeptides that have more specificity and/or selectivity

30 compared to a wild type or reference MTSP-1 polypeptide can be effective at reduced dosage amounts and or frequencies. Dosage levels can be determined based on a variety of factors, such as body weight of the individual, general health, age, the

activity of the specific compound employed, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the disease and the judgment of the treating physician. The amount of active ingredient that can be combined with the carrier materials to produce a single
5 dosage form will vary depending upon the host treated and the particular mode of administration.

Upon improvement of a patient's condition, a maintenance dose of a compound or compositions can be administered, if necessary; and the dosage, the dosage form, or frequency of administration, or a combination thereof can be
10 modified. In some cases, a subject can require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

1. Disease Mediated by Complement Activation

The complement cascade is a dual-edged sword, causing protection against bacterial and viral invasion by promoting phagocytosis and inflammation.
15 Conversely, even when complement is functioning normally, it can contribute to the development of disease by promoting local inflammation and damage to tissues. Thus, pathological effects are mediated by the same mediators that are responsible for the protective roles of complement. For example, the anaphylactic and chemotactic peptide C5a drives inflammation by recruiting and activating neutrophils, C3a can
20 cause pathological activation of other phagocytes, and the membrane attack complex can kill or injure cells. In one example, such as in many autoimmune diseases, complement produces tissue damage because it is activated under inappropriate circumstances such as by antibody to host tissues. In other situations, complement can be activated normally, such as by septicemia, but still contributes to disease
25 progression, such as in respiratory distress syndrome. Pathologically, complement can cause substantial damage to blood vessels (vasculitis), kidney basement membrane and attached endothelial and epithelial cells (nephritis), joint synovium (arthritis), and erythrocytes (hemolysis) if it is not adequately controlled.

Complement has a role in immuno-pathogenesis of a number of disorders,
30 including autoimmune diseases such as rheumatoid arthritis (see, *e.g.*, Wang *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A.* 92:8955-8959; Moxley *et al.* (1987) *Arthritis & Rheumatism* 30:1097-1104), lupus erythematosus (Wang *et al.* (1996) *Proc. Natl.*

Acad. Sci. U.S.A. 90:8563-8568; and Buyon *et al.* (1992) *Arthritis Rheum.* 35:1028-1037) and acute glomerulonephritis (Couser *et al.* (1995) *J Am Soc Nephrol.* 5:1888-1894). Other pathologies that involve activation of the complement system include sepsis (see, *e.g.*, Stove *et al.* (1996) *Clin Diag Lab Immunol* 3:175-183; Hack *et al.* (1989) *Am. J. Med.* 86:20-26), respiratory distress syndrome (see, *e.g.*, Zilow *et al.* (1990) *Clin. Exp. Immunol.* 79:151-157; and Stevens *et al.* (1986) *J. Clin. Invest.* 77:1812-1816), multiorgan failure (see, *e.g.*, Hecke *et al.* (1997) *Shock* 7:74; and Heideman *et al.* (1984) *J. Trauma* 24:1038-1043), ischemia-reperfusion injury such as occurs in cardiovascular disease such as stroke or myocardial infarct (Austen WG *et al.* (2003) *Int J Immunopathol Pharm* 16(1):1-8), age-related macular degeneration (Bradley *et al.* (2011) *Eye* 25: 683-693; Gemenetzi *et al.* (2016) *Eye* 30: 1-14) and renal delayed graft function (Danobeitia *et al.* (2013) [abstract]. *Am J Transplant.* 13 (suppl 5); Yu *et al.* (2016) *Am J Transplant* 16(9):2589-2597; Castellano *et al.* (2010) *Am J Pathol* 176(4):1648-1659). Some exemplary examples of complement-mediated diseases are described below.

a. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory illness. It is an autoimmune disease in which the immune system attacks normal tissue components as if they were invading pathogens. The inflammation associated with rheumatoid arthritis primarily attacks the linings of the joints. The membranes lining the blood vessels, heart, and lungs also can become inflamed. RA is characterized by activated B cells and plasma cells that are present in inflamed synovium, and in established disease lymphoid follicles and germinal centers. This results in high levels of local immunoglobulin production and the deposition of immune complexes, which can include IgG and IgM rheumatoid factors, in the synovium and in association with articular cartilage which can serve as initiators of the complement cascade. Elevated levels of complement components, such as C3a, C5a, and C5b-9 have been found within the inflamed rheumatoid joints. These complement components can exacerbate the inflammation associated with RA by inducing a variety of proinflammatory activities such as for example, alterations in vascular permeability, leukocyte chemotaxis, and the activation and lysis of multiple cell types.

b. Sepsis

Sepsis is a disease caused by a serious infection, such as a bacterial infection, leading to a systemic inflammatory response. The bacterial cell wall component, lipopolysaccharide, is often associated with sepsis, although other bacterial, viral, and fungal infections can stimulate septic symptoms. Septic shock often results if the natural immune system of the body is unable to defend against an invading microorganism such that, for example, the pro-inflammatory consequences of the immune response is damaging to host tissues. The early stages of sepsis are characterized by excessive complement activation resulting in increased production of complement anaphylatoxins, such as C3a, C4a, and C5a which act to increase vascular permeability, stimulate superoxide production from neutrophils and stimulate histamine release. The actions of C5a can contribute to a productive immune response to a bacterial infection, but if left unregulated, C5a also can be severely damaging. In an *E.coli*-induced model of inflammation, blockade of C5a improved the outcome of septic animals by limiting C5a-mediated neutrophil activation that can lead to neutrophil-mediated tissue injury.

The continued impairment of the innate immune response to a bacterial infection often leads to chronic sepsis or septic shock, which can be life-threatening. In the late stage of sepsis, it is the “dormant” activity of neutrophils, as opposed to the hyperactivity that occurs in the early phases, that contributes to continued disease. In the late stage, the major functions of neutrophils including chemotaxis, respiratory burst activity, and ability for bacterial killing are reduced. Complement, and in particular C5a, also plays a role in the later stages of sepsis. Excessive production of C5a during sepsis is associated with the “deactivation” of blood neutrophils, a process that has been linked to C5a-induced down regulation of its own receptor, C5aR, on neutrophils (Guo *et al.* (2003) *FASEB J* 13:1889). The reduced levels of C5aR on neutrophils correlates with a diminished ability of blood neutrophils to bind C5a, impaired chemotactic responses, a loss of superoxide productions, and impaired bactericidal activity. C5aR levels, however, can begin to “recover” at later stages of sepsis and correlate with instances of beneficial disease outcome.

c. Multiple Sclerosis

Multiple sclerosis (MS) and its animal model experimental allergic encephalomyelitis (EAE) are inflammatory demyelinating diseases of the central nervous system (CNS). In MS, inflammation of nervous tissue causes the loss of myelin, a fatty material which acts as a sort of protective insulation for the nerve fibers in the brain and spinal cord. This demyelination leaves multiple areas of scar tissue (sclerosis) along the covering of the nerve cells, which disrupts the ability of the nerves to conduct electrical impulses to and from the brain, producing the various symptoms of MS. MS is mediated by activated lymphocytes, macrophages/microglia and the complement system. Complement activation can contribute to the pathogenesis of these diseases through its dual role: the ability of activated terminal complex C5b-9 to promote demyelination and the capacity of sublytic C5b-9 to protect oligodendrocytes (OLG) from apoptosis.

d. Alzheimer's Disease

Alzheimer's disease (AD) is characterized by tangles (abnormal paired helical filaments of the protein tau, which normally binds to microtubules) and plaques (extracellular deposits composed primarily of beta-amyloid protein) within the brain. Although, the precise cause of AD is not entirely clear, chronic neuroinflammation in affected regions of AD brains indicate that proinflammatory mediators can play a role. The tangles and plaques within an AD brain are deposited with activated complement fragments, such as for example, C4d and C3d. Likewise, dystrophic neurites in AD brain can be immunostained for MAC, indicating autocatalytic attack of these neurites and concomitant neurite loss in AD. Activation of complement in AD occurs by an antibody-independent mechanism induced by aggregated amyloid-beta protein. Further, the complement cascade can be activated by the pentraxins, C-reactive protein (CRP), and amyloid P (AP) which are all upregulated in AD (McGeer *et al.*, (2002) *Trends Mol Med* 8:519). The activation of complement in AD, marked by increases in complement mediators, is not adequately controlled by a compensatory upregulation of complement regulatory proteins such as, for example, CD59. Thus, the proinflammatory consequences of complement activation exacerbates AD progression and likely contributes to neurite destruction.

e. Ischemia-Reperfusion Injury

Ischemia-reperfusion injury is the injury sustained after an ischemic event and subsequent restoration of blood flow and results from the inflammatory response to a hypoxic insult. Ischemia-reperfusion damage can be acute as during cardiac surgery procedures, such as for example following open heart surgery or angioplasty, or chronic as with congestive heart failure or occlusive cardiovascular disease. Examples of injuries that can cause ischemia-reperfusion injury include myocardial infarct (MI) and stroke. The initiation of an inflammatory response is likely caused by the increase in tissue oxygen levels that occur with reperfusion and the concomitant accumulation of metabolites that can generate oxygen free radicals which are immunostimulatory. Ischemia-reperfusion injury is associated with a variety of events including severity of myocardial infarction, cerebral ischemic events, intestinal ischemia, and many aspects of vascular surgery, cardiac surgery, trauma, and transplantation. The injury is manifested by inflammatory events of the innate immune system, particularly activation of the complement system, in response to newly altered tissue as non-self. As such ischemia-reperfusion injury is characterized by tissue edema caused by increased vascular permeability, and an acute inflammatory cell infiltrate caused by influx of polymorphonuclear leukocytes.

Activation of the complement system plays a role in the inflammatory events of ischemia-reperfusion injury. The ischemia injury results in alterations of the cell membrane, affecting lipids, carbohydrates, or proteins of the external surface such that these exposed epitopes are altered and can act as neo-antigens (modified self-antigens). Circulating IgM recognize and bind the neo-antigens to form immune complexes on the injured cell surface. The antigen-antibody complexes formed are classic activators of the classical pathway of complement, although all pathways are likely involved in some way to the exacerbating effects of the injury. The involvement of the classical pathway of complement to ischemia-reperfusion injury is evidenced by mice genetically deficient in either C3 or C4 that display equal protection from local injury in a hind limb and animal model of injury (Austen *et al.* (2003) *Int J Immunopath Pharm* 16:1). Conversely, in a kidney model of ischemia injury, C3-, C5-, and C6-deficient mice were protected whereas C4-deficient mice were not, indicating the importance of the alternative complement pathway (Guo *et al.* (2005)

Ann Rev Immunol 23:821). Mediators induced upon complement activation initiate an inflammatory response directed at the cell membrane at the site of local injury.

A major effector mechanism of complement in ischemia-reperfusion injury is the influx and activation of neutrophils to the inflamed tissue by complement components, such as, for example, C5a. Activation of neutrophils results in increased production of reactive oxygen species and the release of lysosomal enzymes in local injured organs which ultimately results in apoptosis, necrosis, and a loss of organ function. The generation of the terminal MAC, C5b-9, also contributes to local tissue injury in ischemia-reperfusion injury.

10 **f. Ocular Disorders**

In the normal eye, the complement system is continuously activated at low levels; membrane-bound and soluble intraocular complement regulatory proteins tightly regulate this spontaneous complement activation. Low level complement activation protects against pathogens without causing any damage to self-tissue and vision loss. The complement system and complement regulatory proteins control the intraocular inflammation in autoimmune uveitis and play an important role in the development of corneal inflammation, age-related macular degeneration and diabetic retinopathy. The complement system plays an important role in the pathogenesis of diabetic retinopathy (see, *e.g.*, Ghosh *et al.* (2015) *Endocr Rev* 36:272–288) as well as diabetic neuropathy and diabetic cardiovascular disease. Spontaneous complement activation can cause damage to the corneal tissue after the infection. Complement inhibition is a relevant therapeutic target in the treatment of various ocular diseases (see, *e.g.*, Purushottam *et al.* (2007) *Mol Immunol.* 44:3901–3908).

Age-Related Macular Degeneration (AMD)

25 Age-related macular degeneration is a clinical term that describes a variety of diseases that are characterized by the progressive loss of central vision. AMD is the leading cause of vision loss in aged individuals in many industrialized countries (Jager *et al.* (2008) *N Engl J Med* 358:2606-2617). Vision loss occurs due to the progressive degeneration of the macula, the region at the back of the eye comprising a high density of cone photoreceptors, which is specialized for high-acuity, central vision.

AMD can manifest as Dry (non-neovascular) AMD and/or Wet AMD. Dry AMD is the more common (85-90% of cases) and milder form of AMD, and is characterized by small, round, white-yellow lesions (drusen) in and under the macula. Advanced dry AMD, or geographic atrophy, leads to thinning of the retina due to loss of PRE photoreceptors, deterioration of the macula and eventual blindness. Although 5 rarer, vision loss associated with wet AMD is generally more dramatic than in dry AMD. Wet AMD includes the formation of pathogenic blood vessels, termed choroidal neovascularization (CNV), in which abnormal blood vessels develop beneath the retinal pigment epithelium (RPE) layer of the retina. CNV invasion of the 10 retina from the underlying choroid through fractures in Bruch membrane, the extracellular matrix between the choroid and the retinal pigment epithelium (RPE), or their breakage can cause vision loss in AMD (e.g., due to subretinal hemorrhage and/or scarring).

Early clinical hallmarks of AMD include thickening of the Bruch membrane and the appearance of drusen (Gass, J. D. (1972) *Trans. Am. Ophthalmol. Soc.* 70: 15 409-36), which are extracellular lipoproteinaceous deposits consisting of aggregated proteins, such as albumin, apolipoprotein E (APOE), components of the complement pathway (e.g., complement factor H (CFH), C1q, C3, C5, C5b, C6, C7, C8, C9, and vitronectin (Hageman *et al.*, (2001) *Prog. Retin. Eye. Res.* 29:95-112; Hageman *et al.* 20 (2005) *Proc. Nat. Acad. Sci.* 102: 7227-7232; Mullins *et al.* (2000) *FASEB J* 14:835-846; Anderson *et al.*, (2010) *Pro. Retin. Eye Res.* 29:95-112), immunoglobulins and/or amyloid- β (Crabb *et al.* (2002) *Proc Natl Acad Sci* 99:14682-14687; Johnson *et al.* (2002) 99:11830-11835) and lipids and cellular components that are localized between the RPE and the Bruch membrane. Inflammation in AMD is mediated by the 25 deregulation of the alternative complement pathway. Complement components C3 and C5 are principal constituents of drusen in patients with AMD (Mullins *et al.*, (2000) *FASEB J* 14, 835-46; Johnson *et al.*, (2000) *Exp Eye Res* 70, 441-9; Anderson *et al.*, (2002) *Am J Ophthalmol* 134, 411-31; and Leitner *et al.*, (2001) *Exp Eye Res* 73, 887-96). It is hypothesized that drusen biogenesis involves chronic inflammatory 30 processes that either can trigger complement activation and formation of MAC, which can lyse RPE cells or disturb physiological homeostasis in RPE cells, leading to inflammation characteristic of AMD (Johnson *et al.* (2001) *Exp Eye Res* 73, 887-896).

Complement proteins (*e.g.*, C3d) also were detected in blood in AMD patients (Scholl *et al.*, (2008) *PLoS One* 3: e2593), indicating that AMD-induced inflammation can be systemic. There is genetic evidence for a role in complement in the pathogenesis of dry AMD (Klein *et al.* (2005) *Science* 308(5720):385-389; Yates *et al.*, (2007) *NEJM* 357:553-561) and compstatin (and compstatin derivatives APL-1 and APL-2) and POT-4 (Potentia Pharmaceuticals), small peptide inhibitors of C3, may slow the progression of geographic atrophy (Ricklin *et al.* (2008) *Adv. Exp. Med. Biol.* 632: 273-292) in AMD, indicating that C3 (*i.e.*, C3 inhibition) is a viable target for AMD treatment. Recent clinical results have validated these conclusions and findings. C3 is a viable clinical target for complement mediated disorders and conditions or for those in which complement plays a role.

g. Organ Transplantation and Delayed Graft Function (DGF)

Complement plays a role in the pathogenesis of ischemia-reperfusion injury. The mechanism of renal reperfusion injury depends on the generation of C5a and C5b-9, both of which have direct toxicity on the renal tubules contributing to acute tubular necrosis and apoptosis, and leading to post-ischemic acute renal failure and tissue fibrosis. In turn, the generation of these terminal pathway components depends on intra-renal synthesis of C3 and availability of other complement components that are essential for complement activation. The level of expression of C3 in the donor organ is strongly dependent on the cold ischaemic time (Elham *et al.* (2010) *Curr Opin Organ Transplant.* 15:486–491).

Rejection in solid organ transplantation is influenced by the initial inflammatory response and subsequent adaptive alloimmune response, both of which are affected by various complement components. Complement proteins play a significant part in organ damage following transplantation in the process of ischaemia reperfusion and in modulating the activation of the adaptive immune response. Inhibiting complement or modulating the function of complement proteins molecules can reduce transplant organ damage and increase the organ lifespan (see, *e.g.*, Elham *et al.* (2010) *Curr Opin Organ Transplant.* 15:486–491). Targeting complement components for therapeutic intervention can reduce organ damage at the time of organ recovery, transfer and after transplantation. Exemplary of such organs is the kidney.

The modified MTSP-1 polypeptides provided herein can be administered to mitigate and/or treat organ damage following transplantation.

Delayed graft function (DGF), such as delayed graft function of the kidney, liver, lung, and/or heart, is a condition occurring in a subset of organ transplant patients in which the transplanted organ fails to function normally immediately following transplant. Other possible transplants include, but are not limited to, vascular tissue, eye, cornea, lens, skin, bone marrow, muscle, connective tissue, gastrointestinal tissue, nervous tissue, bone, stem cells, islets, cartilage, hepatocytes, and hematopoietic cells. Renal DGF is characterized by acute necrosis of the renal allograft and has been clinically defined by the need for dialysis shortly following transplantation. Acute kidney injury during the transplant process frequently manifests as DGF. The pathology underlying DGF is complex with contributions from donor-derived factors such as donor age and duration of ischemia, and recipient factors such as reperfusion injury, immunological responses and treatment with immunosuppressant medications.

Components of the complement cascade and complement activation play a critical role as mediators of transplant rejection and ischemia-reperfusion injury leading to DGF. Animal studies have established a key role for complement in ischemic reperfusion injury. For example, Eculizumab, a humanized monoclonal antibody directed against C5, blocks complement activation and were shown to prevent delayed graft function in a subset of high-risk kidney transplant patients (see, e.g., Horizon Scanning Research and Intelligence Centre brief, 2016 September; Johnson *et al.* (2015) *Curr Opin Organ Transplant* 20(6):643-651; Yu *et al.* (2016) *Am J Transplant* 16(9):2589-2597). Granular C4d deposition was associated with DGF in human renal allograft recipients (Kikić *et al.* (2014) *Transpl Int* 27(3):312-321). Increased C3 production is associated with kidney transplant rejection (Pratt *et al.* (2002) *Nat Med* 8(6):582-587; Damman *et al.* (2011) *Nephrol Dial Transplant* 26(7):2345-2354). Hence, the modified MTSP-1 polypeptides provided herein, can be used as a therapeutic for preventing or ameliorating or eliminating transplant rejection and DGF.

2. Therapeutic Uses

a. Immune-Mediated Inflammatory Diseases

Modified MTSP-1 polypeptides described herein can be used to treat inflammatory diseases. Inflammatory diseases that can be treated with proteases
5 include acute and chronic inflammatory diseases. Exemplary inflammatory diseases include central nervous system diseases (CNS), autoimmune diseases, airway hyper-responsiveness conditions such as in asthma, rheumatoid arthritis, inflammatory bowel disease, and immune complex (IC)-mediated acute inflammatory tissue injury.

Experimental autoimmune encephalomyelitis (EAE) can serve as a model for
10 multiple sclerosis (MS) (Piddlesden *et al.* (1994) *J Immunol* 152:5477). EAE can be induced in a number of genetically susceptible species by immunization with myelin and myelin components such as myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein (MOG). For example, MOG-induced EAE recapitulates essential features of human MS including the chronic, relapsing clinical disease
15 course the pathohistological triad of inflammation, reactive gliosis, and the formation of large confluent demyelinated plaques. Modified MTSP-1 polypeptides can be assessed in EAE animal models. Modified MTSP-1 polypeptides are administered, such as by daily intraperitoneal injection, and the course and progression of symptoms is monitored compared to control animals. The levels of inflammatory complement
20 components that can exacerbate the disease also can be measured by assaying serum complement activity in a hemolytic assay and by assaying for the deposition of complement components, such as for example C1, C3 and C9.

Complement activation modulates inflammation in diseases such as rheumatoid arthritis (RA) (Wang *et al.*, (1995) *PNAS* 92:8955). Modified MTSP-1
25 polypeptides can be used to treat RA. For example, MTSP-1 polypeptides can be injected locally or systemically. Modified MTSP-1 polypeptides can be dosed daily or weekly. PEGylated MTSP-1 polypeptides can be used to reduce immunogenicity. In one example, type II collagen-induced arthritis (CIA) can be induced in mice as a model of autoimmune inflammatory joint disease that is histologically similar to RA
30 characterized by inflammatory synovitis, pannus formation, and erosion of cartilage and bone. To induce CIA, bovine type II collagen (B-CII) in the presence of complete Freund's adjuvant can be injected intradermally at the base of the tail. After

21 days, mice can be re-immunized using the identical protocol. To examine the effects of a MTSP-1 polypeptide, 3 weeks following the initial challenge with B-CII, a MTSP-1 polypeptide or control can be administered intraperitoneally twice weekly for 3 weeks. Mice can be sacrificed 7 weeks following the initial immunization for histologic analysis. To assess the therapeutic effect of a MTSP-1 polypeptide on established disease, a MTSP-1 polypeptide can be administered daily for a total of 10 days following the onset of clinical arthritis in one or more limbs. The degree of swelling in the initially affected joints can be monitored by measuring paw thickness using calipers. In both models, serum can be drawn from mice for hemolytic assays and measurement of complement markers of activation such as for example C5a and C5b-9. In another example, primate models are available for RA treatments. Response of tender and swollen joints can be monitored in subjects treated with MTSP-1 polypeptides and controls to assess MTSP-1 polypeptide treatment.

Modified MTSP-1 polypeptide can be used to treat immune complex (IC)-mediated acute inflammatory tissue injury. IC-mediated injury is caused by a local inflammatory response against IC deposition in a tissue. The ensuing inflammatory response is characterized by edema, neutrophilia, hemorrhage, and finally tissue necrosis. IC-mediated tissue injury can be studied in an *in vivo* Arthus (RPA) reaction. Briefly, in the RPA reaction, an excess of antibody (such as for example rabbit IgG anti-chicken egg albumin) is injected into the skin of animals, such as for example rats or guinea pigs, that have previously been infused intravenously with the corresponding antigen (*i.e.*, chicken egg albumin) (Szalai *et al.*, (2000) *J Immunol* 164:463). Immediately before the initiation on an RPA reaction, a MTSP-1 polypeptide, or a bolus control, can be administered at the same time as the corresponding antigen by an intravenous injection via the right femoral vein. Alternatively, a MTSP-1 polypeptide can be administered during the initial hour of the RPA reaction, beginning immediately after injection of the antigen and just before dermal injection of the antibody. The effects of a MTSP-1 polypeptide on the generation of complement-dependent IC-mediated tissue injury can be assessed at various times after initiation of RPA by collecting blood to determine the serum hemolytic activity, and by harvesting the infected area of the skin for quantitation of lesion size.

Therapeutic MTSP-1 polypeptides, such as those described herein, can be used to treat sepsis and severe sepsis that can result in lethal shock. A model of complement-mediated lethal shock can be used to test the effects of a MTSP-1 polypeptide as a therapeutic agent. In one such example, rats can be primed with a trace amount of lipopolysaccharide (LPS), followed by the administration of a monoclonal antibody against a membrane inhibitor of complement (anti-Crry) (Mizuno *et al.*, (2002) *Int Arch Allergy Immunol* 127:55-62). A MTSP-1 polypeptide or control can be administered at any time during the course of initiation of lethal shock such as before LPS priming, after LPS priming, or after anti-Crry administration and the rescue of rats from lethal shock can be assessed.

b. Neurodegenerative Disease

Complement activation exacerbates the progression of Alzheimer's disease (AD) and contributes to neurite loss in AD brains. Modified MTSP-1 polypeptides described herein can be used to treat AD. Mouse models that mimic some of the neuropathological and behavioral features of AD can be used to assess the therapeutic effects of MTSP-1 polypeptides. Examples of transgenic mouse models include introducing the human amyloid precursor protein (APP) or the presenilin 1 (PS1) protein with disease-producing mutations into mice under the control of an aggressive promoter. These mice develop characteristics of AD including increases in beta-amyloid plaques and dystrophic neurites. Double transgenic mice for APP and PS1 mutant proteins develop larger numbers of fibrillar beta-amyloid plaques and show activated glia and complement factors associated with the plaque. MTSP-1 polypeptides can be administered, such as by daily intraperitoneal or intravenous injections, and the course and progression of symptoms is monitored compared to control animals.

c. Cardiovascular Disease

Modified MTSP-1 polypeptides provided herein can be used to treat cardiovascular disease. MTSP-1 polypeptides can be used in the treatment of cardiovascular diseases including ischemia reperfusion injury resulting from stroke, myocardial infarction, cardiopulmonary bypass, coronary artery bypass graft, angioplasty, or hemodialysis. MTSP-1 polypeptides also can be used in the treatment of the inflammatory response associated with cardiopulmonary bypass that can

contribute to tissue injury. Generally, a MTSP-1 polypeptide can be administered prior to, concomitantly with, or subsequent to a treatment or event that induces a complement-mediated ischemia reperfusion injury. In one example, a MTSP-1 polypeptide can be administered to a subject prior to the treatment of a subject by a complement-mediated, ischemic-injury inducing event, such as for example coronary artery bypass graft of angioplasty.

Effects of a MTSP-1 polypeptide on treatment of ischemia reperfusion injury can be assessed in animal models of the injury. In one such model, myocardial ischemia is induced in rabbits that have had an incision made in their anterior pericardium by placing a 3-0 silk suture around the left anterior descending (LAD) coronary artery 5-8 mm from its origin and tightening the ligature so that the vessel becomes completely occluded (Buerke *et al.*, (2001) *J Immunol* 167:5375). A MTSP-1 polypeptide, such as for example a modified MTSP-1 polypeptide, or a control vehicle such as saline, can be given intravenously in increasing doses as a bolus 55 minutes after the coronary occlusion (*i.e.*, 5 minutes before reperfusion). Five minutes later (*i.e.*, after a total of 60 minutes of ischemia) the LAD ligature can be untied and the ischemic myocardium can be reperfused for 3 hours. At the end of the reperfusion period, the ligature around the LAD is tightened. Effects of a MTSP-1 polypeptide on ischemia injury can be analyzed by assessing effects on myocardial necrosis, plasma creatine kinase levels, and markers of neutrophil activation such as for example myeloperoxidase activity and superoxide radical release.

In another model of complement-mediated myocardial injury sustained upon perfusion of isolated mouse hearts with Krebs-Henseleit buffer containing 6% human plasma, treatment with modified MTSP-1 polypeptides can be used to limit tissue damage to the heart. In such an example, the buffer used to perfuse the hearts can be supplemented with varying doses of modified MTSP-1 polypeptides. The perfused hearts can be assayed for deposition of human C3 and C5b-9, coronary artery perfusion pressure, end-diastolic pressure, and heart rate.

Modified MTSP-1 polypeptides provided herein can be used as therapeutics prior to or following Cardiopulmonary Bypass (CPB) or coronary artery bypass graft to inhibit the inflammatory immune response that often follows bypass and that can contribute to tissue injury. An *in vitro* recirculation of whole blood in an

extracorporeal bypass circuit can be used to stimulate platelet and leukocyte changes and complement activation induced by CPB (Rinder *et al.* (1995) *J. Clin. Invest.* 96:1564). In such a model, addition of a MTSP-1 polypeptide or control buffer, in varying doses, can be added to a transfer pack already containing blood from a healthy donor and porcine heparin, just prior to addition of the blood to the extracorporeal circuit. Blood samples can be drawn at 5, 15, 30, 45, 60, 75, and 90 minutes after recirculation and assayed for complement studies such as for example hemolytic assays and/or complement activation assays to measure for C5a, C3a, and/or sC5b-9. A pretreatment sample of blood drawn before its addition to the extracorporeal circuit can be used as a control. Flow cytometry of blood samples can be performed to determine levels of adhesion molecules on populations of circulating leukocytes (*i.e.* neutrophils) in the blood such as for example CD11b and P-selectin levels.

d. Age-Related Macular Degeneration (AMD)

Modified MTSP-1 polypeptides described herein can be used to treat Age-Related Macular Degeneration (AMD). Age-Related Macular Degeneration (AMD) that can be treated with proteases include wet AMD, dry AMD and geographic atrophy. Numerous animal models of AMD are available that mimic many of the characteristics of the human disorder (Pennesi *et al.* (2012) *Mol. Aspects Med.* 33(4):487-509). Mutations in complement pathway genes were shown to increase or decrease susceptibility to AMD (Edwards *et al.* (2005) *Science* 308(5720):421-424; Hageman *et al.* (2005) *Proc. Nat. Acad. Sci* 102(20):7227-7232; Klein *et al.* (2005) *Science* 308(5720):385-389). For example, in complement factor H (CFH), which normally interacts with C3b, the single nucleotide polymorphism Y402H prevented binding of C3b with factor B, leading to inhibition of C3 formation. Y402H is associated with an increased risk of AMD in people and the mutation was previously identified in 43-59% of AMD patients (Haines *et al.* (2005) *Science* 308(5720):419-421; Thakkinstian *et al.* (2006) *Hum. Mol. Genet.* 15(18):2784-2790; Zarepari *et al.* (2005) *Am. J. Hum. Genet.* 77(1):149-153).

Genetically modified mice that lack the ability to make CFH develop characteristics of AMD, including retinal abnormalities, decreased visual acuity and complement deposition (Coffey *et al.* (2007) *Proc. Nat. Acad. Sci.* 104:16651-16656).

Mutations in complement proteins Factor B (Montes *et al.* (2009) *Proc. Nat. Acad. Sci.* 106(11):4366-4371), C2 (Gold *et al.* (2006) *Nat. Genet.* 38(4):458-462), and C3 (Maller *et al.* (2007) *Nat. Genet.* 39(10):1200-1201; Yates *et al.* (2007) *New Engl. J. Med.* 357(6):553-561) are associated with increased or decreased risk of developing
5 AMD based on their impact on expression and/or activity of the various complement proteins (Reynolds *et al.* (2009) *Invest. Ophthalmol. Vis. Sci.* 50(12):5818-5827).

Modified MTSP-1 proteases, such as modified MTSP-1 proteases provided herein, wherein an activity, such as substrate specificity or selectivity, of the MTSP-1 protease for cleaving complement protein C3 is altered can be used as therapeutics.

10 The modified MTSP-1 polypeptides provided herein are administered, for example, by monthly or bi-monthly intravitreal injection, and the course and progression of symptoms is monitored compared to control animals or subjects. The levels of complement components that can exacerbate the disease also can be measured by assaying serum complement activity in a hemolytic assay and by assaying for the
15 deposition of complement components, such as for example C1, C3 and C9.

Complement activation plays a role in disease progress in Age-Related Macular Degeneration (AMD) (see *e.g.*, Bradley *et al.*, (2011) *Eye* 25:683-693; Gemenetzi *et al.* (2016) *Eye* 30:1-14). Modified MTSP-1 polypeptides can be used to treat AMD. For example, MTSP-1 polypeptides or a pharmaceutical composition
20 containing MTSP-1 polypeptides, such as the modified MTSP-1 polypeptides described herein, can be injected intravitreally or periocularly. Modified MTSP-1 polypeptides can be dosed daily or weekly or less frequently, such as for example, monthly or less frequently, such as bi-monthly. For AMD, modified MTSP-1 polypeptides that are further "modified" for extended duration in the eye (*e.g.*, fusion
25 proteins, PEGylation, etc.) monthly dosing can be used. Also, depending upon the particular modification, bi-monthly dosing and tri-monthly (every 3 months) also are contemplated. The modified MTSP-1 polypeptides can be modified, such as by PEGylation, to reduce potential immunogenicity and/or to increase serum half-life. For AMD, modified MTSP-1 polypeptides that are not further modified for extended
30 duration in the eye (*e.g.*, fusion proteins, PEGylated proteins) monthly or bi-monthly administration is contemplated. If modified, such as by PEGylation, dosing can be effected every 3 months or more.

e. Organ Transplant

Delayed Graft Function

Modified MTSP-1 polypeptides described herein can be used to treat Delayed Graft Function (DGF), including DGF, such as, for example, DGF as a result of Ischemia-Reperfusion Injury in kidney transplant recipients. MTSP-1 polypeptides also can be used in the treatment of the inflammatory response associated with organ transplant that can contribute to tissue injury. Generally, a MTSP-1 polypeptide can be administered prior to, concomitantly with, or subsequent to a treatment or event that induces a complement-mediated ischemia reperfusion injury. In one example, a MTSP-1 polypeptide can be administered to a subject prior to the treatment of a subject by a complement-mediated, ischemic-injury inducing event, such as for example kidney transplant or kidney allograft.

Effects of a MTSP-1 polypeptide on treatment of delayed graft function, for example delayed graft function as a result of ischemia-reperfusion injury, can be assessed in animal models of the injury, which mimic characteristics displayed in human kidney allografts or transplants.

The presence of early biomarkers of early graft dysfunction leading to DGF, including biomarkers for tubular epithelial cell injury can indicate the need for therapeutics. Biomarkers of DGF (*i.e.*, serum creatine) have been identified (Malyszko *et al.* (2015) *Nature Scientific Reports* 5:11684; Wanga *et al.* (2015) *PLoS One* 10(9):e0136276). Early detection of biomarkers for DGF and therapeutic intervention, such as, for example, therapeutic treatment with a modified MTSP-1 polypeptide, can improve clinical outcomes.

Complement activation modulates disease progress in disorders such as delayed graft function after organ transplant, for example kidney transplant (Yu *et al.* (2016) *Am J of Transplantation* 16(9):2589-2597). Modified MTSP-1 polypeptides can be used to treat DGF. For example, MTSP-1 polypeptides can be administered for systemic delivery or can be injected directly into the graft or the surrounding tissues. Modified MTSP-1 polypeptides can be administered prior to, during or after transplant. Modified MTSP-1 polypeptides can be dosed daily or weekly or less frequently, such as for example, monthly or less frequently, such as bi-monthly. In some instances a single systemic dose of the modified MTSP-1 polypeptide is

administered. Multiple infusions of the modified MTSP-1 polypeptide over several hours are also considered. Modified MTSP-1 polypeptides can be delivered chronically, if needed, for example, the modified MTSP-1 polypeptides, such as the modified MTSP-1 polypeptides described herein, can be delivered on a daily basis or on another schedule to maintain an effective amount in the allograft recipient. Modified MTSP-1 polypeptides can be used to prolong allograft survival in a recipient, in particular, chronic survival of the allograft. PEGylated MTSP-1 polypeptides can be used to reduce immunogenicity.

3. Combination Therapies

MTSP-1 polypeptides provided herein can be used in combination with other existing drugs and therapeutic agents to treat diseases and conditions. Such treatments can be performed in conjunction with other anti-inflammatory drugs and/or therapeutic agents. Examples of anti-inflammatory drugs and agents useful for combination therapies include non-steroidal anti-inflammatory drugs (NSAIDs) including salicylates, such as aspirin, traditional NSAIDs such as ibuprofen, naproxen, ketoprofen, nabumetone, piroxicam, diclofenac, or indomethacin, and Cox-2 selective inhibitors such as celecoxib (sold under the trademark Celebrex[®]) or Rotecoxin (sold under the trademark Vioxx[®]). Other compounds useful in combination therapies include antimetabolites such as methotrexate and leflunomide, corticosteroids or other steroids such as cortisone, dexamethasone, or prednisone, analgesics such as acetaminophen, aminosaliclates such as mesalamine, and cytotoxic agents such as azathioprine (sold under the trademark Imuran[®]), cyclophosphamide (sold under the trademark Cytosan[®]), and cyclosporine A. Additional agents that can be used in combination therapies include biological response modifiers. Biological response modifiers can include pro-inflammatory cytokine inhibitors including inhibitors of TNF-alpha such as etanercept (sold under the trademark Enbrel[®]), infliximab (sold under the trademark Remicade[®]), or adalimumab (sold under the trademark Humira[®]), and inhibitors of IL-1 such as anakinra (sold under the trademark Kineret[®]). Biological response modifiers also can include anti-inflammatory cytokines such as IL-10, B cell targeting agents such as anti-CD20 antibodies (sold under the trademark Rituximab[®]), compounds targeting T antigens, adhesion molecule blockers, chemokines receptor antagonists, kinase

inhibitors such as inhibitors to mitogen-activated protein (MAP) Kinase c-Jun N-terminal Kinase (JNK), or nuclear factor (NF) κ B, and peroxisome proliferator-activated receptor-gamma (PPAR- γ) ligands. Additional agents that can be used in combination therapies include immunosuppressants. Immunosuppressants can include
5 tacrolimus or FK-506; mycophenolic acid; calcineurin inhibitors (CNIs); CsA; sirolimus or other agents known to suppress the immune system.

MTSP-1 polypeptides provided herein also can be used in combination with agents that are administered to treat cardiovascular disease and/or administered during procedures to treat cardiovascular disease such as for example those described herein
10 that contribute to inflammatory conditions associated with complement-mediated ischemia-reperfusion injury. For example, MTSP-1 polypeptides provided can be administered in combination with anti-coagulants. Examples of exemplary anti-coagulants include, but are not limited to, heparin, warfarin, acenocoumarol, phenindione, EDTA, citrate, oxalate, and direct thrombin inhibitors such as
15 argatroban, lepirudin, bivalirudin, and ximelagatran.

MTSP-1 polypeptides provided herein also can be used in combination with agents that are administered to treat DGF. MTSP-1 polypeptides provided herein can, for example, be administered in combination with an immunosuppressive agent. Such combination is useful in prolonging allograft survival in a recipient, in particular,
20 chronic survival of the allograft. In preferred embodiments, the combination is formulated and prepared such that it is suitable for chronic administration to the recipient of the allograft, for example, stable formulations are employed. In certain embodiments, the combination is formulated and prepared such that it is suitable for concurrent administration of the modified MTSP-1 polypeptides and the
25 immunosuppressive drug to the recipient of the allograft. In certain embodiments, the combination is formulated and prepared such that it is suitable for sequential (in either order) administration of the modified MTSP-1 polypeptides and the immunosuppressive drug to the recipient of the allograft.

MTSP-1 polypeptides provided herein also can be used in combination with
30 agents that are administered to treat macular degeneration. For example, modified MTSP-1 poly peptides can be administered with any one or more of ranibizumab (sold under the trade name LucentisTM); bevacizumab (sold under the trade name

Avastin™); pegaptanib sodium (sold under the trade name Macugen™); aflibercept (sold under the trade name Eylea™); and verteporfin (sold under the trade name Visudyne™). MTSP-1 polypeptides provided herein also can be used in combination with an implantable telescope, laser treatment or laser photocoagulation, surgery, and/or photodynamic therapy, alone or in combination with the therapeutic verteporfin, to treat macular degeneration.

Additional agents, such as other complement inhibitors, can be used as anti-inflammatory drugs in combination therapy with modified MTSP-1 polypeptides as described herein. Examples of such other complement inhibitors include cobra venom factor (CVF), polyanionic molecules such as heparin, dextran sulphate, polyvinyl sulphate, polylysine, or suramin, natural molecules such as K-76COOH, Rosmarinic acid, or extract of the Chinese medicinal herb Ephedra, synthetic molecules such as afamastat mesilate (FUT-175), a synthetic inhibitor of C1s (C1s-INH-248), or an inhibitor against C1s and fD (BCX-1470), peptide inhibitors such as compstatin, antibody inhibitors of complement such as anti-C5 (N19-8), a humanized anti-C5 (h5G1.1), anti-C6, or anti-C8 antibodies, and soluble forms of membrane complement regulators such as soluble CR1 (sCR1), soluble DAF (sDAF), soluble MCP (sMCP), or soluble CD59 (sCD59) (Morgan *et al.*, (2003) *Mol Immunol.* 40:159).

Pharmaceutical compositions containing a MTSP-1 polypeptides described herein can be used to treat any one or more inflammatory diseases or conditions mediated by complement activation. Also provided are combinations of a MTSP-1 polypeptides and another treatment or compound for treatment of an inflammatory disease or condition. The MTSP-1 polypeptides and the anti-inflammatory agent can be packaged as separate compositions for administration together or sequentially or intermittently. Alternatively, they can be provided as a single composition for administration or as two compositions for administration as a single composition. The combinations can be packaged as kits, optionally with additional reagents, instructions for use, vials and other containers, syringes and other items for use of the modified MTSP-1 polypeptides.

I. EXAMPLES

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

Example 1

5 Cloning and Expression of Modified MTSP-1 Polypeptides and Screening for Modified MTSP-1 polypeptides that Cleave C3 in a Target Site

A. Cloning and Mutagenesis of MTSP-1

A nucleic acid encoding amino acids 615-855 with the C122S replacement of the human MTSP-1 polypeptide set forth in SEQ ID NO: 1 was prepared. The
10 construct included the pro-region, activation sequence, and protease domain, and contained residues 598 to the C-terminus of the sequence published by Takeuchi *et al.* (1999) *Proc. Natl. Acad. Sci. U.S.A.* 96:11054 and SEQ ID NO:1 (*i.e.*, corresponding to residues 598 to 855 of the sequence of amino acids set forth in SEQ ID NO:1).

Modified MTSP-1 polypeptides were generated by Quikchange site directed
15 mutagenesis (Stratagene) according to the manufacturer's instructions with specifically designed oligonucleotides that served as primers to incorporate designed mutations into the newly synthesized DNA. Briefly, a PCR sample reaction was set up containing the wild type MTSP-1 as a template and oligonucleotide primers designed to contain the desired mutation(s). Following PCR, each reaction product
20 was digested with DpnI to remove dam methylated parental strands of DNA. The DNA was then transformed into *E. coli* XL-1 Blue Supercompetent cells (Stratagene) and plated on selective agar containing 50 µg/ml carbenicillin. Plasmid DNA was isolated from selected clones, and sequenced to verify incorporation of mutation(s) at the desired location(s) within the MTSP-1 gene and the absence of any additional,
25 undesired mutations.

B. Preparation of MTSP-1 Polypeptides

1. Transformation

The protease domain of the wild-type and modified MTSP-1 polypeptides (both containing the C122S replacement) as detailed in Section A, above, were cloned
30 into the pQE-80 expression vector (Qiagen) and the resulting constructs transformed into BL21 Gold (DE3) *E. coli* cells (Agilent Technologies, Catalog number: 230132). Approximately 50 µL of chemically competent BL21 Gold (DE3) cells were

transformed with the appropriate plasmid DNA (typically approximately 5 ng of purified plasmid DNA or 5-10 μ L of a ligation reaction mixture). Cells and DNA were incubated on ice for 30 minutes, heat shocked at 42 °C for 45 sec, and then incubated on ice for 2 minutes. 450 μ L of room temperature Terrific Broth (TB media) (VWR International, Catalog number: 100219-866) were added, and the cells were grown in the TB media for 1 hour with shaking at 240 rpm at 37 °C. 20 μ L of solution containing the transformed cells were spread on a 2x YT medium + 100 μ g/mL carbenicillin plate from Teknova (Catalog number: Y4420) and incubated overnight at 37 °C. Isolated colonies were then selected and used for plasmid preparations. The resulting plasmids were subjected to DNA sequencing to confirm the presence of the coding sequence for the desired MTSP-1 polypeptide.

2. Expression of MTSP-1 Polypeptides

Five hundred μ L of an overnight culture of cells that had been transformed with a pQE-80 expression plasmid containing the coding sequence for the desired MTSP-1 polypeptide were added to 100 mL of Terrific Broth/Carbenicillin₁₀₀ containing 2.1 mL of Solution 1, 5.4 mL of Solution 2, and 107 μ L of Solution 3 from Overnight ExpressTM Autoinduction System 1 in a 500 mL Erlenmeyer flask. The flask was placed into an Infors Multitron Shaker set at 210 rpm. The culture was grown (with shaking) overnight at 37 °C. The following morning, 20 μ L of 1M Isopropyl β -D-1-thiogalactopyranoside (IPTG) was added to the culture to induce expression of the MTSP-1 polypeptide, and the culture was grown at 37 °C with shaking for an additional 2 hours. This “induced culture” was collected in a 250 mL conical centrifuge bottle and spun at 3600 rpm for 10 min at 4 °C in an AllegraTM 6R centrifuge with a GH-3.8/GH-3.8A rotor. The resulting cell pellet was either stored at -20 °C or further processed immediately as described below.

3. Isolation of MTSP-1 Polypeptide Inclusion Bodies

The bacterial cell pellet from the 100 mL culture was resuspended in 60 mL BugBuster® extraction reagent (Merck Millipore, NC9591474) containing 60 μ L rLysozymeTM (Sigma, Catalog number: L6876) by vortexing followed by shaking at 240 rpm for 1 hr at 37 °C to facilitate lysis of the bacteria. After bacterial lysis, insoluble material was pelleted by centrifugation at 3,600 rpm for 10 minutes at 4 °C, and the supernatant was decanted. The resulting pellet was resuspended by

homogenizing in 100 mL of 50 mM Tris pH 8.0 using a Power Gen 500 homogenizer (Fisher Scientific, 14-261-04P) with a 20 x 195 mm generator probe using 2 x 5 second pulses repeated until the pellet was well dispersed. The resuspended material was centrifuged at 3,600 rpm for 10 minutes at 4 °C, supernatant decanted, and the
5 pellet was allowed to air dry for 10 to 15 minutes. The pellet of inclusion bodies (IB) was weighed and stored at -20 °C until use.

4. Resuspension and Unfolding of Inclusion Bodies Containing MTSP-1 Polypeptides

The insoluble MTSP-1 polypeptides were isolated from inclusion bodies and
10 denatured in the presence of reducing agent. 4-5 grams of the IB pellet were resuspended in 25 mL of 50mM Tris, pH 8.0 by homogenization to form the IB solution. 75 mL of unfolding buffer (6M GuHCl, 50 mM Tris pH 8.0, (Teknova, Catalog number: G0380)) was added to the IB solution. The resulting IB solution was agitated at 240 rpm at 37 °C for at least 1 hour, or until the inclusion bodies were fully
15 dissolved.

5. Refolding of MTSP-1 Polypeptides

Five ml of the resuspended, denatured MTSP polypeptide solution described above was dripped slowly into ≥ 100 ml of Refolding Buffer (1.5 M Arginine, 50 mM Tris pH 7.5, 150 mM NaCl) at a dilution of 1:20 or greater (or approximately ≤ 100
20 μg protein/ml refolding buffer), with stirring. The protein solution in Refolding Buffer was incubated on a shaker at 150 rpm for 24 hours at room temperature to allow folding to take place.

The resulting protein solution was transferred to 12,000-14,000 Dalton molecular weight cutoff (MWCO) Spectra/Por® regenerated cellulose dialysis tubing
25 (VWR) and dialyzed in 180 L of 25 mM Tris, pH 8.0 for at least 4 hours. The following day, the samples were transferred to a new tank of 180 L of 25 mM Tris, pH 8.0 and allowed to dialyze overnight. The following day, the samples were transferred to a third tank of 180 L of 25 mM Tris, pH 8.0 and dialyzed for at least 18 hours. Samples were dialyzed at least overnight, and for up to multiple days. Samples
30 dialyzed for one day were incubated at room temperature and samples dialyzed for more than one day were incubated at 4 °C. The ratio of total dialysis buffer volume to total sample volume was at least 100. Following dialysis, the protease samples were

removed from the dialysis tubing and filtered using a 500 mL, 0.22 μ m flask (Millipore), and the conductivity of the solution was measured. The conductivity of the solution was adjusted to prevent non-specific binding to the Benzamidine column during the activation step described below. The NaCl concentration was adjusted to approximately 0.5 M NaCl (*e.g.*, 390 mL of 5 M NaCl was added to 3.9 L of dialyzed protein). The conductivity of the solution should be approximately 1.3 ms (/cm).

6. Activation of MTSP-1 Polypeptides

After filtration of the solution containing refolded MTSP-1 polypeptide, the NaCl concentration was adjusted to approximately 0.5 M by addition of 5M NaCl. Twenty mL of immobilized trypsin agarose beads were packed into an Econo-Pak disposable column (Bio-Rad; Catalog number 7321010) and the column was equilibrated with 200 mL (*i.e.*, 10 column volumes) of Chromatography Solution Buffer A (25mM Tris pH 8.0, 0.5M NaCl). The refolded MTSP-1 polypeptide solution (see above) was loaded on the column, and the flow through containing the activated MTSP-1 polypeptide was collected. The flow through fractions that contained protein were combined and dialyzed overnight in 25 mM Tris buffer (pH = 8.0) and buffer exchanged twice in 150 liters. The conductivity of the resulting, activated MTSP-1 polypeptide solution was confirmed to be less than 2 ms/cm, or adjusted appropriately with 25 mM Tris, pH = 8.0.

7. Purification of MTSP-1 Polypeptides

The MTSP-1 polypeptides can be and have been purified according to the following steps:

1. Measure the conductivity of the activated sample using a SevenEasy Conductivity Meter. If the measurement is < 3 ms/cm, then proceed to step 2 below. If the measurement is > 3 ms/cm, dilute sample with Chromatography Solution Buffer A (25mM Tris pH 8.0, 0.5M NaCl) until conductivity reaches < 3 ms/cm.
2. Using an AKTAPURIFIER, load sample onto a 5 mL HiTrap Q HP cation exchange column pre-equilibrated with 5 column volumes (CV) of Chromatography Solution Buffer A at a flow rate of 8 mL/min.
3. Wash the column with 5 column volumes of Chromatography Solution Buffer A.

4. Elute with 15 column volumes of 0-50% NaCl gradient using Chromatography Solutions Buffer A/Buffer B at 5 mL/min. Collect 2 ml fractions.
5. The column is washed with 3 CV of Chromatography Solution Buffer B, and then re-equilibrated with 5 CV of Chromatography Solution Buffer A prior to loading of the next sample.
6. Active MTSP-1 is located by activity assay, where 5 μ l of fraction is mixed with 50 μ l of Assay Buffer containing 200 μ M of an appropriate quenched fluorescence substrate (add QHAR QF substrate).
7. Read activity on a Molecular Devices M5 plate reader at 30 °C. Set Excitation at 490 nm and Emission at 520 nm.
8. Concentrate the four most active fractions using a 15 mL Amicon Ultra 10K Centrifugal Filter.
9. Measure concentration by A_{280} using the Nanodrop Spectrophotometer.
10. Continue concentrating until achieving an approximate final concentration of 200 μ M.
11. To assess quality of purified product, load 2 μ g/lane of sample in 2X Sample Buffer containing 2X NuPAGE Sample Reducing Agent on a 4-12% NuPAGE Novex Bis-Tris gel. Run the gel in 1X MES Running Buffer at 200V for 30 min. Visualize the gel by staining with Coomassie Blue followed by destaining.
12. Snap freeze the sample in liquid nitrogen and store at -80 °C.

8. Endotoxin Removal from Purified MTSP-1 Polypeptides for use in *in vivo* Models

- 25 Removal of high molecular weight Endotoxin was achieved by passing the sample through a 15 ml Amicon Ultra-15 Centrifugal Filter Unit 100K membrane (Fisher Scientific). The sample was filtered by spinning at 4000 RPM for 20 minutes. If sample had not passed through the filter after 20 minutes, the centrifugation step was repeated. Then, the sample was transferred to a clean falcon tube. To ensure
- 30 complete removal of small molecular weight Endotoxin, the sample was passed over a 2 ml Cellufine ET clean S gravity column (Fisher Scientific). At least 24 hours prior to addition of the sample, the 2 ml Cellufine ET clean S column was prepared. 4 mL

of Cellufine ET clean S slurry and 10 mL Endo-Free 20% Ethanol solution (Fisher Scientific) was added to the Econo-Pac Chromatography Gravity Column. The 20% EtOH solution was passed through the column, followed by 25 mL of 80% EtOH, 0.2N NaOH. The bottom of the gravity column was capped and the column was filled
5 with 80% EtOH, 0.2N NaOH, covered and incubated at room temp for at least 16 hours. After at least 16 hours, the 80% EtOH, 0.2N NaOH was allowed to pass through the column. The column was rinsed with 25 mL endotoxin-free water and the water was allowed to pass through the column. Next, the column was equilibrated with 2 x 20 mL sterile endo-free phosphate buffered saline (PBS). The sample was
10 then added to the column and the eluted sample was collected. The column was washed with 10 mL endo-free PBS to ensure that the sample had completely passed through the column.

Protein concentration, A_{280} , was measured using a NanoDrop® Spectrophotometer (NanoDrop) and use of a theoretical extinction coefficient of
15 $2.012\text{mg}/A_{280}$. If necessary, active protein was concentrated using 15 mL Amicon Ultra-15 10K membrane Centrifugal Filter Units (Fischer Scientific) to approximately 2.5 mg/ml in citrate-buffered saline (20 mM Sodium Citrate pH 5.0, 50 mM NaCl). To assess the quality of the purified product, 2 μg of sample in 1x NuPAGE LDS Sample buffer (Invitrogen, Corp.) containing 2x NuPAGE sample reducing agent
20 (Invitrogen) was loaded on a 12-well 4-12% NuPAGE Novex 4-12% Bis-Tris Gel (Invitrogen), and run in 1X NuPAGE MES SDS Running Buffer (Invitrogen) at 200 V for 30 minutes. The cell was stained with Coomassie Blue followed by destaining to visualize protein bands. Protein was snap-frozen in liquid nitrogen and stored at -80°C .

25 **C. Selection and Identification of Modified MTSP-1 Polypeptides That Cleave C3 to Inactivate it**

Modified MTSP-1 polypeptides were identified by screening a library of modified MTSP-1 polypeptides against a modified serpin ATIII as described in detail in U.S. Patent No. 8,211,428 (see, also U.S. Publication No. US-2014-0242062-A1,
30 now U.S. Patent No. 9,795,655). An inhibitory serpin, or fragment thereof, capable of forming a covalent acyl enzyme intermediate between the serpin and protease is used for screening. Generally, the serpin that is used is one that targets and regulates the

wild type protease *in vivo*. Any serpin, however, that reacts with and irreversibly inhibits the target protease can be used as a “bait” for these selection experiments.

In the assay, a serpin modified by replacement of its reactive site loop (RSL) to include a target sequence (*i.e.*, the target site in C3 for cleavage to inactive C3)

- 5 captures modified proteases that cleave the target site to form stable complexes. The captured modified protease is then isolated/identified. For the MTSP-1 polypeptides, the “bait” serpin was ATIII that was modified by replacing the residues indicated below with QHARASHLG (residues 737-745 of C3, SEQ ID NO: 9), which is the targeted site for inactivation of human C3.

- 10 ATIII "bait" (SEQ ID NO: 692) with inserted sequence QHARASHLG corresponding to the targeted site of C3 (residues 737-745 of SEQ ID NO:9):

	10	20	30	40	50	60
	HGSPVDICTA	KPRDIPMNP	CIYRSPEKKA	TEDEGSEQKI	PEATNRRVWE	LSKANSRFAT
	70	80	90	100	110	120
15	TFYQHLADSK	NDNDNIFLSP	LSISTAFAMT	KLGACNDTLQ	QLMEVFKFDT	ISEKTSQDQH
	130	140	150	160	170	180
	FFFAKLNCRL	YRKANKSSKL	VSANRLFGDK	SLTFNETYQD	ISELVYGAKL	QPLDFKENAE
	190	200	210	220	230	240
20	QSRAAINKWV	SNKTEGRITD	VIPSEAINEL	TVLVLVNTIY	FKGLWKSDFS	PENTRKELFY
	250	260	270	280	290	300
	KADGESCSAS	MMYQEGKFRY	RRVAEGTQVL	ELPFKGDDIT	MVLILPKPEK	SLAKVEKELT
	310	320	330	340	350	360
	PEVLQEWLDE	LEEMMLVVHM	PRFRIEDGFS	LKEQLQDMGL	VDLFSPEKSK	LPGIVAEGRD
	370	380	390	400	410	420
25	DLYVSDAFHK	AFLEVNEEGS	EAAASTAVVQ	QHARASHLGRV	TFKANRPFLV	FIREVPLNTI
	430	440				
	IFMGRVANPC	VKGGGSDYKD	DDDK			

The mutations in the ATIII with reference to the position in SEQ ID NO: 692 are summarized as follows:

RCL	QHARASHLG	390	398
C-Terminus	GGGSDYKDDDDK	433	444
Mutation	I390Q	390	390
Mutation	A391H	391	391
Mutation	G392A	392	392
Mutation	S394A	394	394
Mutation	L395S	395	395
Mutation	N396H	396	396
Mutation	P397L	397	397
Mutation	N398G	398	398

Flag Tag DYKDDDDK 437 444

In order to perform the selection for protease variants which are trapped by the QHAR-ASHLG modified ATIII bait, a library of MTSP variants was displayed on the surface of M13 bacteriophage, fused to the C-terminus of phage coat protein P3. Several MTSP libraries were designed by substituting the natural codons with NNK codons at positions in MTSP hypothesized to be important for substrate recognition and cleavage based on molecular modeling or were “second sphere” positions that contact mutated residues that were previously selected and proved to be advantageous. These positions corresponded to both prime side or non-prime side sites on MTSP, including positions 40, 41, 60b, 60g, 96-99 (plus insertions of 1 and 2 amino acids within the 96-99 region), 151, 175, 192, 217, and 224. To ensure sufficient representation for each variant in the phage library, the size of each constructed library (measured by CFUs generated of transformed library DNA) was significantly greater than the calculated diversity for all libraries that contained 5 or 6 randomized positions and comparable to the calculated diversity for libraries that contained 7 randomized positions. After construction of the MTSP phage libraries, 96 colonies from each library were sequenced to confirm mutation frequency and distribution and to assess the overall library quality. High quality libraries (*i.e.*, those containing the expected frequency of mutations, no contamination, etc.) were then subjected to selection by incubating with the multiple concentrations of the biotinylated bait serpin for various lengths of time. The trapped biotinylated-MTSP-phage complex was captured on avidin coated plates, washed with 6M Guanidine hydrochloride to remove high affinity, non-covalent protease-serpin complexes, and then eluted with DTT. On some occasions a counterselection, using alpha 2-macroglobulin or naturally occurring serpins, such as ATIII was performed. Frequently, the selection and counterselection were performed simultaneously by incubating the library with both target serpin and counterselection serpin(s) in the same reaction. Typically, the counterselection serpin(s) would be present in molar excess over the selection serpin. Several rounds of selection were performed, then individually outgrown colonies were screened by enzyme assay for performance against a peptide corresponding to the target substrate. Colonies producing variants with high activity for cleavage of the target sequence were further characterized by

DNA sequencing of their phagemid DNA to identify the identity of the mutations in the MTSP-1 coding sequence.

D. Modified MTSP-1 Polypeptides

Table 14 below sets forth modifications and the sequences of exemplary protease domains of modified MTSP-1 polypeptides that were generated and selected to inactivate C3, with the mutations indicated using numbering relative to the mature MTSP-1 polypeptide set forth in SEQ ID NO:1 (mature MTSP-1 numbering), and also chymotrypsin numbering (additional modifications are set forth in Table 15). While the SEQ ID NOs. reference protease domains, it is understood that the mutations can be included in mature modified MTSP-1 polypeptides, catalytically active portions thereof that contain the referenced modifications, and active forms and activated two chain forms.

The C122S replacement, or other conserved replacement for S, is included to eliminate dimerization of the protease and reduce the potential for formation of “inappropriate” disulfide bonds during the folding process; while advantageous, it is an optional mutation.

Table 14. Modified MTSP-1 Polypeptides		
Mature MTSP-1 numbering	Chymotrypsin numbering	SEQ ID NO.*
I640R/F706T/InsE/T707G/F708L/C731S/G759N/Q783L/Q802E	I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E	21
Q637H/I640A/D661V/F664R/Y666W/F706T/InsE/T707G/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	22
Q637H/I640A/D661T/F664K/Y666W/F706T/InsE/T707G/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	23
Q637H/I640S/D661T/F664S/Y666W/F706D/InsV/T707P/F708L/C731S/G759H/Q783L/Q802E	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	24
Q637H/I640S/D661T/F664S/Y666W/F706D/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	25
Q637H/I640A/D661T/F664K/Y666W/F706T/InsE/T707G/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	26
Q637H/I640S/D661T/F664S/Y666W/F706D/InsV/T707P/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192D	27
Q637H/I640A/D661V/F664R/Y666W/F706T/InsE/T707G/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	28

Table 14. Modified MTSP-1 Polypeptides		
Mature MTSP-1 numbering	Chymotrypsin numbering	SEQ ID NO.*
Q637H/I640A/D661V/F664R/Y666W/D705I/F706Y/InsN/T707G/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D	29
Q637H/I640S/D661T/F664S/Y666W/D705K/F706D/InsA/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D	30
Q637H/I640A/D661V/F664R/Y666W/D705P/F706W/InsN/T707G/F708L/C731S/G759N/Q783L/Q802E	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/F97W/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192E	31
Q637H/I640A/D661V/F664R/Y666W/D705I/F706N/T707G/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	32
Q637H/I640S/D661T/F664S/Y666W/D705Y/F706E/InsV/T707G/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97E/ins97aV/T98G/F99L/C122S/G151H/Q175L/Q192D	33
Q637H/I640S/D661T/F664S/Y666W/D705L/F706D/InsG/T707N/F708L/C731S/G759H/Q783L/Q802E	Q38H/I41S/D60bT/F60eS/Y60gW/D96L/F97D/ins97aG/T98N/F99L/C122S/G151H/Q175L/Q192E	34
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35
Q637H/I640S/D661T/F664S/Y666W/D705V/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	36
Q637H/I640S/D661T/F664S/Y666W/D705K/F706D/InsA/T707P/F708L/C731S/G759N/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D	37
Q637H/I640S/D661T/F664S/Y666W/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	38
Q637H/I640S/D661T/F664S/Y666W/D705K/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	39
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L	40
I640E/F708L/C731S/G759N/Q802T	I41E/F99L/C122S/G151N/Q192T	41
I640D/C731S/G759N/Q802T	I41D/C122S/G151N/Q192T	42
I640S/F708L/C731S/G759N/Q802V	I41S/F99L/C122S/G151N/Q192V	43
I640E/F708L/C731S/G759N/Q802T	I41E/F99L/C122S/G151N/Q192T	44
I640D/Y658F/D705E/F708L/C731S/G759N/Q802T	I41D/Y59F/D96E/F99L/C122S/G151N/Q192T	45
I640D/Y658F/C731S/G759N/Q802T	I41D/Y59F/C122S/G151N/Q192T	46
I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	47
Q637H/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	48
Q637H/I640S/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	49

Table 14. Modified MTSP-1 Polypeptides		
Mature MTSP-1 numbering	Chymotrypsin numbering	SEQ ID NO.*
Q637H/I640S/D661T/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	50
Q637H/I640S/D661T/F664S/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	51
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/T707P/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D	52
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/F708L/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/F99L/C122S/G151H/Q175L/Q192D	53
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/C731S/G759H/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/C122S/G151H/Q175L/Q192D	54
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	55
Q637H/I640S/D661T/F664S/Y666W/D705K/F706G/InsV/T707P/F708L/C731S/G759H/Q802D	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q192D	56
Q637H/I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802D	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D	57
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	58
Q637H/I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	59
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802D	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D	63
Q637H/I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	64
Q637H/I640S/D661Y/D705K/F706G/InsV/T707P/F708L/C731S/Q802D/D828V	Q38H/I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V	65
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802G/D828V	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	66
I640S/D661Y/D705K/F706G/InsV/T707P/F708L/C731S/Q802D/D828V	I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V	67
I640S/D705M/F706G/InsV/T707P/F708L/C731S/Q802G/D828V	I41S/D96M/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	68
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802V/D828I	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192V/D217I	69
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802H	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192H	70
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802N/D828V	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192N/D217V	71
I640S/D661Y/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802D	I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	72
Q637H/I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q802G/D828V	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	73
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802V	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192V	74

Table 14. Modified MTSP-1 Polypeptides		
Mature MTSP-1 numbering	Chymotrypsin numbering	SEQ ID NO.*
I640S/P648S/D705K/F706G/InsV/T707P/F708L/C731S/Q802G/D828V	I41S/P49S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V	75
I640S/D705K/F706G/InsV/T707P/F708L/C731S/Q783L/Q802N/D828V	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192N/D217V	76
I640T/F706W/F708L/C731S/G759N/Q783M/Q802G/D828L	I41T/F97W/F99L/C122S/G151N/Q175M/Q192G/D217L	77
I640G/F706L/F708L/C731S/Q783A/Q802T/D828V	I41G/F97L/F99L/C122S/Q175A/Q192T/D217V	78
I640G/F706V/F708L/C731S/G759Q/Q783M/Q802A/D828L	I41G/F97V/F99L/C122S/G151Q/Q175M/Q192A/D217L	79
I640G/F706I/F708L/C731S/G759L/Q783M/Q802S/D828V	I41G/F97I/F99L/C122S/G151L/Q175M/Q192S/D217V	80
I640G/F706S/F708L/C731S/G759N/Q783L/Q802G/D828I	I41G/F97S/F99L/C122S/G151N/Q175L/Q192G/D217I	81

* SEQ ID of the protease domain containing the replacements

Example 2

In vitro Cleavage of Complement Protein C3

The activity of the modified MTSP-1 polypeptides was determined by cleavage of the substrate complement protein, human C3, by measuring the amount of intact human C3 remaining after incubation with various concentrations of the protease for 1 hour at 37 °C. In this assay, signal is generated in the presence of intact human C3, and is lost as the C3 is cleaved.

2 µM plasma purified human C3 (hC3; Complement Technologies; Tyler, TX) was incubated with the modified MTSP-1 polypeptides (0 – 250 nM) for 1 hour at 37 °C in buffer containing 50 mM Tris, pH 8.0, 50 mM NaCl, and 0.01% Tween-20. The activity of the modified MTSP-1 polypeptides was quenched by the addition of EGR-CMK (Haematologic Technologies, EGRCK-01) to a final concentration of 10 µM and the hC3/modified MTSP-1 polypeptide mixture was allowed to stand for 30 minutes at ambient temperature.

Residual levels of undigested human C3 were quantified using an Amplified Luminescent Proximity Homogeneous Assay Screen (AlphaScreen®; Perkin Elmer). α-mouse IgG-coated acceptor beads at 100 µg/mL (Perkin Elmer #6760606) were incubated with 5 nM mouse α -hC3a mAb (Abcam #ab11872-50) in 50 mM Tris, pH 8.0, 50 mM NaCl, 0.01% Tween-20 and 0.2% BSA to form the acceptor bead mixture. The acceptor bead mixture was shielded from light and placed on a rotating shaker for 30 – 60 minutes. The hC3/modified MTSP-1 polypeptide reaction mixtures

(prepared above) were diluted 1600-fold into 50 mM Tris, pH 8.0, 50 mM NaCl, 0.01% Tween-20, 0.2% BSA and 4 μ L aliquots were placed in duplicate wells of a 384-well Optiplate (Perkin Elmer #6007299). 8 μ L of a α -hC3 mAb/acceptor beads mixture was incubated with 8 μ L of 25 nM biotinylated goat α -hC3 pAb (prepared using EZ-Link Sulfo-NHS-LC-Biotin kit from Thermo Scientific #21327 from the unbiotinylated version from Complement Technologies #A213). The plate was then shielded from light and incubated for 30 minutes at ambient temperature. After this incubation, 4 μ L of 100 μ g/mL streptavidin-coated donor beads (Perkin Elmer #6760606) were added to each well and incubated for 60 minutes, shielded from light.

The alphascreen signal (Excitation = 680 nm, Emission = 570 nm) was then measured using an Envision 2104 Multilabel plate reader (Perkin Elmer). This signal (corresponding to the concentration of remaining hC3 ([hC3])) was plotted as a function of modified MTSP-1 polypeptide concentration ([Alterase]) and the data were fitted to the four parameter equation below to determine the concentration of modified MTSP-1 polypeptide (the 'alterase' concentration) required to cleave 50% of the available hC3 (EC_{50}), the Hill slope (Hill) as well as the maximum (Max) and minimum (Min) signals in the assay.

$$[hC3] = Min + \frac{Max - Min}{1 + \left(\frac{[Alterase]}{EC_{50}} \right)^{Hill}}$$

The cleavage of hC3 by modified MTSP-1 polypeptides with the sequence set forth in SEQ ID NO: 35 was measured independently a total of 46 times, using 9 different lots of the protease. The modified MTSP-1 polypeptide with the sequence set forth in SEQ ID NO: 35 cleaved complement protein C3 with a lower EC_{50} than the reference MTSP-1 polypeptide set forth in SEQ ID NO: 4, which has an EC_{50} =13.9 nM (n=235; SD=4.1). The average EC_{50} value for the modified MTSP-1 polypeptide with the sequence set forth in SEQ ID NO: 35 was determined to be 6.9 nM (n=46, SD=2.6). C3 cleavage reactions were performed 1-12 times for all other modified MTSP-1 polypeptides listed in Table 15.

Table 15 sets forth exemplary modifications, and the EC_{50} for polypeptides, as set forth in the Sequence Listing, that contain these modifications. It is understood

that the sequence listing sets forth the protease domain, but that these same mutations can be included in full-length modified MTSP-1, and various forms thereof, and catalytically active forms thereof. As set forth, all include the replacement of the free cysteine C122S; the replacement reduces aggregation, and can be optional.

5 **Table 15. hC3 Cleavage with Modified MTSP-1 Polypeptides**

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
4	C122S	13.9
23	Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	14.4
24	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	6.68
32	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	2.87
35	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D	6.86
36	Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	2.85
37	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D	5.92
38	Q38H/I41S/D60bT/F60eS/Y60gW/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	169
39	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	12
40	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L	1.45
42	I41D/C122S/G151N/Q192T	85.2
43	I41S/F99L/C122S/G151N/Q192V	34.4
44	I41E/F99L/C122S/G151N/Q192T	124
45	I41D/Y59F/D96E/F99L/C122S/G151N/Q192T	54.9
46	I41D/Y59F/C122S/G151N/Q192T	56.7
47	I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	17.1
48	Q38H/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	215
49	Q38H/I41S/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	13.1
50	Q38H/I41S/D60bT/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	8.64
51	Q38H/I41S/D60bT/F60eS/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	22.2
52	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D	7.88
53	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/F99L/C122S/G151H/Q175L/Q192D	9.83

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
54	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/C122S/G151H/Q175L/Q192D	18.3
55	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	5.25
56	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q192D	19.9
57	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D	108
58	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	68.6
59	Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	22
77	I41T/F97W/F99L/C122S/G151N/Q175M/Q192G/D217L	12.1
78	I41G/F97L/F99L/C122S/Q175A/Q192T/D217V	7.75
79	I41G/F97V/F99L/C122S/G151Q/Q175M/Q192A/D217L	9.74
80	I41G/F97I/F99L/C122S/G151L/Q175M/Q192S/D217V	2.84
81	I41G/F97S/F99L/C122S/G151N/Q175L/Q192G/D217I	6.84
154	F97E/F99L/C122S/D217I/K224N	6.33
155	C122S/G193A	44.7
156	C122S/G193E	119
157	D96_F97delinsWYY/T98P/F99L/C122S	22.6
158	F97D/F99L/C122S/Q192G	78.1
159	H40R/I41H/F97D/F99L/C122S/Q192G	35.4
160	C122S/G151N/G193A	85.7
161	H40R/I41H/C122S/G151N	59.6
162	H40R/I41H/F97D/C122S/G151N	110
163	H40R/I41H/F97E/C122S	51.7
164	F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E	259
165	H40R/I41H/Y60gH/F97D/F99L/C122S/G151N/Q175M/D217I/K224S	7.41
166	H40R/I41H/F97D/F99L/C122S/G151D/Q192G	1530
167	H40R/I41H/F97D/F99L/Q192G	24.1
168	H40R/I41H/Y60gH/F97D/F99L/C122S/G151N/Q175A/Q192H/D217I/K224R	19.8
169	H40R/I41H/Y60gF/F97D/F99L/C122S/Q192G/D217M/K224R	38
170	H40R/I41H/Y60gF/F97D/F99L/C122S/Q192G/D217R/K224A	25.9
171	H40R/I41H/F97D/F99L/C122S/Q175L/Q192G/D217K/K224A	14.1
172	H40R/I41H/F97D/F99L/C122S/Q175M/Q192G/D217V/K224Y	2.76
173	H40R/I41H/F97D/F99L/C122S/Q175K/Q192G/D217I/K224H	19.4
174	H40R/I41H/F97D/F99L/C122S/Q175M/Q192G/D217S	24.4
175	H40R/I41H/Y60gF/F97D/F99L/C122S/Q175M/Q192G/D217W/K224R	9.92
176	H40R/I41H/Y60gN/F97D/F99L/C122S/G151N/Q175K/Q192S/D217S/K224L	187
177	H40R/I41H/Y60gH/F97D/F99L/C122S/Q175M/Q192G/D217I/K224L	3.72
178	H40K/I41L/Y60gF/F97D/F99L/C122S/G151N/Q175R	237
179	H40R/I41H/Y60gL/F97D/F99L/C122S/G151N	54.9

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
180	H40K/I41M/Y60gG/F97D/F99L/C122S/G151N/Q175R/Q192R/D217V/K224S	509
181	H40K/I41M/Y60gF/F97D/F99L/C122S/G151N/Q175L/Q192D	589
182	H40R/I41H/F97D/C122S/G151N/Q175M/Q192A/D217S/K224R	470
183	H40R/I41H/Y60gH/F97D/F99L/C122S/Q175M/Q192G/D217I/K224R	7.94
184	H40R/I41H/F97D/F99L/C122S/G151D/Q175M/Q192G/D217V	70.8
185	H40R/I41H/F97D/F99L/C122S/G151N/Q175M/Q192A/D217N/K224R	563
186	H40R/I41H/F97D/F99L/C122S/G151N/Q175L/Q192A/D217N/K224R	540
187	H40K/I41M/F97D/F99L/C122S/G151N/Q175M/Q192D/D217N/K224R	9.74
188	H40K/I41M/F97D/F99L/C122S/G151N/Q175L/Q192A/D217N/K224R	1290
189	H40R/I41H/F97D/F99L/C122S/Q175M/Q192D/D217N/K224R	9990
190	H40R/I41H/F97D/F99L/C122S/Q175M/D217N/K224R	103
191	H40K/I41M/F97D/F99L/C122S/Q175M/Q192D/D217N/K224R	9.64
192	H40K/I41M/F97D/F99L/C122S/G151N/Q175M/Q192A/D217N/K224R	1230
193	H40K/I41M/F97D/F99L/C122S/Q175M/D217N/K224R	144
194	H40R/I41H/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E	5860
195	H40R/I41H/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G	46
196	H40R/I41H/F97E/ins97aE/T98G/F99L/C122S/Q175L/Q192G	82.4
197	H40R/I41H/F97D/F99L/C122S/G151N/Q192H	179
198	H40R/I41H/F97D/F99L/C122S/G151N/L153R	59.9
199	H40R/I41H/F97D/C122S/G151N/L153R/V202M	103
200	H40R/I41H/F97D/F99L/C122S/G151N/Q192H/P232S	262
201	H40R/I41H/F97D/ins97aE/T98G/F99L/C122S/Q175L/Q192G	39.7
202	H40R/I41H/F97D/C122S/G151N/L153R	126
203	H40K/I41M/F99L/C122S/T150A/G151R/Q192G	110
204	H40R/I41H/F97D/C122S/G133D/G151N	60.4
205	I41R/F99L/C122S/Q192G	53.8
206	H40R/I41H/F99L/C122S/G151K/Q192G	1520
207	I41R/ins97aE/F97T/T98G/F99L/C122S/G151E/Q175L/Q192E	126
208	K86R/K110R/C122S/K134R/K157R/K224R/K239R	17.3
209	H40R/I41H/K86R/F97D/K110R/C122S/K134R/G151N/K157R/K224R/K239R	304
210	K86R/F97T/ins97aE/T98G/F99L/K110R/C122S/K134R/K157R/Q175L/Q192E/K224R/K239R	253
211	H40R/I41H/F97D/F99L/C122S/Q175R/Q192G/D217H/K224S	45.2
212	H40R/I41H/F97D/F99L/C122S/Q192G/D217I/K224S	19.3
213	H40R/I41H/F97D/F99L/C122S/Q192G/D217K/K224A	23.4
214	H40R/I41H/F97D/F99L/C122S/Q175R/Q192G/D217E/K224R	31.2
215	H40R/I41H/F97D/C122S/Q175R/Q192G/D217I/K224Q	93.1
216	H40P/I41R/F99L/C122S/Q192G	62.4
217	H40P/I41R/F99L/C122S/G151K/Q192G	96.1
218	H40R/I41H/F99L/C122S/G151E/Q192G	829

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
219	I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175L/Q192E	163
220	I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175T/Q192E	743
221	I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175T/Q192D	1620
222	I41R/ins97aE/F97T/T98G/F99L/C122S/G151E/Q175T/Q192D	1770
223	H40P/I41R/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	442
224	H40P/I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175L/Q192E	212
225	I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192E	311
226	I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192D	622
227	I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175T/Q192E	1410
228	I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175T/Q192D	9990
229	I41R/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	523
230	H40P/I41R/F99L/C122S/G151E/Q192G	153
231	I41R/F97T/ins97aE/T98G/F99L/C122S/G151E/Q175T/Q192E	363
232	I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175S/Q192E	267
233	I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175I/Q192E	1030
234	H40R/I41H/Y60gF/F97D/F99L/C122S/Q175K/Q192G/D217R/K224Q	93.4
235	H40R/I41H/F97D/F99L/C122S/Q175L/Q192G/D217Q/K224R	14.9
236	H40R/I41H/F97D/F99L/C122S/G151N/Q192N/D217L/K224R	346
237	H40R/I41H/F97D/F99L/C122S/G151N/Q192H/D217K/K224A	137
238	ins97aV/F97D/T98P/F99L/C122S/Q192G	53.5
239	F97N/ins97aT/T98Y/F99N/C122S	184
240	F97M/ins97aD/T98D/F99L/C122S/Q192T	151
241	ins97aV/F97Q/T98P/F99L/C122S/Q175F/Q192D	248
242	ins97aD/F97T/T98S/F99L/C122S/Q192E/D217Y/K224R	5000
243	ins97aN/F97H/T98D/F99L/C122S/Q192E/D217Q/K224S	2750
244	F97Q/ins97aT/T98M/C122S/Q192E/D217R/K224L	2450
245	ins97aD/F97Q/T98G/F99L/C122S/Q175L/Q192E/D217F/K224S	5560
246	ins97aD/F97G/T98N/F99L/C122S/Q192E/D217Y/K224R	9870
247	ins97aE/F97Y/T98S/F99L/C122S/Q192T/D217Q/K224R	249
248	ins97aG/F97N/T98D/F99L/C122S/Q192E/D217H/K224A	2790
249	ins97aA/F97G/T98N/F99L/C122S/Q175M/Q192T/K224A	200
250	I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175S/Q192D	2080
251	I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175I/Q192D	8370
252	I41R/F97T/ins97aE/T98G/F99L/C122S/G151D/Q175I/Q192E	2070
253	I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175I/Q192D	1750
254	S90T/D96A/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	280
255	Y59F/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	341
256	ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E/Q209L	383
257	Y59F/D96V/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	293
258	D96V/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	258
259	I41R/ins97aE/F97T/T98G/F99L/C122S/G151S/Q175L/Q192E	274

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
260	E24K/ins97aE/F97T/T98G/F99L/C122S/A152S/Q175L/Q192D	291
261	ins97aE/F97T/T98G/F99L/C122S/L153Q/Q175L/Q192D	332
262	ins97aE/F97T/T98G/F99L/C122S/I136M/L155M/N170D/Q175L/Q192E	429
263	I41R/ins97aE/F97T/T98G/F99L/A112V/C122S/Q175L/Q192E	288
264	Y59F/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192D	289
265	Y59F/G60dS/R84H/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E/V212I	102
266	Y59F/ins97aE/F97T/T98G/F99L/C122S/L153Q/Q175L/Q192E	237
267	I41R/Y59F/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	288
268	I41R/Y59F/G60dS/R84H/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E/V212I	143
269	I41R/Y59F/ins97aE/F97T/T98G/F99L/C122S/L153Q/Q175L/Q192E	253
270	I41R/F97W/F99L/C122S/G151N/Q192G	97.3
271	F97D/ins97aV/T98P/F99L/C122S/G151N/Q192G	87
272	I41D/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	157
273	I41D/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192E	148
274	Q38E/H40R/I41H/F97D/F99L/C122S/Q192G	30.9
275	H40R/I41H/F97D/F99L/Q175R/Q192G/D217E/K224R	21.9
276	I41R/ins97aV/F97D/T98P/F99L/C122S/G151N/Q192G	232
277	ins97aV/F97D/T98P/F99L/C122S/Q175L/Q192E	158
278	I41R/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192E	187
279	Q38E/H40R/I41H/D60bE/F97D/F99L/C122S/Q192G	28.1
280	Q38E/H40R/I41H/D60bN/F97D/F99L/C122S/Q192G	39.5
281	Q38E/H40R/I41H/D60bK/F97D/F99L/C122S/Q175L/Q192G	15.3
282	Q38E/H40R/I41H/D60bN/F60eT/F97D/F99L/C122S/Q175L/Q192G	9.42
283	Q38R/I41S/D60bH/F60eV/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E	35.2
284	Q38G/H40R/I41H/D60bK/F97D/F99L/C122S/Q175L/Q192G	20.6
285	I41D/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192E/Q209L	103
286	Q38G/H40R/I41H/D60bN/F97D/F99L/C122S/Q175L/Q192G	0.867
287	Q38R/I41S/D60bH/F60eV/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192E	22.5
288	H40R/I41H/F97D/ins97aV/T98P/F99L/C122S/Q175R/Q192G/D217E/K224R	65.8
289	Q38H/I41S/D60bA/F60eV/Y60gF/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192T	7.46
290	Q38E/I41S/D60bH/F60eI/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V	10.4
291	Q38R/I41S/D60bH/F60eI/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	27.3
292	Q38E/I41S/D60bV/F60eK/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192I	20.4
293	Q38R/I41E/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192T	63.3

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
294	Q38H/I41A/D60bV/F60eR/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	2.37
295	Q38H/I41A/D60bA/F60eR/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E	12
296	F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192E	194
297	ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192G	38.5
298	Q38G/H40R/I41H/D60bN/F60eT/F97D/F99L/C122S/Q175L/Q192G	11.9
299	Q38G/H40R/I41H/D60bK/F60eT/F97D/F99L/C122S/Q175L/Q192G	21.3
300	Q38E/H40R/I41H/D60bK/F60eT/F97D/F99L/C122S/Q175L/Q192G	16.6
301	Q38H/I41S/D60bA/F60eV/Y60gF/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192T	14.2
302	Q38E/I41S/D60bH/F60eI/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192V	11.5
303	Q38R/I41S/D60bH/F60eI/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192E	32.9
304	Q38E/I41S/D60bV/F60eK/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192I	19.1
305	Q38R/I41E/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192T	105
306	Q38H/I41A/D60bV/F60eR/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192D	7.74
307	Q38H/I41A/D60bA/F60eR/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192E	14.2
308	Q38H/I41S/D60bT/F60eS/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192E	29.8
309	Q38H/I41S/D60bV/F60eQ/Y60gF/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192I	5.95
310	Q38H/I41A/D60bV/F60eI/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	7.64
311	Q38H/I41A/D60bV/F60eT/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	1.39
312	Q38H/I41A/F60eA/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	5.93
313	Q38H/I41A/D60bE/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	5.38
314	Q38H/I41A/D60bT/F60eK/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	3.82
315	Q38H/I41A/D60bT/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	2.28
316	Q38H/I41S/D60bS/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E	8.35
317	Q38H/I41S/D60bT/F60eS/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	45.4
318	Q38R/I41T/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192G	30.6
319	Q38S/I41S/F60eR/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192S	6.26

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
320	Q38H/I41T/D60bV/F60eQ/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G	4.93
321	Q38G/H40R/I41H/D60bH/F60eK/F97T/ins97aE/T98G/F99L/C122S/Q175L/V183A/Q192G	27.7
322	Q38H/I41A/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G	3.9
323	Q38L/I41T/D60bR/F60eL/Y60gM/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192G	23.7
324	Q38F/I41S/D60bF/F60eR/Y60gF/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192V	1.96
325	Q38V/I41S/D60bT/F60eT/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175H/Q192S	18.5
326	Q38W/I41A/ins97aV/F97D/T98P/F99L/C122S/G151T/Q175S/Q192D	68
327	Q38T/I41S/D60bV/F60eR/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175R/Q192V	15.7
328	Q38H/I41S/D60bT/F60eS/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175A/Q192D	67.8
329	Q38H/I41S/D60bT/F60eT/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192V	5.08
330	Q38Y/I41A/D60bL/F60eQ/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175M/Q192A	1.53
331	Q38L/I41T/D60bA/F60eL/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175M/Q192T	20.2
332	Q38R/I41S/D60bY/F60eD/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175M/Q192A	3.22
333	Q38W/I41S/D60bG/F60eI/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175A/Q192D	43.1
334	Q38T/I41S/D60bG/F60eM/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175S/Q192S	28.8
335	I41T/D60bW/F60eH/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192G	3.1
336	Q38D/I41S/D60bT/F60eR/ins97aV/F97D/T98P/F99L/C122S/G151K/Q175S/Q192V	48.1
337	Q38H/I41S/D60bF/F60eV/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192A	1.57
338	Q38L/I41A/D60bH/F60eT/ins97aV/F97D/T98P/F99L/C122S/G151Q/Q175A/Q192G	5.73
339	Q38H/I41A/D60bE/F60eH/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	8.28
340	Q38H/I41A/D60bV/F60eI/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	2.91
341	Q38E/I41S/D60bV/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	12.1
342	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192D	12.6
343	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175A/Q192D	22.6

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
344	Q38H/I41A/D60bV/F60eR/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192D	6.06
345	Q38H/I41A/D60bT/F60eH/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	6.95
346	D60bY/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G	4.1
347	I41T/D60bY/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G	3.88
348	Q38E/I41S/D60bT/F60eR/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V	32.7
349	Q38H/I41A/D60bK/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192D	22.3
350	Q38H/I41S/D60bA/F60eV/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E/Q209L	16.9
351	Q38H/I41A/D60bT/F60eR/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V	6.54
352	Q38K/I41S/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V	43
353	Q38F/I41A/D60bT/F60eG/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	1.25
354	Q38H/I41A/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192A	3.09
355	Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192A	2.71
356	Q38H/I41A/D60bV/F60eA/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V	1.57
357	Q38E/I41V/D60bF/F60eK/Y60gF/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G	14.2
358	Q38H/H40P/I41A/F60eQ/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192D	5.04
359	Q38R/I41V/D60bV/F60eV/Y60gF/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192G	18.3
360	Q38L/H40P/I41T/D60bV/F60eH/Y60gL/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192A	6.47
361	Q38H/I41A/D60bV/F60eH/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	5.31
362	Q38H/I41S/D60bA/F60eV/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192V	10.9
363	Q38R/I41T/D60bH/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192G	26.2
364	Q38H/I41S/D60bT/F60eR/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	15.4
365	Q38K/I41T/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192A	37.8
366	Q38H/I41A/D60bT/F60eK/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	14.6
367	Q38L/I41T/D60bV/F60eH/Y60gL/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192S	13.1
368	ins97aA/F97G/T98L/C122S/Q175M/Q192A/D217I/K224R	0.866
369	Q38H/I41A/D60bY/F60eT/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	4.77

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
370	ins97aY/F97H/F99L/C122S/Q175M/Q192A/D217V	5.72
371	ins97aL/F97Q/T98G/F99L/C122S/Q175M/Q192S/D217I	6.67
372	ins97aY/F97G/T98V/C122S/Q175M/Q192S/D217V	2.42
373	Q38Y/I41S/D60bR/F60eE/Y60gF/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192V	25
374	Q38H/I41S/D60bT/F60eS/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192V	20.2
375	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192V	7.43
376	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175A/Q192D	22.5
377	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192E	6.78
378	Q38H/I41A/D60bE/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D	13.8
379	Q38H/I41A/D60bT/F60eK/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D	10.6
380	Q38H/I41A/D60bV/F60eI/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D	6.42
381	Q38E/I41S/D60bV/F60eK/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D	22.9
382	Q38H/I41S/L52M/D60bG/ins97aV/F97D/T98P/F99L/M117K/C122S/I136L/Q192G/D217A	22
383	Q38E/I41A/D60bH/ins97aV/F97D/T98P/F99L/C122S/Q192G/Q209L/D217H	10.2
384	I41S/D60bT/F93L/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217H	27.7
385	I41T/D60bH/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217I	4.52
386	Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/M117L/C122S/I136T/Q192G/D217I	2.43
387	Q38R/I41T/D60bT/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217N/L233Q	39.8
388	Q38H/I41A/D60bW/ins97aV/F97D/T98P/F99L/C122S/I136M/Q192G/D217N	3.06
389	Q38H/I41S/P49Q/D60bS/F93L/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217Q	48.3
390	Q38H/I41S/D60bT/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217S	22.2
391	Q38H/I41S/D60bS/F93L/D96Y/ins97aV/F97D/T98P/F99L/C122S/I136F/Q192G/D217V	9.56
392	Q38H/I41T/D60bH/ins97aV/F97D/T98P/F99L/C122S/I136F/L153P/Q192G/D217Y	25.5
393	Q38H/I41S/D60bT/F93L/ins97aV/F97D/T98P/F99L/S115N/C122S/Q192V/F208L/D217Q	45.8
394	Q38K/I41T/D60bY/ins97aV/F97D/T98P/F99L/C122S/I136T/Q192G/F208V/D217R	19.5
395	Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217	7.05

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
	17V	
396	Q38H/I41S/D60bG/ins97aV/F97D/T98P/F99L/M117T/C122S/N164D/Q192G/D217E	10.3
397	Q38K/I41S/D60bV/ins97aV/F97D/T98P/F99L/M117T/C122S/Q145E/Q175L/Q192G	11.8
398	Q38H/I41S/D60bT/F60eT/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192V	5.52
399	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192D	15.4
400	Q38H/I41A/D60bV/F60eR/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D	5.93
401	Q38H/I41S/L52M/D60bH/D96V/ins97aV/F97D/T98P/F99L/C122S/T150A/Q192G/Q209L/D217T	16.9
402	I41S/D60bS/D96V/ins97aV/F97D/T98P/F99L/C122S/Q192G/F208L/D217N	52.4
403	Q38H/I41S/D60bT/S90T/F97D/ins97aV/T98P/F99L/C122S/S127N/I136F/Q192G/D217Q	21.2
404	Q38H/I41S/D60bT/F93S/ins97aV/F97D/T98P/F99L/C122S/I136L/Q192G/D217A	37
405	I41S/D60bH/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192G/D217N	20.6
406	L33M/Q38H/I41A/D60bA/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217N	50
407	Q38H/I41S/D60bY/D96Y/ins97aV/F97D/T98P/F99L/L106M/C122S/I136M/Q192G/Q209L/D217T	1.97
408	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G/F99L/C122S/G151N/Q175L/Q192D	2.23
409	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aA/F97D/T98P/F99L/C122S/G151H/Q175L/Q192D	7.09
410	Q38H/I41T/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G/F99L/C122S/G151N/Q175L/Q192D	9.75
411	Q38H/I41A/D60bV/F60eR/Y60gW/D96Y/ins97aI/F97E/T98N/F99M/C122S/G151N/Q175L/Q192V	4.36
412	Q38H/I41A/D60bV/F60eR/Y60gW/D96S/ins97aR/F97A/T98S/F99L/C122S/G151N/Q175L/Q192T	2.07
413	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151N/Q175L/Q192E	1.51
414	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/F99L/C122S/G151H/Q175L/Q192D	5.53
415	Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/ins97aV/F97E/T98G/F99L/C122S/G151H/Q175L/Q192D	4.62
416	Q38H/I41S/D60bA/Y60gG/ins97aV/F97D/T98P/F99L/C122S/H143T/G151N/Q175L/Q192A	4.22
417	Q38H/I41S/D60bT/F60eH/Y60gF/ins97aV/F97D/T98P/F99L/C122S/H143R/G151N/Q175L/Q192S	21
418	Q38H/I41S/D60bS/F60eQ/Y60gF/ins97aV/F97D/T98P/F99L/C122S/H143R/G151N/Q175L/Q192T	12.9
419	Q38H/I41S/D60bF/F60eT/ins97aV/F97D/T98P/F99L/C122S/H143Q/G1	3.07

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
	51N/Q175L/Q192G	
420	Q38H/I41S/D60bF/F60eQ/Y60gF/ins97aV/F97D/T98P/F99L/C122S/H143A/G151N/Q175L/Q192A	4.58
421	Q38H/I41S/D60bT/F60eT/ins97aV/F97D/T98P/F99L/C122S/H143Q/G151Q/Q175L/Q192G	6.69
422	Q38H/I41S/D60bQ/F60eQ/F97D/ins97aV/T98P/F99L/C122S/H143Q/G151Q/Q175L/Q192G	8.5
423	Q38H/I41S/D60bS/F60eQ/ins97aV/F97D/T98P/F99L/C122S/H143A/G151N/Q175L/Q192G	26.3
424	Q38H/I41A/D60bV/F60eR/Y60gW/D96Q/F97E/ins97aD/T98S/F99L/C122S/G151N/Q175L/Q192R	4.6
425	Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97D/ins97aE/T98S/F99L/C122S/G151H/Q175L/Q192A	1.17
426	Q38H/I41S/D60bT/F60eS/Y60gW/D96L/ins97aG/F97D/T98N/F99L/C122S/G151H/Q175L/Q192E	1.59
427	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D	6.86
428	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G/F99L/C122S/G151H/Q175L/Q192D	1.57
429	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151H/Q175L/Q192D	2.52
430	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/F99L/C122S/G151N/Q175L/Q192D	4.9
431	Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/ins97aV/F97E/T98G/F99L/C122S/G151N/Q175L/Q192D	4.13
432	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151H/Q175L/Q192E	1.11
433	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151N/Q175L/Q192D	2.54
434	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151H/Q175L/Q192D	1.83
435	Q38H/I41A/D60bV/F60eR/Y60gW/F97D/F99L/C122S/G151H/Q175L/Q192D	3.72
436	Q38H/I41S/D60bT/F60eS/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	3.04
437	Q38H/I41A/D60bV/F60eR/Y60gW/F97D/F99L/C122S/G151N/Q175L/Q192D	7.04
438	I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192E	6.33
439	Q38H/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192E	66.7
440	Q38H/I41S/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192E	3.83
441	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	3.19
442	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/T98P/F99L/C122S/G151H/Q175L/Q192E	25.7

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
443	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/F99L/C122S/G151H/Q175L/Q192E	7.82
444	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/C122S/G151H/Q175L/Q192E	11.5
445	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/Q175L/Q192E	4.86
446	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q192E	11.9
447	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L	1.31
448	Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192E	4.07
449	Q38H/I41S/D60bT/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L/Q192E	10.4
450	Q38H/I41S/D60bT/F60eG/Y60gW/D96V/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	4.47
451	Q38K/I41G/F60eG/Y60gW/D96P/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	62.7
452	Q38Y/I41E/D60bS/F60eV/Y60gF/D96W/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	227
453	Q38H/I41S/D60bT/F60eG/D96Y/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	9.56
454	Q38V/I41G/F60eG/Y60gW/D96P/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	27.4
455	Q38Y/I41A/D60bT/F60eG/Y60gW/D96V/F97N/T98G/F99L/C122S/G151H/Q175L/Q192D	5.06
456	Q38H/I41S/D60bT/F60eG/D96P/F97N/T98G/F99L/C122S/G151Q/Q175L/Q192D	34.2
457	Q38K/I41G/D60bT/F60eG/Y60gW/D96P/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	27.4
458	Q38K/I41G/D60bT/F60eG/Y60gW/D96L/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	12.5
459	Q38E/I41S/D60bV/F60eK/Y60gW/D96P/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	45.9
460	Q38E/I41S/D60bW/F60eG/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	22.3
461	Q38M/I41S/F60eH/Y60gW/D96Y/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	21.6
462	Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97D/ins97aE/T98G/F99M/C122S/G151N/Q175L/Q192R	13.1
463	Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97E/ins97aT/T98G/F99M/C122S/G151N/Q175L/Q192G	16.9
464	Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97E/ins97aS/T98G/F99M/C122S/G151N/Q175L/Q192G	21.3
465	Q38H/I41A/D60bV/F60eR/Y60gW/D96W/F97D/ins97aD/T98G/F99L/C122S/G151N/Q175L/Q192G	5.28
466	Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97Y/ins97aE/T98G/F99M/C	7.16

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
	122S/G151N/Q175L/Q192R	
467	Q38H/I41A/D60bV/F60eR/Y60gW/D96W/F97D/ins97aT/T98G/F99L/C122S/G151N/Q175L/Q192G	4.9
468	Q38H/I41S/D60bT/F60eK/Y60gF/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	20.6
469	Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97S/ins97aH/T98G/F99L/C122S/G151N/Q175L/Q192G	3.14
470	Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97Y/ins97aN/T98G/F99M/C122S/G151N/Q175L/Q192G	3.76
471	Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97S/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D	5.17
472	Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97Y/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D	3.13
473	Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97N/ins97aE/T98S/F99L/C122S/G151H/Q175L/Q192D	4.53
474	Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97R/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D	5.71
475	Q38H/I41A/D60bT/F60eK/Y60gF/F97T/ins97aE/T98G/F99L/C122S/H143R/G151N/Q175L/Q192V	24.5
476	Q38Y/I41S/D60bV/F60eR/Y60gF/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	5.25
477	Q38E/I41S/D60bV/F60eK/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	19.1
478	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	5.12
479	Q38H/I41S/F60eT/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	35.7
480	Q38H/I41S/D60bT/F60eK/D96V/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	13.3
481	I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	9.47
482	Q38Y/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	47.7
483	Q38Y/I41S/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	10.4
484	Q38Y/I41S/D60bT/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	3.08
485	Q38Y/I41S/D60bT/F60eR/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	16.4
486	Q38Y/I41S/D60bT/F60eR/Y60gW/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	15.9
487	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/T98G/F99L/C122S/G151N/Q175L/Q192D	3.27
488	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/F99L/C122S/G151N/Q175L/Q192D	10.8
489	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/C122S/G151N/Q175L/Q192D	33.6

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
490	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q192D	56.7
491	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L	1.08
492	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/Q175L/Q192D	3.75
493	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/M117K/C122S/G151H/Q175L/Q192D	4.75
494	L36Q/Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	5.49
495	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/T150S/G151H/Q175L/Q192D/Q209L	2.88
496	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D	1.43
497	I41G/F97A/F99L/C122S/G151H/Q175L/Q192G/D217L	47.8
498	I41G/F97S/F99L/C122S/G151N/Q175I/Q192T/D217T	84.4
499	I41R/F97A/F99L/C122S/G151N/Q175R/Q192G/D217Q	401
500	I41S/F97E/F99L/C122S/G151N/Q175G/Q192R/D217A	74.3
501	I41G/F97S/F99L/C122S/G151T/Q175R/Q192A/D217Y	52.8
502	I41G/F97L/F99L/C122S/G151N/Q175A/Q192V/D217R	34
503	I41G/F97T/F99M/C122S/G151D/Q175T/Q192T/D217V	45.6
504	I41G/F97L/F99L/C122S/G151T/Q175M/Q192D/D217M	36.8
505	F97S/F99L/C122S/G151N/Q175I/Q192T/D217T	524
506	I41G/F99L/C122S/G151N/Q175I/Q192T/D217T	108
507	I41G/F97S/C122S/G151N/Q175I/Q192T/D217T	860
508	I41G/F97S/F99L/C122S/Q175I/Q192T/D217T	155
509	I41G/F97S/F99L/C122S/G151N/Q192T/D217T	105
510	I41G/F97S/F99L/C122S/G151N/Q175I/D217T	107
511	I41G/F97S/F99L/C122S/G151N/Q175I/Q192T	97.7
512	F97R/ins97aT/T98V/C122S/Q175M/Q192T/D217S	42.2
513	F97V/ins97aH/T98R/F99L/C122S/Q175R/Q192G/D217S	905
514	F97Q/F99L/C122S/Q175N/Q192V/D217G	3670
515	F97L/ins97aM/T98N/F99L/C122S/Q175T/Q192T/D217S	256
516	F97S/ins97aN/T98G/F99M/C122S/Q175T/Q192T/D217S	2400
517	I41T/F97H/F99L/C122S/G151N/Q175H/Q192V/D217L	131
518	I41R/F97T/F99L/C122S/G151N/Q175T/Q192T/D217I	159
519	I41E/F97V/F99L/C122S/G151N/Q175L/Q192S/D217H	49.4
520	I41D/F97R/F99L/C122S/G151Q/Q175R/Q192V/D217L	88
521	I41E/F97R/F99L/C122S/G151Q/Q175G/Q192T/D217V	13
522	I41D/F97T/F99L/C122S/G151N/Q175S/Q192T/D217A	70.9
523	I41E/F97A/F99M/C122S/G151N/Q175R/Q192S/D217E	485
524	I41G/F99L/C122S/Q175I/Q192T/D217T	81.8
525	I41G/F99L/C122S/G151N/Q192T/D217T	44.7

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
526	I41G/F99L/C122S/G151N/Q175I/Q192T	51.6
527	F97V/F99L/C122S/G151N/Q175L/Q192S/D217H	91.6
528	I41E/F99L/C122S/G151N/Q175L/Q192S/D217H	27.1
529	I41E/F97V/F99L/C122S/Q175L/Q192S/D217H	44.3
530	I41E/F97V/F99L/C122S/G151N/Q192S/D217H	42.2
531	I41E/F97V/F99L/C122S/G151N/Q175L/D217H	16.5
532	I41E/F97V/F99L/C122S/G151N/Q175L/Q192S	51.2
533	F97R/F99L/C122S/G151Q/Q175R/Q192V/D217L	137
534	I41D/F99L/C122S/G151Q/Q175R/Q192V/D217L	31.6
535	I41D/F97R/F99L/C122S/Q175R/Q192V/D217L	50.6
536	I41D/F97R/F99L/C122S/G151Q/Q192V/D217L	42.3
537	I41D/F97R/F99L/C122S/G151Q/Q175R/D217L	19.4
538	I41D/F97R/F99L/C122S/G151Q/Q175R/Q192V	79.4
539	I41E/F97R/F99L/C122S/G151Q/Q175G/Q192T	41.1
540	I41D/F99L/C122S/G151N/Q175S/Q192T/D217A	30.5
541	I41D/F97T/F99L/C122S/Q175S/Q192T/D217A	52.1
542	I41D/F97T/F99L/C122S/G151N/Q192T/D217A	70.4
543	I41D/F97T/F99L/C122S/G151N/Q175S/D217A	25.5
544	I41D/F97T/F99L/C122S/G151N/Q175S/Q192T	56.7
545	F97T/F99L/C122S/G151N/Q175S/Q192T/D217A	172
546	I41S/F97Q/F99L/C122S/Q175W/Q192V/D217R	50.6
547	I41G/F97L/F99L/C122S/G151N/Q192V/D217L	112
548	I41G/F97A/F99L/C122S/G151N/Q175M/Q192S	73.1
549	I41G/F97V/F99L/C122S/G151N/Q192T/D217V	30.5
550	I41D/F97R/F99L/C122S/Q175L/Q192T/D217I	5.72
551	I41E/F97S/F99L/C122S/Q175L/Q192V/D217A	89.9
552	F97L/F99L/C122S/Q175K/Q192V/D217M	463
553	F97E/F99L/C122S/G151A/Q192V	1040
554	F97E/F99L/C122S/Q175H/Q192V/D217P	7770
555	F97R/ins97aI/T98P/C122S/Q175M/Q192V/D217I	23.6
556	I41D/F99L/C122S/G151N/Q192T/D217A	45.1
557	I41D/F99L/C122S/G151N/Q175S/Q192T	28.6
558	I41D/F97T/F99L/C122S/G151N/Q192T	84.3
559	I41D/F99L/C122S/G151N/Q192T	47
560	I41D/F99L/C122S/Q175S/Q192T	27.4
561	I41D/F99L/C122S/Q192T	59.4
562	Q38R/I41G/Y60gG/F99M/C122S/G151N/Q192R	147
563	Q38K/I41G/Y60gG/F99L/C122S/G151N/Q192H	17.9
564	Q38L/I41R/Y60gF/F99L/C122S/G151N/Q192A	151
565	Q38K/I41D/Y60gG/F99L/C122S/G151N	52.7
566	Q38R/I41R/Y60gF/F99L/C122S/G151N/Q192G	197

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
567	Q38S/I41S/Y60gW/F99L/C122S/G151D/Q192T	15
568	Q38K/I41G/Y60gW/F99L/C122S/G151N/Q192A	9.96
569	Q38H/I41S/Y60gW/C122S/G151H/Q192A	8.96
570	Q38K/I41S/Y60gW/F99L/C122S/G151N/Q192G	35.1
571	Q38F/I41S/Y60gA/C122S/G151N/Q192R	33.1
572	Q38R/I41S/Y60gW/F99L/C122S/G151N/Q192E	116
573	Q38K/I41R/Y60gG/F99L/C122S/G151N/Q192G	335
574	Q38R/I41R/F99L/C122S/G151N/Q192G	248
575	Q38R/I41R/Y60gL/F99L/C122S/G151N/Q192G	388
576	I41E/C122S/G151N/Q175L/Q192A	45
577	I41S/F99M/C122S/G151N/Q175L/Q192G	62
578	I41E/F99L/C122S/G151N/Q175L/Q192A	28.5
579	I41S/F99L/C122S/G151H/Q175L/Q192V	20.9
580	I41G/F99L/C122S/G151N/Q192A	61
581	I41S/F99M/C122S/G151N/Q175G/Q192R	95.3
582	I41E/F99L/C122S/G151N/Q175R/Q192H	102
583	I41S/F99M/C122S/G151N/Q175E/Q192R	297
584	I41E/F99L/C122S/G151N/Q192V	156
585	I41E/F99L/C122S/G151N/Q192S	112
586	I41S/F99L/C122S/G151N/Q175P/Q192V	35.8
587	I41E/F99L/C122S/G151N/Q175G/Q192T	30.2
588	I41S/C122S/G151N/Q175R/Q192R	134
589	I41S/F99M/C122S/G151N/Q175P/Q192S	139
590	I41S/C122S/G151N/Q175D/Q192R	96.8
591	I41E/F99L/C122S/G151N/Q175R/Q192T	155
592	I41G/F99L/C122S/G151N/Q175R/Q192A	74.5
593	F99L/C122S/G151N/Q192T	225
594	I41D/F99L/C122S/G151N	16.9
595	I41S/F99L/C122S/Q175P/Q192V	64.3
596	I41S/F99L/C122S/G151N/Q175P	13.9
597	I41E/F99L/C122S/Q175G/Q192T	33.9
598	I41E/F99L/C122S/G151N/Q175G	20
599	I41D/Y59F/F99L/C122S/G151N/Q192T/V213A	414
600	I41D/G43A/F99L/C122S/G151N/Q192T/P232S/K239R	37.6
601	I41D/G43A/D96E/F99L/C122S/G151N/Q192T	45
602	I41D/D96E/F99L/C122S/G151N/Q192T	51.5
603	I41D/D96E/C122S/G151N/Q192T	78.8
604	I41D/D96E/F99L/C122S/G151N/Q192T/D217E	27.6
605	I41D/F99L/M117T/C122S/G151N/Q192T/A204D/D217E	25.3
606	I41D/F99L/C122S/G151N/Q192T/D217E	22
607	I41D/F99L/C122S/I136M/G151N/Q192T/D217L/K224R	32.2

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
608	I41D/F60eI/D96E/F99L/C122S/G151N/Q192T	47.9
609	I41D/C122S/G151N/Q192T/D217E	34.2
610	D96E/C122S/G151N/Q192T	298
611	Y59F/C122S/G151N/Q192T	288
612	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/F99L/C122S/G151H/Q175L/Q192D	7.34
613	I41S/ins97aV/C122S/Q192D	336
614	I41S/F97L/F99L/C122S/Q192S	19.1
615	I41T/F97R/ins97aV/T98L/C122S/Q192S	13.2
616	I41S/F97V/T98N/F99L/C122S/Q192S	29.4
617	I41S/F97G/ins97aA/T98L/C122S/Q192A	6.75
618	I41S/F97D/F99L/C122S/Q192V	31
619	I41E/F97L/F99L/C122S/Q192A	47.4
620	I41S/F97A/ins97aV/T98L/C122S/Q192A	5.3
621	I41S/F97del/T98S/F99L/C122S/Q192S	23.2
622	I41A/Y60gW/D96F/F97G/F99M/C122S/Q175W/Q192A	4.06
623	I41G/Y60gW/F99L/C122S/Q175R/Q192S	6.95
624	I41A/Y60gW/ins97aE/F99L/C122S/Q175M/Q192T	8.9
625	I41T/ins97aA/F99Y/C122S/Q175L/Q192A	28
626	I41A/ins97aY/F99L/C122S/Q175R/Q192H	14.8
627	I41S/ins97aT/F99L/C122S/Q175R/Q192H	27.5
628	I41S/Y60gW/ins97aN/F99L/C122S/Q175R/Q192T	12
629	Q38H/I41S/D96S/ins97aK/C122S/G151N/Q192A	16.7
630	Q38H/I41A/D96A/ins97aA/C122S/G151D/Q192T	9.25
631	Q38H/I41S/D96Q/ins97aT/C122S/G151N/Q192A	17.9
632	Q38H/I41T/D96M/ins97aA/C122S/G151D	10.8
633	Q38Y/I41A/D96I/ins97aQ/C122S	4.26
634	Q38H/I41S/D96K/ins97aT/C122S/G151K/Q192A	19.2
635	Q38W/I41S/D96R/ins97aA/C122S/G151N/Q192A	9.5
636	Q38H/I41A/D96R/ins97aQ/C122S	7.6
637	Q38F/I41V/D96Q/ins97aT/C122S/G151D	9.89
638	L33M/Q38F/I41S/D96A/ins97aW/C122S/G151N/Q192S	10.6
639	Q38H/I41S/D96V/ins97aA/C122S/G151N/Q192A	16
640	Q38H/I41T/D96K/ins97aL/C122S/G151N/Q192A	44.7
641	Q38H/I41S/D96Q/ins97aA/C122S/Q192T	10.2
642	Q38W/I41V/D96R/ins97aA/C122S/G151N	4.49
643	Q38Y/I41T/D96M/ins97aS/C122S/G151N	12.5
644	Q38H/I41S/D96K/ins97aS/C122S/G151P/Q192S	25.6
645	Q38H/I41S/D96G/ins97aG/C122S/G151N/Q192A	34.6
646	Q38H/I41S/D96K/ins97aD/C122S/G151N/Q192S	26.8
647	I41S/D96E/ins97aG/C122S/G151Q/Q192A	44.4

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
648	I41S/Y59F/ins97aV/C122S/G187D/Q192V/D217V	8.35
649	A35V/I41S/Y59F/C122S/Q192D/D217V	39.8
650	I41S/F93L/ins97aV/C122S/Q192V/D217V	9.82
651	I41S/S90P/ins97aV/C122S/Y146E/Q192N/D217V	6.47
652	I41S/S90T/ins97aV/C122S/Q192N/D217V	13.4
653	I41S/S90T/ins97aV/C122S/Q192V/D217V	10.5
654	I41S/Y59F/ins97aV/C122S/Q192G	25.6
655	I41S/Y59F/F97S/ins97aV/S116Y/C122S/Q192G/D217V	8.22
656	I41S/ins97aV/C122S/Q192G/Q209L	33.4
657	Q38H/I41S/ins97aV/A112V/C122S/Q192A/Q209L	10.9
658	I41S/ins97aV/C122S/Q192V/D217V	11
659	I41S/Y59F/ins97aV/C122S/Q192A	16.6
660	I41A/F97G/ins97aM/T98L/C122S	40.1
661	I41G/F97E/F99L/C122S/Q192A	30.1
662	I41S/F97V/ins97aV/T98P/C122S	30.9
663	I41S/T98S/F99L/C122S/Q192A	17.4
664	I41S/F97Q/F99L/C122S/Q192S	53.5
665	I41G/F97L/F99L/C122S/Q192S	41.4
666	I41S/F97G/ins97aA/T98P/C122S/Q192A	57.2
667	I41A/F97G/ins97aV/T98E/C122S	18.1
668	I41A/F97S/ins97aA/C122S	19.8
669	I41A/F97W/T98S/F99L/C122S/Q192A	27
670	I41L/N95D/D96T/F97W/F99L/C122S/Q192A	62.6
671	I41T/Y60gL/N95D/D96F/F97S/F99L/C122S/Q175S/Q192A	247
672	I41A/Y60gW/N95D/D96F/F97G/F99L/C122S/Q175H/Q192A	17.5
673	I41A/Y60gW/F99L/C122S/Q175T/Q192A	17.6
674	Q38M/I41T/D96M/ins97aH/C122S/G151E	19.1
675	Q38H/I41T/D96R/ins97aG/C122S/G151S	54.1
676	I41S/D60bY/ins97aV/T98N/C122S/Q192H	8.1
677	I41S/Y59F/D60bY/ins97aV/C122S/Q192G	5.24
678	I41S/D60bY/ins97aV/A112V/C122S/Q192G/Q209L	4.76
679	A35T/I41S/Y59F/ins97aV/C122S/Y146F/V183A/Q192G/R235H	18.4
680	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175H/Q192D	195
681	I41S/ins97aV/C122S/N164D/Q192G/R235H	46.4
682	I41S/Y59F/ins97aV/C122S/Q192G/N223D	34.1
683	I41S/ins97aV/C122S/N164D/Q192G/R235L	49.7
684	I41S/Y59F/F97Y/ins97aV/C122S/Q192G	29.1
685	I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192V	32.3
686	I41S/F99L/C122S/G151N/Q175M/Q192G/D217V	3.19
687	I41S/F97L/F99L/C122S/G151N/Q192G/D217V	11.9
688	I41S/F97S/F99L/C122S/G151N/Q175L/Q192A/D217L	11.2

SEQ ID NO.*	Chymotrypsin Numbering MODIFICATIONS	EC ₅₀ (nM)
689	I41G/F97R/F99L/C122S/G151N/Q175L/Q192S/D217V	4.18
690	I41T/F97L/F99L/C122S/G151N/Q175S/Q192S/D217W	24.2
691	I41D/F97T/F99M/C122S/Q192V/D217M	63.8

* SEQ ID of the protease domain containing the replacements; it is understood that these replacements can be included in full-length MTSP-1 and in other variants, including catalytically active fragments thereof.

Among these of interest are those with an EC₅₀ for hC3 cleavage of less than 10, such

5 as, but are not limited to, for example:

EC ₅₀ (nM)	Mutation string	SEQ ID NO.
0.866	ins97aA/F97G/T98L/C122S/Q175M/Q192A/D217I/K224R	368
0.867	Q38G/H40R/I41H/D60bN/F97D/F99L/C122S/Q175L/Q192G	286
1.08	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L	491
1.11	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151H/Q175L/Q192E	432
1.17	Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97D/ins97aE/T98S/F99L/C122S/G151H/Q175L/Q192A	425
1.25	Q38F/I41A/D60bT/F60eG/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	353
1.31	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175L	447
1.39	Q38H/I41A/D60bV/F60eT/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E	311
1.43	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D	496
1.45	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L	40
1.51	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151N/Q175L/Q192E	413
1.53	Q38Y/I41A/D60bL/F60eQ/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175M/Q192A	330
1.57	Q38H/I41S/D60bF/F60eV/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192A	337
1.57	Q38H/I41A/D60bV/F60eA/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V	356
1.57	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G/F99L/C122S/G151H/Q175L/Q192D	428
1.59	Q38H/I41S/D60bT/F60eS/Y60gW/D96L/ins97aG/F97D/T98N/F99L/C122S/G151H/Q175L/Q192E	426
1.83	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151H/Q175L/Q192D	434
1.96	Q38F/I41S/D60bF/F60eR/Y60gF/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192V	324
1.97	Q38H/I41S/D60bY/D96Y/ins97aV/F97D/T98P/F99L/L106M/C122S/I136M/Q192G/Q209L/D217T	407

EC ₅₀ (nM)	Mutation string	SEQ ID NO.
2.07	Q38H/I41A/D60bV/F60eR/Y60gW/D96S/ins97aR/F97A/T98S/F99L/C122S/G151N/Q175L/Q192T	412
2.23	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G/F99L/C122S/G151N/Q175L/Q192D	408
2.28	Q38H/I41A/D60bT/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	315
2.37	Q38H/I41A/D60bV/F60eR/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D	294
2.42	ins97aY/F97G/T98V/C122S/Q175M/Q192S/D217V	372
2.43	Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/M117L/C122S/I136T/Q192G/D217I	386
2.52	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151H/Q175L/Q192D	429
2.54	Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G/F99L/C122S/G151N/Q175L/Q192D	433
2.71	Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192A	355
2.76	H40R/I41H/F97D/F99L/C122S/Q175M/Q192G/D217V/K224Y	172
2.84	I41G/F97I/F99L/C122S/G151L/Q175M/Q192S/D217V	80
2.85	Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	36
2.87	Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	32
2.88	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/T150S/G151H/Q175L/Q192D/Q209L	495
2.91	Q38H/I41A/D60bV/F60eI/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	340
3.04	Q38H/I41S/D60bT/F60eS/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	436
3.06	Q38H/I41A/D60bW/ins97aV/F97D/T98P/F99L/C122S/I136M/Q192G/D217N	388
3.07	Q38H/I41S/D60bF/F60eT/ins97aV/F97D/T98P/F99L/C122S/H143Q/G151N/Q175L/Q192G	419
3.08	Q38Y/I41S/D60bT/Y60gW/D96M/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	484
3.09	Q38H/I41A/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192A	354
3.1	I41T/D60bW/F60eH/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192G	335
3.13	Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97Y/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D	472
3.14	Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97S/ins97aH/T98G/F99L/C122S/G151N/Q175L/Q192G	469
3.19	Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	441
3.19	I41S/F99L/C122S/G151N/Q175M/Q192G/D217V	686
3.22	Q38R/I41S/D60bY/F60eD/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175M/Q192A	332
3.27	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/T98G/F99L/C122S/G151N/Q175L/Q192D	487
3.72	H40R/I41H/Y60gH/F97D/F99L/C122S/Q175M/Q192G/D217I/K224L	177
3.72	Q38H/I41A/D60bV/F60eR/Y60gW/F97D/F99L/C122S/G151H/Q175L/Q192D	435

EC ₅₀ (nM)	Mutation string	SEQ ID NO.
3.75	Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/Q175L/Q192D	492
3.76	Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97Y/ins97aN/T98G/F99M/C122S/G151N/Q175L/Q192G	470
4.53	Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97N/ins97aE/T98S/F99L/C122S/G151H/Q175L/Q192D	473
5.92	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D	37
6.86	Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D	35

Example 3

Confirmation of cleavage at the targeted Q H A R ↓ A S H L site in C3

Two independent analytical methods were used to characterize the cleavage site(s) of C3 by the MTSP-1 protease domain variant that contains the modifications

- 5 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D: (a) direct analysis of cleavage products by MALDI-MS with identification of released peptides in the 1-40 kDa range and (b) LC-tandem MS of a labeled proteolytic digest with sequence analysis of product peptides that contain a neo-N-terminus. These experiments were performed as follows:

- 10 (a) C3 (1 mg/ml in PBS buffer) was incubated with u-PA protease variant at enzyme to substrate ratios of 1:50 for a total of one hour. Samples (50 µl) were removed from these reactions at 0, 5, 10, 20, 40, and 60 minutes, and the cleavage reaction was terminated in each sample by addition of 1 µl 1% TFA and flash freezing in dry ice. Samples were then reduced with 25 mM TCEP (1hr at 37 °C), then
- 15 desalted via C18 solid phase extraction (Agilent Omix). The resulting cleavage products were analyzed directly by MALDI-MS (ABI 4700). At each time point after 0 minutes a fragment of MW 8289 ±1 Da was observed, indicating cleavage at the arginine in the QHAR|ASHG site in C3. No additional C3 cleavage sites were observed in these reactions.

- 20 (b) The C3/ protease variant mixture (10 µl) was denatured in 6M guanidine, then cysteine side chains were reduced (30 mM TCEP) and alkylated (iodoacetamide). The ε-amino group of lysine side chains was blocked by treatment with O-methylisourea (3 µl OMU, 8 µl 1M NaOH, 15 min at 65 °C; quench with 2 µl 1:1 TFA-water, followed by SPE cleanup) and then peptide amino termini were

labeled with SulfoNHS–SS–biotin (50 mM HEPES, 250 uM biotin reagent, 30 min at RT). After proteolytic digestion with either trypsin or Glu-C, the biotin-labeled peptides were captured by avidin beads. Cleavage of the biotin label was achieved with reduction (TCEP), giving a neo-N-terminal peptide fraction with a N-thioacyl label. This peptide fraction was analyzed by LC-tandem MS (Thermo LTQ-XL); the major C3-related component identified was the peptide (N-thioacyl)-ASHGLAR, indicating cleavage at the QHAR|ASHG site in C3.

Q H A R ↓ A S H L 737-744

P4 P3 P1 ↓P1' P4'.

Example 4

***Ex Vivo* Pharmacodynamic (PD) Analysis of MTSP-1 Variants in Cynomolgus Monkey Plasma**

The cleavage of C3 in anti-coagulated EDTA-treated cynomolgus monkey plasma by the wild type and modified MTSP-1 polypeptides was measured as described below. A C3 ELISA was used to measure the effective dose (ED₅₀) of wild type and modified MTSP-1 polypeptides required to cleave 50% of the C3 in the “test,” anti-coagulated plasma. The cleavage reactions contained 80% plasma, and each protease was assayed at 9 different concentrations in addition to a zero protease control. The highest concentration of wild type MTSP-1 used in this reaction was 6 μM and the next eight concentrations were prepared by sequential dilutions by a factor of 1.5. The highest concentration used for MTSP-1 variant proteins was 150 nM and, as with the wild type protein, the next eight concentrations were prepared by sequential dilutions by a factor of 1.5. Following addition of test protease, the reaction was incubated for 10 minutes at 37 °C. The reaction was then rapidly quenched by addition of the protease inhibitor 10 μM EGR-CMK (Glu-Gly-Arg-chloromethyl ketone) and the quenched samples were placed at room temperature for 30 minutes before performing the C3 ELISA. Cleavage reactions were diluted 1:2700 in BSA-PBST and uncleaved C3 was “captured” with Goat anti huC3 (A213 CompTech) (adsorbed to a microtiter plate) and “detected” by 0.5 μg/ml MAB anti-huC3a (Abcam ab11872) in 1% BSA-PBST. The ELISA was then “developed” using Goat anti Mouse HRP conjugate and the WesternBright Sirius Western Blotting Detection Kit following the manufacturer’s directions.

Table 16. hC3 cleavage with modified MTSP-1 polypeptides in Cynomolgus monkey plasma		
Chymotrypsin numbering	SEQ ID NO.*	ED₅₀ 80% cynomolgus plasma (nM)
Wild-type MTSP-1 protease domain with C122S	4	2800
I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E	21	2200
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	22	101
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	23	195
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	24	76
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	25	152
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	26	136
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192D	27	118
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	28	133
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D	29	37
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D	30	85
Q38H/I41A/D60bV/F60eR/Y60gW/D96P/F97W/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192E	31	73
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	32	58
Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97E/ins97aV/T98G/F99L/C122S/G151H/Q175L/Q192D	33	133
Q38H/I41S/D60bT/F60eS/Y60gW/D96L/F97D/ins97aG/T98N/F99L/C122S/G151H/Q175L/Q192E	34	70
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35	92
Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	36	103
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D	37	37

* SEQ ID of the protease domain containing the replacements

Example 5

***Ex vivo* Stability of Modified MTSP-1 Polypeptides in Cynomolgus Monkey Vitreous Humor**

5 The *ex vivo* stability of modified MTSP-1 polypeptides was assessed in purchased cynomolgus monkey vitreous humor or Phosphate Buffered Saline (PBS) negative control. Modified MTSP-1 polypeptides that exhibit stability in vitreous humor can be used for treatment of AMD.

80% Cynomolgus vitreous humor (obtained from BioCemed; Catalog Nos.
10 BC7615-V1, BC60815-V1, BC33115-V6) in buffer containing 50 mM Tris pH 8.0, 50 mM NaCl, and 0.01% Tween-20 or PBS control was incubated with modified

MTSP-1 polypeptides at a final concentration of 0.1 μ M. The mixture was incubated at 37 °C for 7 days. The residual protease activity was assayed with 100 μ M fluorogenic substrate AGR-ACC (7-amino-4-carbamoylmethyl-coumarin) in 50 mM Tris, pH 8.0, 50 mM NaCl, 0.01% Tween-20 and the results were assessed at 5 excitation wavelength=380 nm and emission wavelength=460 nm. The results show that the modified MTSP-1 polypeptides with the sequences set forth in SEQ ID NOS: 35, 38-40, and 47-56 exhibit comparable residual activity (*i.e.*, stability) after incubation in cynomolgus plasma and PBS. The results are set forth in Table 17 below.

Table 17: Stability of MTSP-1 polypeptides in vitreous humor			
Chymotrypsin numbering	SEQ ID NO.*	Activity (%) on Day 7	
		vitreous	PBS
Wild-type MTSP-1 protease domain with C122S	4	59	63
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35	92	94
Q38H/I41S/D60bT/F60eS/Y60gW/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	38	73	91
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	39	77	85
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L	40	18	23
I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	47	86	87
Q38H/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	48	76	78
Q38H/I41S/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	49	87	81
Q38H/I41S/D60bT/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	50	85	91
Q38H/I41S/D60bT/F60eS/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	51	85	93
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D	52	19	34
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/F99L/C122S/G151H/Q175L/Q192D	53	66	82
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/C122S/G151H/Q175L/Q192D	54	94	98
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	55	74	87
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q192D	56	90	94

10 * SEQ ID of a protease domain containing the replacements

The *ex vivo* stability of the modified MTSP-1 polypeptides in purchased Cynomolgus monkey vitreous humor after 7 and 28 days was assessed as above. The

results show that the modified MTSP-1 polypeptides provided herein are relatively stable for at least 7 days in vitreous humor. The results are set forth in Table 18 below.

Table 18		Activity (%) at 37°C	
Chymotrypsin numbering	SEQ ID NO.*	Day 7	Day 28
Wild-type MTSP-1 protease domain with C122S	4	67	47
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35	91	68
I41E/F99L/C122S/G151N/Q192T	41	100	91
I41D/C122S/G151N/Q192T	42	71	35
I41S/F99L/C122S/G151N/Q192V	43	79	ND
I41E/F99L/C122S/G151N/Q192T	44	91	90
I41D/Y59F/D96E/F99L/C122S/G151N/Q192T	45	85	ND
I41D/Y59F/C122S/G151N/Q192T	46	88	86
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D	57	95	80
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	58	96	75
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D	59	92	63

* SEQ ID of the protease domain containing the replacements

5

Example 6

Ex Vivo Pharmacodynamic Activity in Human Plasma

Serial dilutions of modified MTSP-1 polypeptides (or buffer) were added to human plasma (that contains ~ 8 μ M endogenous C3) to create reaction mixtures that contained 6000, 4000, 2667, 1778, 1185, 790, 527, 351, 234 or 0 nM concentrations of each variant polypeptide and 80% human plasma. Similar reaction mixtures were prepared for wild type MTSP with the wild type MTSP present at concentrations of 150, 100, 67, 44, 30, 20, 13, 9, 6 or 0 nM. These reaction mixtures were incubated for 1 hour at 37 °C and quenched with 10 μ M EGR-CMK. Each reaction mixture was diluted 1: 15,625 in PBST buffer containing 1% BSA and the residual, uncleaved C3 concentration in the mixture was “detected” using mAb anti-huC3a (Abcam ab11872) and the assay signal was “developed” using HRP conjugate Goat anti Mouse-HRP (JIR 115-035-003) and the WesternBright Sirius Western Blotting Detection Kit. These data were used to calculate the concentration of each MTSP polypeptide required to cleave 50% of the C3 present in the plasma during the 1 hour incubation (*i.e.*, the ED₅₀).

20

The results are shown in Table 19 below, which sets forth the ED₅₀ (nM) of hemolysis in 80% human plasma by the reference MTSP-1 protease domain comprising the WT-MTSP-1 protease domain with the C122S replacement, and the modified MTSP-1 polypeptides. As shown in Table 19, the ED₅₀ for the reference MTSP-1 polypeptide in 80% human plasma is 3500 nM whereas exemplary MTSP-1 polypeptides have increased ability to cleave complement as indicated by a lower ED₅₀ (e.g., between 24 nM and 835 nM). For example, the modified MTSP-1 polypeptide with the sequence set forth in SEQ ID NO: 35, which contain the replacements Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, was approximately 140-fold more potent than the reference MTSP-1 protease domain with the C122S replacement.

Table 19		
Chymotrypsin numbering	SEQ ID NO.*	ED₅₀ 80% human plasma (60 min, nM)
Wild-type MTSP-1 protease domain with C122S	4	3500
I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E	21	835
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	22	52
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	23	65
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	24	50
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	25	50
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	26	38
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192D	27	41
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	28	32
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D	29	27
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D	30	34
Q38H/I41A/D60bV/F60eR/Y60gW/D96P/F97W/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192E	31	47
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	32	24
Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97E/ins97aV/T98G/F99L/C122S/G151H/Q175L/Q192D	33	38
Q38H/I41S/D60bT/F60eS/Y60gW/D96L/F97D/ins97aG/T98N/F99L/C122S/G151H/Q175L/Q192E	34	39
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35	25
Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	36	27

Table 19		
Chymotrypsin numbering	SEQ ID NO.*	ED ₅₀ 80% human plasma (60 min, nM)
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D	37	44

* SEQ ID of the protease domain containing the replacements

Example 7

Cleavage of Proteinase-activated Receptor 2 (PAR-2)

A. Activity of Mutants in a Proteinase-activated Receptor 2 Cell-Based Assay

5 Wild type MTSP-1 is an efficient activator of PAR-2, G-protein-coupled receptor expressed in vascular endothelial cells and a variety of epithelial cells that is involved in inflammatory diseases such as arthritis, lung inflammation (asthma), inflammatory bowel disease, sepsis, and pain disorders. Reduced PAR-2 activity by an anti-C3 variant MTSP-1 polypeptide, therefore, increases C3 selectivity for that

10 engineered protease. Consequently, the modified MTSP-1 polypeptides were tested for their activity (*i.e.*, ability to activate) on the proteinase-activated receptor 2 (PAR-2) in a cell based assay (Millipore). The ED₅₀ (nM) of PAR-2 cleavage by the proteases were measured by plotting the fraction cleavage vs. protease concentration on a 4 parameter logistic curve fit (SoftMax Pro software, Molecular Devices, CA). A

15 catalytically inactive version of MTSP-1 was provided as a negative control. Decreased PAR-2 activity in this assay (*i.e.*, a higher ED₅₀ for PAR-2 cleavage versus wild type MTSP-1) for a variant MTSP-1 polypeptide indicates that the variant protein displays more restricted specificity than wild type MTSP-1. Increased specificity versus PAR-2 indicates that the variant also can exhibit decreased non-

20 specific cleavage of other proteins compared with wild type MTSP-1. The results of these assays (see Table 20 below) demonstrate that the polypeptides display significantly reduced PAR-2 activity compared with wild type MTSP-1.

Another assay used to mimic the proteolytic activation of PAR-2 *in vivo* measures the activity of variant MTSP-1 polypeptides on a quenched fluorescence

25 peptidic substrate containing the peptide sequence SKGR↓SL, the P4 – P2' sequence (Ser 33 to Leu 38) of the activation cleavage site in PAR-2. Cleavage of R↓S site in this peptidic substrate produces a fluorescence signal allowing measurement of the reaction rate with a fluorescence plate reader. Reduced activity towards the SKGR/S

peptidic substrate compared with that of wild type MTSP-1 indicates that the variant MTSP-1 polypeptide possesses enhanced substrate specificity.

- Exemplary results are shown in Table 20, below. All tested modified MTSP-1 polypeptides exhibited at least a 30-fold increased ED₅₀ and decreased k_{cat}/K_m compared to wild-type MTSP-1 protease domain with the C122S replacement set forth in SEQ ID NO: 4. The data indicate that the modified MTSP-1 polypeptides selected for cleavage of C3 have significantly reduced activity for a native substrate.

Table 20.			
Chymotrypsin numbering	SEQ ID NO.*	SKGR/SL k_{cat}/K_m (M⁻¹s⁻¹)	PAR-2 Cell Based Assay ED₅₀ (nM)
Wild-type MTSP-1 protease domain with C122S	4	200000	1.4
I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192E	21	<100	2600
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	22	925	690
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	23	245	1900
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	24	959	1800
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	25	1730	640
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	26	742	560
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192D	27	1730	n.d.
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151H/Q175L/Q192D	28	1360	430
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D	29	2320	450
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151H/Q175L/Q192D	30	4030	420
Q38H/I41A/D60bV/F60eR/Y60gW/D96P/F97W/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192E	31	1620	n.d.
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D	32	3560	150
Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97E/ins97aV/T98G/F99L/C122S/G151H/Q175L/Q192D	33	865	n.d.
Q38H/I41S/D60bT/F60eS/Y60gW/D96L/F97D/ins97aG/T98N/F99L/C122S/G151H/Q175L/Q192E	34	1300	n.d.
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35	6210	n.d.
Q38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	36	4990	n.d.

Table 20.			
Chymotrypsin numbering	SEQ ID NO.*	SKGR/SL k_{cat}/K_m ($M^{-1}s^{-1}$)	PAR-2 Cell Based Assay ED_{50} (nM)
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P/F99L/C122S/G151N/Q175L/Q192D	37	2060	n.d.

* SEQ ID of the protease domain containing the replacements

Example 8

Pharmacokinetic and Pharmacodynamic Activity in Cynomolgus Monkey

Vitreous Humor *in vivo*

- 5 The *in vivo* pharmacodynamic activity in vitreous humor (cynomolgus monkey model) of the modified MTSP-1 polypeptide set forth in SEQ ID NO: 35, which is the protease domain that contains the replacements Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, was assessed. The ability to cleave and inactivate C3 in vitreous
- 10 humor are indicative of a candidate for treatment of AMD.
- Twelve naive cynomolgus monkeys were assigned to a single treatment group. Study animals were intravitreally administered a single dose of 125 μ g of modified MTSP-1 polypeptide in one eye. The isolated protease domain whose sequence is set forth in SEQ ID NO: 35, which has a molecular weight of approximately 25 kDa, was
- 15 administered. The right eye received the test article and the left eye was injected with vehicle control. Four animals were sacrificed at each of the following time points: 24 hours post-dose, day 2 and on day 6. Vitreous humor samples were collected from both the right and left eyes and analyzed for modified MTSP-1 polypeptide stability and level of C3 after treatment with modified MTSP-1 polypeptide or vehicle control;
- 20 C3 and modified MTSP-1 polypeptide concentrations were determined by ELISA as detailed above.

- The concentration of the modified MTSP-1 polypeptide present in vitreous humor samples obtained 24 hours post-dose and on day 2, day 6, day 7, and day 28 was measured by ELISA. Proteolytic activity of the MTSP-1 polypeptides (and other serine proteases) in the vitreous samples was quenched by the addition of EGR-CMK (Haematologic Technologies, EGRCK-01) to a final concentration of 10 μ M, and the
- 25 mixture was allowed to stand for 30 minutes at ambient temperature before performing the ELISA.

The half-life of the modified MTSP-1 polypeptide of SEQ ID NO: 35 was determined to be approximately 1.7 days, which corresponds to approximately 5 days in a human system (Deng *et al.* (2011) *MAbs* 3(1): 61-66). *In vivo* recovery (*i.e.*, the peak level of modified MSTP-1 polypeptide detected divided by the dose of the modified MTSP-1 polypeptide) of the modified MTSP-1 polypeptide set forth in SEQ ID NO: 35 was calculated by ELISA from the observed maximum level of the modified MTSP-1 polypeptide set forth in SEQ ID NO: 35. The theoretical predicted value for 100% *in vivo* recovery was 2.5 μ M. The measured *in vivo* recovery of the MTSP-1 protease domain (SEQ ID NO: 35) containing the replacements Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D was calculated to be approximately 59% of the predicted value, or approximately 1.5 μ M. There was substantial variation between two separate experiments (measurement 1=100% and measurement 2=18% recovery), indicating either poor intravitreal injections or inappropriate sample handling, storage, or dilution, and therefore incomplete local delivery of active anti-C3 protease into the vitreous, in the second experiment.

C3 levels in vitreous humor were measured by ELISA. C3 levels in vehicle-injected negative control eye ranged between 0.4 nM- 50 nM (2 samples from vehicle-injected eyes differed significantly from the other 10, likely due to blood contamination during harvesting of the vitreous with a needle). The baseline level of C3 prior to MSTP-1 administration was approximately 2.2 nM. C3 was undetectable in the variant-treated eye 1, 2, 6, and 7 days after the single injection of the anti-C3 MTSP polypeptide. 28 days after the single injection, the C3 concentration was approximately 1.4 nM in the eye treated with modified MTSP-1 polypeptide set forth in SEQ ID NO: 35, which is approximately 64% of the baseline level before treatment.

Results show that the modified MTSP-1 polypeptide catalytically eliminates C3. It had a half-life of 1.7 days, as assessed by ELISA and enzyme assays, and suppresses vitreal complement for at least, or longer than, 7 days. Doses of up to 1 mg/eye were well tolerated. PK/PD modeling indicates a suppression of C3 for 3 months or more in humans.

Example 9**Exemplary Mutations at Positions in MTSP-1**

Exemplary positions and mutations of MTSP-1 polypeptides, including the full-length, precursor and protease domains and catalytically active portions thereof, are set forth in Table 21 below.

Table 21. Exemplary mutations at positions in MTSP-1					
Chymotrypsin numbering	Mature numbering	WT	SEQ ID NO. 35	Exemplary mutations	Conservative to Mutations
38	637	Q	H	H	N, Q
41	640	I	S	S, R, A, E, D	T, K, Q
59	658	Y		F	M, L, Y
60b	661	D	T	T, V	S, I, L
60e	664	F	S	S, R, K	T, Q, E
60g	666	Y	W	W	Y
96	705	D	K	K, V, Y, L, I, P	R, Q, E, W, F
97	706	F	G	G, T, D, E, N, Y, W	P, S, Q, H, F
Ins97a			V	V, E, A, G, N	I, L, S, P, Q, H, D
98	707	T	P	P, G, N	Q, H
99	708	F	L	L	I, V
151	759	G	H	H, N	Q
175	783	Q	L	L	I, V
192	802	Q	D	D, E	Q

The replacements are in any form of MTSP-1, including the protease domain (SEQ ID NO: 2 or 4) and the full length (SEQ ID NO: 1 or 3). The replacements can be combined, including as exemplified herein, including up to as many as 15-18 or more replacements.

Example 10***In vivo* Safety, Tolerability, and Toxicity Studies (Cynomolgus Monkey) of MTSP-1 Variants Following Intravitreal Injection**

Safety and tolerability of Modified MTSP-1 polypeptides following intravitreal injection were assessed *in vivo* in cynomolgus monkeys. Three naive cynomolgus monkeys were assigned to each of three treatment groups. Study animals were intravitreally administered either 12.5 µg, 37.5 µg or 125 µg per eye, of each modified MTSP-1 polypeptide. The right eye received the test polypeptide and the left eye was injected with vehicle control. Animals were clinically observed (*i.e.*, food consumption) and ophthalmic examinations were conducted. Ophthalmic examination included slit-lamp biomicroscopy and indirect ophthalmoscope observations, followed

by color fundus photography or optical coherence tomography (OCT) prior to dosing (T=0) and on days 2, 8 and 15 post-dosing. All observations continued for up to 4 weeks or until resolution.

The no-observed-adverse-effect-level (NOAEL) was assessed for all animals.

- 5 The NOAEL for animals administered a modified MTSP-1 polypeptide with the sequence set forth in SEQ ID NO:42 was $\geq 37.5 \mu\text{g}$ (equivalent to $\geq 125 \mu\text{g/eye}$ in man). No adverse effects were noted for animals administered a modified MTSP-1 polypeptide with the sequence set forth in SEQ ID NO:35; therefore, the NOAEL for animals administered a modified MTSP-1 polypeptide set forth in SEQ ID NO:35 was
- 10 $\geq 125 \mu\text{g}$ (equivalent to $\geq 375 \mu\text{g/eye}$ in man).

Example 11

Pharmacodynamic Activity, Safety/Toxicity, and Therapeutic Index Following Intravenous Injection of MTSP-1 Polypeptides

- The NOAEL following intravenous injection was assessed in a cynomolgus
- 15 monkey model. The highest non-toxic dose for cynomolgus monkeys administered a modified MTSP-1 polypeptide set forth in SEQ ID NO:35 was $\geq 4 \text{ mg/kg}$. The ED_{50} for inactivation of circulating C3 was also measured. The C3 activity (*i.e.*, ED_{50} for inactivation of C3) for animals administered a modified MTSP-1 polypeptide set forth in SEQ ID NO:35 was 0.07 mg/kg , which was significantly lower than that of WT
- 20 MTSP-1. The “therapeutic index” (T.I.) of an anti-C3 MTSP-1 variant polypeptide was defined as the ratio of the NOAEL and the ED_{50} for inactivation of C3 *in vivo*. The results are set forth in Table 22, below:

Table 22.				
Chymotrypsin numbering	SEQ ID NO.	C3 destruction ED_{50} (mg/kg)	NOAEL (mg/kg)	Single Bolus T.I.
Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	22	0.2	≥ 0	NA
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D	23	0.2	≥ 4	~20
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192E	24	0.1	≥ 2	~20
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97Y/ins97aN/T98G/F99L/C122S/G151N/Q175L/Q192D	29	0.06	≥ 1	~17
Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D	35	0.07	≥ 4	>57

Example 12

Demonstration that the modified MTSP-1 polypeptides cleave C3 and inhibit complement activation

A. Demonstration of the complement inhibitory effect of an anti-C3 protease (Sequence ID NO:35) in human plasma

1. *In vitro* inhibition of complement activation in human plasma by the MTSP-1 variant polypeptide of Sequence ID NO:35

Studies were performed to assess the anti-complement activity of MTSP-1 polypeptide modified to cleave C3 in human plasma. The test article in these experiments, exemplary of the modified polypeptides described in this application, was the modified MTSP-1 polypeptide of SEQ ID NO:35, which is the protease domain that contains the replacements Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D. The test article (referred to as test article #1, below), and experimental controls were exposed to the test system, pooled citrated plasma.

The extent of complement inhibition was assessed by measuring inhibition of the standard classical pathway hemolytic assay (CH50). The test citrated plasma was exposed to the test article prior to complement analysis. The extent of complement inhibition is the decrease in hemolytic lysis in the CH50 and C3 Function testing compared with that observed with control (*i.e.*, untreated) citrated plasma. The C3 Function testing allows for analysis of the specific inhibition of the C3 component of the complement cascade.

2. Test Systems

Testing was performed with human citrated plasma pool only (NHS, pools of 3-5 normal individuals).

3. Route of Administration

The test article was added to the test system at a ratio of one part to nine parts (1:9, V:V). This ratio maintains appropriate concentration of the test system so there is sufficient concentration of the complement control proteins. The testing was performed by mixing 450 μ L of test system with 50 μ L of prepared test article in a 1.5 mL polypropylene microcentrifuge snap cap tube. The mixture was prepared on ice and then vortexed to mix. After all experimental mixtures (positive and negative

controls and multiple concentrations of test article) were prepared, they were transferred to a $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ water bath and incubated for 1 hour ± 10 minutes. After the mixtures were incubated, if necessary, any particulates were removed by centrifugation, and all samples aliquoted on ice and immediately frozen at -70°C or below.

4. Test Articles Descriptions

Test Article	Storage	Concentration	Other Considerations
Test Article #1	$\leq -65^{\circ}\text{C}$	4 mg/mL 151.6 μM	- 100 μL is provided - Buffer is PBS

5. Control Articles

Positive Control #2	Source	Storage	Concentration	Other Considerations
HAGG (Activator of the Classical Pathway)* 1	Exserra Biolabs	-70°C	10 mg/mL	None

*HAGG -heat activated gamma globulin

Negative Control #1	Source	Storage	Concentration	Other Considerations
Saline	Exserra Biolabs	4°C	0.9% Saline (154 mmol NaCl)	None

6. Control and Test Article Preparation

Five concentrations of test article were used with the highest level at 2000 nM. Lower levels were generated with a five-fold serial dilution.

Dilution Table:

Concentration in test (nM)	10x Concentration (μM)	Amount of Stock to add (μL)	Which stock	Amount of saline	Total Volume (μL)
2000	20	30	151.6	200	230
400	4	40	20	160	200
80	0.8	40	4	160	200
16	0.16	40	0.8	160	200
3.2	0.032	40	0.16	160	200

All dilutions to be made with saline unless otherwise indicated

7. Experimental Design & Data

The testing included five concentrations of test article.

Test or Control Article	Tube Label	Final Concentration (nM unless indicated)
Test Article #1	1-A	2000
	1-B	400
	1-C	80
	1-D	16
	1-E	3.2
Saline	11-S	NA
Neat (no additive)	12-N	NA
Zymosan	13-Z	1 mg/mL
HAGG	14-H	1 mg/mL

8. Results

Test or Control Article	Tube Label	Final Concentration (nM unless indicated)	Data U/mL	% Inhibition
Test Article #1	1-A	2000	5.56	92%
	1-B	400	10.84	84%
	1-C	80	41.45	40%
	1-D	16	68.97	1%
	1-E	3.2	72.98	-5%
Saline	S	NA	69.32	
HAGG	H	1 mg/mL	8.16	

These data demonstrate that an anti-C3 MTSP-1 polypeptide (Sequence ID NO:35) effectivity inhibits complement activity in human plasma with 40 % inhibition observed at a “dose” of 80 nM anti-C3 MTSP-1 variant (Sequence ID NO:35) and near complete inhibition (*i.e.*, 94%) observed at the highest dose of the MTSP-1 polypeptide used in the studies.

B. Demonstration that cleavage at the QHAR/ASHL site inactivates human C3

To confirm that the complement inhibition by Test Article 1 (MTSP-1 polypeptide of Sequence ID NO:35) demonstrated above is mediated by cleavage of C3 at the QHAR/ASHL site, the experiment described below was performed.

1. Experimental Design Summary

The complement function assay was performed with serum deficient of C3 (purchased from Complement Technologies; catalog No. A314). C3 (also purchased from Complement Technologies; catalog No. A113) was added back to the serum with and without pre-incubation with a composition containing the test article #1 (the modified MTPS-1 polypeptide of SEQ ID NO:35). The degree to which the pre-incubation with Test Article #1 inhibits complement function reflects the level of inhibition of C3.

2. Description of Purified C3 Reagent

Normal concentration of C3 in human serum is ~1 mg/mL. The concentration of the C3 from Complement Technologies is 1.1 mg/ml. The C3 was added to the depleted C3 serum at a 1/50 dilution.

3. Test Article Description

Test Article	Storage	Concentration	Other Considerations
Test Article #1	≤ -65°C	4 mg/mL 151.6 µM	- 100 µL is provided - Buffer is PBS

4. Controls

Positive Control #2	Source	Concentration
HAGG (Activator of the Classical Pathway)*	Exsera Biolabs	10 mg/mL

*HAGG -heat activated gamma globulin

Negative Control #1	Source	Concentration
Saline	Exsera Biolabs	0.9% Saline (154 mmol NaCl)

5. Control and Test Article Preparation

5 Dilution Table:

Concentration in test (nM)	10x Concentration (μM)	Amount of Stock to add (μL)	Which stock	Amount of saline	Total Volume (μL)
NT	20	30	151.6	200	230
200	2	20	20	180	200
40	0.4	40	2	160	200
8	0.08	40	0.4	160	200

All dilutions made with saline unless otherwise indicated.

6. Experimental Design: Test Conditions 1 and 2

Test Condition 1:

Components (Tube 1 and Tube 2) were incubated separately for 2 hours at 37°C (±2°C). Tube 1 contained 100 μL C3, and tube 2 contained 25 μL of the test article (TA, MTSP-1 polypeptide or saline). Samples were frozen at -80 °C or below until testing in C3H50 with depleted serum. Each tube was incubated at 37 °C for 2 hours. 90 μL C3 from tube 1 was combined with 10 μL (TA, polypeptide or saline) from tube 2, then mixed and frozen immediately at 80 °C; no prior cleavage of C3 by the TA before addition to C3H50 at 1/50 dilution.

Test Condition 2:

Components were mixed in tube 3 (90 μL C3 and 10 μL TA, light vortex), and incubated for 2 hours (pre-cleavage of C3 at the QHAR site (residues 737-740 of SEQ ID NO:9) at 37°C (±2°C), frozen immediately, and added to C3H50 at 1/50.

Test or Control Article	Tube Label	Purified C3 (Y/N)	Test Conditions	Final Concentration in Test Condition (nM unless indicated)	Expected Outcome
Saline Only	S	N	Test Condition #1	NA	Zero C3H50
Saline	SC	Y	Test Condition #2	NA	Full C3H50
Test Article #1	1-A	Y	Test Condition #1	200	Full C3H50

Test or Control Article	Tube Label	Purified C3 (Y/N)	Test Conditions	Final Concentration in Test Condition (nM unless indicated)	Expected Outcome
Test Article #1	1-B	Y	Test Condition #2	40	or mildly inhibited
	1-C	Y		8	
	2-A	Y		200	Low C3H50 inverse to TA concentration
	2-B	Y		40	
	2-C	Y		8	
Neat	N	N	Test Condition #1	NA	
Zymosan	Z	N	Test Condition #1	1 mg/mL	
HAGG	H	N	Test Condition #1	1 mg/mL	

7. Readout of Complement Activation or Inhibition

Modified C3H50 Hemolytic Function. C3H50 is a measure of the functional activity but with specific emphasis on C3, as it requires the C3 added exogenously.

- 5 The serum was made deficient in C3. The prepared experimental conditions (conditions 1 and 2) are added to the deficient serum at a 1/50 dilution for the testing. The in-test incubation with the red blood cells was performed at 22°C for 45 minutes.

8. Results

- 10 The results show that inhibition of complement activation, as assessed by hemolytic activity, is mediated by cleavage of C3.

Test or Control Article	Tube Label	Purified C3 (Y/N)	Test Conditions*	Final Concentration in Test Condition (nM)	Hemolytic Activity (U/mL)
Saline Only	S	N	Test Condition #1	NA	82.43
Saline	SC	Y	Test Condition #2	NA	375.81
Test Article #1	1-A	Y	Test Condition #1	200	437.77
	1-B	Y		40	594.13
	1-C	Y		8	470.03
Test Article #1	2-A	Y	Test Condition #2	200	73.67
	2-B	Y		40	97.89
	2-C	Y		8	295.35

*Test condition # 1: Incubate components separately for 2 hours at 37°C (±2°C). Then freeze at -80°C or below until testing in C3H50 (C3 hemolytic activity) with depleted serum (*i.e.*, no pre-cleavage of serum C3).

- 15 *Test condition # 2: Mix components together with light vortexing and incubate for 2 hours at 37°C (±2°C) (*i.e.*, pre-cleavage of serum C3 by the MTSP-1 polypeptide (Sequence ID NO:35).

These data demonstrate that preincubation of C3 with the MTSP-1 variant of Sequence ID NO:35 (that cleaves C3 at the QHAR/ASHL site) substantially inhibits complement activation in human serum. A 1 hour preincubation of human serum with

the MTSP-1 variant reduces the hemolytic activity of the serum by approximately 80%.

Example 13

Site Specific Mutagenesis of an Exemplary MTSP-1 Variant to Establish Structure-Activity Relationships for Individual Mutations in MTSP-1

To assess the effect of each replacement, insertion or deletion, site specific mutagenesis was used to create 14 variants of the MTSP-1 variant that contains the modifications

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/

Q175L/Q192D (starting variant). Each of the 14 variants contained a single mutation (compared with the starting variant) in which each single mutated residue in the starting variant (except C122S) was “reverted” (one in each variant) to the corresponding amino acid present in wild type MTSP-1. These variants are shown in Table 23 below with reference to the WT MTSP-1 protease domain set forth in SEQ ID NO: 4. Shaded cells indicate that the modified MTSP-1 polypeptides are mutated at this residue when compared with the reference MTSP-1 polypeptide set forth in SEQ ID NO: 4. Unshaded cells indicate that the modified MTSP-1 polypeptides contain the same amino acid as the reference MTSP-1 polypeptide set forth in SEQ ID NO: 4.

The anti-C3 activity of each selected variant was assessed by measuring the ED₅₀ for C3 cleavage as described above, and the stability of each variant was assessed by measuring the residual enzymatic activity, using the fluorogenic substrate AGR-ACC, after incubation for 7 days in either buffer [Phosphate Buffered Saline (PBS)] or 80% cynomolgus monkey vitreous humor as shown below. These data demonstrate that approximately 50% of the “starting variant” polypeptides exhibit greater activity against C3 in vitreous humor than the reference wild type MTSP-1 protease domain, whose sequence is set forth in SEQ ID NO:4. In addition, 12/14 of the modified MTSP-1 polypeptides are more stable in vitreous humor compared with the reference wild-type protease domain of SEQ ID NO:4, with some showing more stability than others. Therapeutic candidates for ocular indications such as AMD, including those in the table below, are variants that exhibit high C3 cleavage activity and high stability in vitreous humor.

The C3 activity (*i.e.*, ED₅₀) of the modified MTSP-1 polypeptides was measured *in vitro* as described above. The stability of the MTSP-1 polypeptides after incubation for 7 days in either cynomolgus monkey vitreous humor or Phosphate Buffered Saline (PBS) was measured with an activity assay using the fluorogenic substrate AGR-ACC.

Table 23.

	Mutation by Chymotrypsin Numbering															MTSP-1 Polypeptide Stability (% Activity) on Day 7	
SEQ ID NO:	Q38	I41	D60b	F60e	Y60g	D96	F97	Ins 97a	T98	F99	G151	Q175	Q192	hC3 cleavage (ED ₅₀ , nM)	Vitreous	PBS	
4	Q	I	D	F	Y	D	F		T	F	G	Q	Q	13.6	59	63	
35	H	S	T	S	W	K	G	V	P	L	H	L	D	4.6	92	94	
47	Q	S	T	S	W	K	G	V	P	L	H	L	D	17	86	87	
48	H	I	T	S	W	K	G	V	P	L	H	L	D	205	76	78	
49	H	S	D	S	W	K	G	V	P	L	H	L	D	13	87	81	
50	H	S	T	F	W	K	G	V	P	L	H	L	D	8.7	85	91	
51	H	S	T	S	Y	K	G	V	P	L	H	L	D	22	85	93	
38	H	S	T	S	W	D	G	V	P	L	H	L	D	11.9	73	91	
39	H	S	T	S	W	K	F	V	P	L	H	L	D	20	77	85	
52	H	S	T	S	W	K	G		P	L	H	L	D	7.9	19	34	
53	H	S	T	S	W	K	G	V	T	L	H	L	D	9.9	66	82	
54	H	S	T	S	W	K	G	V	P	F	H	L	D	18	94	98	
55	H	S	T	S	W	K	G	V	P	L	G	L	D	5.3	74	87	
56	H	S	T	S	W	K	G	V	P	L	H	Q	D	20	90	94	
40	H	S	T	S	W	K	G	V	P	L	H	L	Q	1.6	18	23	

The data in the examples and above indicate that the modified MTSP-1 polypeptides cleave human C3 efficiently and maintain 59-94% of this activity after incubation for 7 days in vitreous humor.

For example, the modified MTSP-1 polypeptides cleave human C3 between residues 740 and 741 (SEQ ID NO:9) to thereby inactivate C3:

Residue no.
737-744

Q H A R ↓ A S H L
P4 P3 P1 ↓ P1' P4'.

Functional consequences of the modified MTSP-1 polypeptides, such as the modified

5 MTSP-1 polypeptides that contain the mutations:

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,

10 where C122S is included to reduce aggregation (see, *e.g.*, SEQ ID NO:35, which sets forth a protease domain of a modified MTSP-1 polypeptides that contains these mutations) are as follows:

Q38H – This mutation increases C3 activity by approximately 3.7-fold.

I41S – This mutation increases anti-C3 activity by approximately 44.6-fold.

15 D60bT- This mutation increases anti-C3 activity by approximately 2.8-fold.

F60eS - This mutation increases anti-C3 activity by approximately 1.9-fold.

Y60gW - This mutation increases the enzyme's substrate specificity and increases anti-C3 activity by approximately 4.8-fold.

D96K - This mutation increases anti-C3 activity by approximately 2.6-fold.

20 F97G - This mutation increases anti-C3 activity by approximately 4.3-fold and increases substrate specificity.

Insert 97aV: This mutation increases the modified MTSP-1 polypeptide substrate specificity, increases the modified MTSP-1 polypeptides' stability following 1 week incubation at 37 °C by about 4.8-fold, and increases anti-C3 activity by
25 approximately 1.7-fold.

T98P: This mutation increases the enzyme's stability following 1 week incubation at 37 °C by 1.4-fold and increases anti-C3 activity by approximately 2.2-fold.

F99L: This mutation increases anti-C3 activity by approximately 3.9-fold.

30 G151H: This mutation increases anti-C3 activity by approximately 1.2-fold.

Q175L: This mutation increases anti-C3 activity by approximately 4.3-fold.

Q192D: This mutation increases stability in vitreous humor following 1 week incubation at 37 °C by 5.1-fold.

Among the polypeptides, those containing the mutations

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/C122S/G151H/

- 5 Q175L/Q192D and I41D/C122S/G151N/Q192T are for use for treating DGF and/or AMD.

- All residues in the MTSP-1 polypeptides are referenced by chymotrypsin numbering. Unmodified MTSP-1 polypeptides include those of SEQ ID NOs.: 1-4, WT full-length MTSP-1, WT protease domain MTSP-1, WT mature MTSP-1, full-
10 length MTSP-1 with C122S, protease domain MTSP-1 with C122S, mature MTSP-1 with C122S, respectively, where numbering is by chymotrypsin numbering. All modified MTSP-1 polypeptides can include the replacement C122S in place of C122C.

* * *

- 15 Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

WHAT IS CLAIMED:

1. A modified membrane type serine protease 1 (MTSP-1) polypeptide, comprising the amino acid modification Q38H, whereby the modified MTSP-1 polypeptide has increased activity/specificity for a complement protein compared to the unmodified active form of the MTSP-1 polypeptide, wherein:

further 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 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 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 any of claims 1-6, further comprising a modification corresponding to I41S.

8. The modified MTSP-1 polypeptide of any of claims 1-6, further comprising one or more modifications corresponding to I41S, D60bT, F60eS, Y60gW, F97G, ins97aV, D96K, T98P, F99L, G151H, Q175L, or Q192D.

9. The modified MTSP-1 polypeptide of any of claims 1-6, 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.

10. The modified MTSP-1 polypeptide of any of claims 1-6, further comprising
modifications selected from among combinations that include one or more of modifications
I41S, D60bT, F60eS, Y60gW, D96K, F97G, Ins97aV, and G151H as follows:

G151H, Ins97aV, Ins97aV/G151H, F97G, F97G/G151H, F97G/Ins97aV,
F97G/Ins97aV/G151H, D96K, D96K/G151H, D96K/Ins97aV, D96K/Ins97aV/G151H,
D96K/F97G, D96K/F97G/G151H, D96K/F97G/Ins97aV, D96K/F97G/Ins97aV/G151H,
Y60gW, Y60gW/G151H, Y60gW/Ins97aV, Y60gW/Ins97aV/G151H, Y60gW/F97G,
Y60gW/F97G/G151H, Y60gW/F97G/Ins97aV, Y60gW/F97G/Ins97aV/G151H,
Y60gW/D96K, Y60gW/D96K/G151H, Y60gW/D96K/Ins97aV,
Y60gW/D96K/Ins97aV/G151H, Y60gW/D96K/F97G, Y60gW/D96K/F97G/G151H,

Y60gW/D96K/F97G/Ins97aV, Y60gW/D96K/F97G/Ins97aV/G151H, F60eS, F60eS/G151H,
 F60eS/Ins97aV, F60eS/Ins97aV/G151H, F60eS/F97G, F60eS/F97G/G151H,
 F60eS/F97G/Ins97aV, F60eS/F97G/Ins97aV/G151H, F60eS/D96K, F60eS/D96K/G151H,
 F60eS/D96K/Ins97aV, F60eS/D96K/Ins97aV/G151H, F60eS/D96K/F97G,
 F60eS/D96K/F97G/G151H, F60eS/D96K/F97G/Ins97aV,
 F60eS/D96K/F97G/Ins97aV/G151H, F60eS/Y60gW, F60eS/Y60gW/G151H,
 F60eS/Y60gW/Ins97aV, F60eS/Y60gW/Ins97aV/G151H, F60eS/Y60gW/F97G,
 F60eS/Y60gW/F97G/G151H, F60eS/Y60gW/F97G/Ins97aV,
 F60eS/Y60gW/F97G/Ins97aV/G151H, F60eS/Y60gW/D96K, F60eS/Y60gW/D96K/G151H,
 F60eS/Y60gW/D96K/Ins97aV, F60eS/Y60gW/D96K/Ins97aV/G151H,
 F60eS/Y60gW/D96K/F97G, F60eS/Y60gW/D96K/F97G/G151H,
 F60eS/Y60gW/D96K/F97G/Ins97aV, F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, D60bT,
 D60bT/G151H, D60bT/Ins97aV, D60bT/Ins97aV/G151H, D60bT/F97G,
 D60bT/F97G/G151H, D60bT/F97G/Ins97aV, D60bT/F97G/Ins97aV/G151H, D60bT/D96K,
 D60bT/D96K/G151H, D60bT/D96K/Ins97aV, D60bT/D96K/Ins97aV/G151H,
 D60bT/D96K/F97G, D60bT/D96K/F97G/G151H, D60bT/D96K/F97G/Ins97aV,
 D60bT/D96K/F97G/Ins97aV/G151H, D60bT/Y60gW, D60bT/Y60gW/G151H,
 D60bT/Y60gW/Ins97aV, D60bT/Y60gW/Ins97aV/G151H, D60bT/Y60gW/F97G,
 D60bT/Y60gW/F97G/G151H, D60bT/Y60gW/F97G/Ins97aV,
 D60bT/Y60gW/F97G/Ins97aV/G151H, D60bT/Y60gW/D96K,
 D60bT/Y60gW/D96K/G151H, D60bT/Y60gW/D96K/Ins97aV,
 D60bT/Y60gW/D96K/Ins97aV/G151H, D60bT/Y60gW/D96K/F97G,
 D60bT/Y60gW/D96K/F97G/G151H, D60bT/Y60gW/D96K/F97G/Ins97aV,
 D60bT/Y60gW/D96K/F97G/Ins97aV/G151H, D60bT/F60eS, D60bT/F60eS/G151H,
 D60bT/F60eS/Ins97aV, D60bT/F60eS/Ins97aV/G151H, D60bT/F60eS/F97G,
 D60bT/F60eS/F97G/G151H, D60bT/F60eS/F97G/Ins97aV,
 D60bT/F60eS/F97G/Ins97aV/G151H, D60bT/F60eS/D96K, D60bT/F60eS/D96K/G151H,
 D60bT/F60eS/D96K/Ins97aV, D60bT/F60eS/D96K/Ins97aV/G151H,
 D60bT/F60eS/D96K/F97G, D60bT/F60eS/D96K/F97G/G151H,
 D60bT/F60eS/D96K/F97G/Ins97aV, D60bT/F60eS/D96K/F97G/Ins97aV/G151H,
 D60bT/F60eS/Y60gW, D60bT/F60eS/Y60gW/G151H, D60bT/F60eS/Y60gW/Ins97aV,
 D60bT/F60eS/Y60gW/Ins97aV/G151H, D60bT/F60eS/Y60gW/F97G,
 D60bT/F60eS/Y60gW/F97G/G151H, D60bT/F60eS/Y60gW/F97G/Ins97aV,

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D60bT/F60eS/Y60gW/F97G/Ins97aV/G151H, D60bT/F60eS/Y60gW/D96K,
 D60bT/F60eS/Y60gW/D96K/G151H, D60bT/F60eS/Y60gW/D96K/Ins97aV,
 D60bT/F60eS/Y60gW/D96K/Ins97aV/G151H, D60bT/F60eS/Y60gW/D96K/F97G,
 D60bT/F60eS/Y60gW/D96K/F97G/G151H, D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV,
 D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, I41S, I41S/G151H, I41S/Ins97aV,
 I41S/Ins97aV/G151H, I41S/F97G, I41S/F97G/G151H, I41S/F97G/Ins97aV,
 I41S/F97G/Ins97aV/G151H, I41S/D96K, I41S/D96K/G151H, I41S/D96K/Ins97aV,
 I41S/D96K/Ins97aV/G151H, I41S/D96K/F97G, I41S/D96K/F97G/G151H,
 I41S/D96K/F97G/Ins97aV, I41S/D96K/F97G/Ins97aV/G151H, I41S/Y60gW,
 I41S/Y60gW/G151H, I41S/Y60gW/Ins97aV, I41S/Y60gW/Ins97aV/G151H,
 I41S/Y60gW/F97G, I41S/Y60gW/F97G/G151H, I41S/Y60gW/F97G/Ins97aV,
 I41S/Y60gW/F97G/Ins97aV/G151H, I41S/Y60gW/D96K, I41S/Y60gW/D96K/G151H,
 I41S/Y60gW/D96K/Ins97aV, I41S/Y60gW/D96K/Ins97aV/G151H,
 I41S/Y60gW/D96K/F97G, I41S/Y60gW/D96K/F97G/G151H,
 I41S/Y60gW/D96K/F97G/Ins97aV, I41S/Y60gW/D96K/F97G/Ins97aV/G151H,
 I41S/F60eS, I41S/F60eS/G151H, I41S/F60eS/Ins97aV, I41S/F60eS/Ins97aV/G151H,
 I41S/F60eS/F97G, I41S/F60eS/F97G/G151H, I41S/F60eS/F97G/Ins97aV,
 I41S/F60eS/F97G/Ins97aV/G151H, I41S/F60eS/D96K, I41S/F60eS/D96K/G151H,
 I41S/F60eS/D96K/Ins97aV, I41S/F60eS/D96K/Ins97aV/G151H, I41S/F60eS/D96K/F97G,
 I41S/F60eS/D96K/F97G/G151H, I41S/F60eS/D96K/F97G/Ins97aV,
 I41S/F60eS/D96K/F97G/Ins97aV/G151H, I41S/F60eS/Y60gW,
 I41S/F60eS/Y60gW/G151H, I41S/F60eS/Y60gW/Ins97aV,
 I41S/F60eS/Y60gW/Ins97aV/G151H, I41S/F60eS/Y60gW/F97G,
 I41S/F60eS/Y60gW/F97G/G151H, I41S/F60eS/Y60gW/F97G/Ins97aV,
 I41S/F60eS/Y60gW/F97G/Ins97aV/G151H, I41S/F60eS/Y60gW/D96K,
 I41S/F60eS/Y60gW/D96K/G151H, I41S/F60eS/Y60gW/D96K/Ins97aV,
 I41S/F60eS/Y60gW/D96K/Ins97aV/G151H, I41S/F60eS/Y60gW/D96K/F97G,
 I41S/F60eS/Y60gW/D96K/F97G/G151H, I41S/F60eS/Y60gW/D96K/F97G/Ins97aV,
 I41S/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, I41S/D60bT, I41S/D60bT/G151H,
 I41S/D60bT/Ins97aV, I41S/D60bT/Ins97aV/G151H, I41S/D60bT/F97G,
 I41S/D60bT/F97G/G151H, I41S/D60bT/F97G/Ins97aV,
 I41S/D60bT/F97G/Ins97aV/G151H, I41S/D60bT/D96K, I41S/D60bT/D96K/G151H,
 I41S/D60bT/D96K/Ins97aV, I41S/D60bT/D96K/Ins97aV/G151H, I41S/D60bT/D96K/F97G,

I41S/D60bT/D96K/F97G/G151H, I41S/D60bT/D96K/F97G/Ins97aV,
 I41S/D60bT/D96K/F97G/Ins97aV/G151H, I41S/D60bT/Y60gW,
 I41S/D60bT/Y60gW/G151H, I41S/D60bT/Y60gW/Ins97aV,
 I41S/D60bT/Y60gW/Ins97aV/G151H, I41S/D60bT/Y60gW/F97G,
 I41S/D60bT/Y60gW/F97G/G151H, I41S/D60bT/Y60gW/F97G/Ins97aV,
 I41S/D60bT/Y60gW/F97G/Ins97aV/G151H, I41S/D60bT/Y60gW/D96K,
 I41S/D60bT/Y60gW/D96K/G151H, I41S/D60bT/Y60gW/D96K/Ins97aV,
 I41S/D60bT/Y60gW/D96K/Ins97aV/G151H, I41S/D60bT/Y60gW/D96K/F97G,
 I41S/D60bT/Y60gW/D96K/F97G/G151H, I41S/D60bT/Y60gW/D96K/F97G/Ins97aV,
 I41S/D60bT/Y60gW/D96K/F97G/Ins97aV/G151H, I41S/D60bT/F60eS,
 I41S/D60bT/F60eS/G151H, I41S/D60bT/F60eS/Ins97aV,
 I41S/D60bT/F60eS/Ins97aV/G151H, I41S/D60bT/F60eS/F97G,
 I41S/D60bT/F60eS/F97G/G151H, I41S/D60bT/F60eS/F97G/Ins97aV,
 I41S/D60bT/F60eS/F97G/Ins97aV/G151H, I41S/D60bT/F60eS/D96K,
 I41S/D60bT/F60eS/D96K/G151H, I41S/D60bT/F60eS/D96K/Ins97aV,
 I41S/D60bT/F60eS/D96K/Ins97aV/G151H, I41S/D60bT/F60eS/D96K/F97G,
 I41S/D60bT/F60eS/D96K/F97G/G151H, I41S/D60bT/F60eS/D96K/F97G/Ins97aV,
 I41S/D60bT/F60eS/D96K/F97G/Ins97aV/G151H, I41S/D60bT/F60eS/Y60gW,
 I41S/D60bT/F60eS/Y60gW/G151H, I41S/D60bT/F60eS/Y60gW/Ins97aV,
 I41S/D60bT/F60eS/Y60gW/Ins97aV/G151H, I41S/D60bT/F60eS/Y60gW/F97G,
 I41S/D60bT/F60eS/Y60gW/F97G/G151H, I41S/D60bT/F60eS/Y60gW/F97G/Ins97aV,
 I41S/D60bT/F60eS/Y60gW/F97G/Ins97aV/G151H, I41S/D60bT/F60eS/Y60gW/D96K,
 I41S/D60bT/F60eS/Y60gW/D96K/G151H, I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV,
 I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV/G151H,
 I41S/D60bT/F60eS/Y60gW/D96K/F97G, I41S/D60bT/F60eS/Y60gW/D96K/F97G/G151H,
 I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV,
 I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, and the same modifications
 except C122S is not modified and is C122C.

11. The modified MTSP-1 polypeptide of any of claims 1-6, comprising the modifications selected from among:

Q38H/G151H, Q38H/Ins97aV, Q38H/Ins97aV/G151H, Q38H/F97G, Q38H/F97G/G151H,
 Q38H/F97G/Ins97aV, Q38H/F97G/Ins97aV/G151H, Q38H/D96K, Q38H/D96K/G151H,
 Q38H/D96K/Ins97aV, Q38H/D96K/Ins97aV/G151H, Q38H/D96K/F97G,

Q38H/D96K/F97G/G151H, Q38H/D96K/F97G/Ins97aV,
Q38H/D96K/F97G/Ins97aV/G151H, Q38H/Y60gW, Q38H/Y60gW/G151H,
Q38H/Y60gW/Ins97aV, Q38H/Y60gW/Ins97aV/G151H, Q38H/Y60gW/F97G,
Q38H/Y60gW/F97G/G151H, Q38H/Y60gW/F97G/Ins97aV,
Q38H/Y60gW/F97G/Ins97aV/G151H, Q38H/Y60gW/D96K, Q38H/Y60gW/D96K/G151H,
Q38H/Y60gW/D96K/Ins97aV, Q38H/Y60gW/D96K/Ins97aV/G151H,
Q38H/Y60gW/D96K/F97G, Q38H/Y60gW/D96K/F97G/G151H,
Q38H/Y60gW/D96K/F97G/Ins97aV, Q38H/Y60gW/D96K/F97G/Ins97aV/G151H,
Q38H/F60eS, Q38H/F60eS/G151H, Q38H/F60eS/Ins97aV, Q38H/F60eS/Ins97aV/G151H,
Q38H/F60eS/F97G, Q38H/F60eS/F97G/G151H, Q38H/F60eS/F97G/Ins97aV,
Q38H/F60eS/F97G/Ins97aV/G151H, Q38H/F60eS/D96K, Q38H/F60eS/D96K/G151H,
Q38H/F60eS/D96K/Ins97aV, Q38H/F60eS/D96K/Ins97aV/G151H,
Q38H/F60eS/D96K/F97G, Q38H/F60eS/D96K/F97G/G151H,
Q38H/F60eS/D96K/F97G/Ins97aV, Q38H/F60eS/D96K/F97G/Ins97aV/G151H,
Q38H/F60eS/Y60gW, Q38H/F60eS/Y60gW/G151H, Q38H/F60eS/Y60gW/Ins97aV,
Q38H/F60eS/Y60gW/Ins97aV/G151H, Q38H/F60eS/Y60gW/F97G,
Q38H/F60eS/Y60gW/F97G/G151H, Q38H/F60eS/Y60gW/F97G/Ins97aV,
Q38H/F60eS/Y60gW/F97G/Ins97aV/G151H, Q38H/F60eS/Y60gW/D96K,
Q38H/F60eS/Y60gW/D96K/G151H, Q38H/F60eS/Y60gW/D96K/Ins97aV,
Q38H/F60eS/Y60gW/D96K/Ins97aV/G151H, Q38H/F60eS/Y60gW/D96K/F97G,
Q38H/F60eS/Y60gW/D96K/F97G/G151H, Q38H/F60eS/Y60gW/D96K/F97G/Ins97aV,
Q38H/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/D60bT, Q38H/D60bT/G151H,
Q38H/D60bT/Ins97aV, Q38H/D60bT/Ins97aV/G151H, Q38H/D60bT/F97G,
Q38H/D60bT/F97G/G151H, Q38H/D60bT/F97G/Ins97aV,
Q38H/D60bT/F97G/Ins97aV/G151H, Q38H/D60bT/D96K, Q38H/D60bT/D96K/G151H,
Q38H/D60bT/D96K/Ins97aV, Q38H/D60bT/D96K/Ins97aV/G151H,
Q38H/D60bT/D96K/F97G, Q38H/D60bT/D96K/F97G/G151H,
Q38H/D60bT/D96K/F97G/Ins97aV, Q38H/D60bT/D96K/F97G/Ins97aV/G151H,
Q38H/D60bT/Y60gW, Q38H/D60bT/Y60gW/G151H, Q38H/D60bT/Y60gW/Ins97aV,
Q38H/D60bT/Y60gW/Ins97aV/G151H, Q38H/D60bT/Y60gW/F97G,
Q38H/D60bT/Y60gW/F97G/G151H, Q38H/D60bT/Y60gW/F97G/Ins97aV,
Q38H/D60bT/Y60gW/F97G/Ins97aV/G151H, Q38H/D60bT/Y60gW/D96K,
Q38H/D60bT/Y60gW/D96K/G151H, Q38H/D60bT/Y60gW/D96K/Ins97aV,

Q38H/D60bT/Y60gW/D96K/Ins97aV/G151H, Q38H/D60bT/Y60gW/D96K/F97G,
Q38H/D60bT/Y60gW/D96K/F97G/G151H, Q38H/D60bT/Y60gW/D96K/F97G/Ins97aV,
Q38H/D60bT/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/D60bT/F60eS,
Q38H/D60bT/F60eS/G151H, Q38H/D60bT/F60eS/Ins97aV,
Q38H/D60bT/F60eS/Ins97aV/G151H, Q38H/D60bT/F60eS/F97G,
Q38H/D60bT/F60eS/F97G/G151H, Q38H/D60bT/F60eS/F97G/Ins97aV,
Q38H/D60bT/F60eS/F97G/Ins97aV/G151H, Q38H/D60bT/F60eS/D96K,
Q38H/D60bT/F60eS/D96K/G151H, Q38H/D60bT/F60eS/D96K/Ins97aV,
Q38H/D60bT/F60eS/D96K/Ins97aV/G151H, Q38H/D60bT/F60eS/D96K/F97G,
Q38H/D60bT/F60eS/D96K/F97G/G151H, Q38H/D60bT/F60eS/D96K/F97G/Ins97aV,
Q38H/D60bT/F60eS/D96K/F97G/Ins97aV/G151H, Q38H/D60bT/F60eS/Y60gW,
Q38H/D60bT/F60eS/Y60gW/G151H, Q38H/D60bT/F60eS/Y60gW/Ins97aV,
Q38H/D60bT/F60eS/Y60gW/Ins97aV/G151H, Q38H/D60bT/F60eS/Y60gW/F97G,
Q38H/D60bT/F60eS/Y60gW/F97G/G151H, Q38H/D60bT/F60eS/Y60gW/F97G/Ins97aV,
Q38H/D60bT/F60eS/Y60gW/F97G/Ins97aV/G151H, Q38H/D60bT/F60eS/Y60gW/D96K,
Q38H/D60bT/F60eS/Y60gW/D96K/G151H, Q38H/D60bT/F60eS/Y60gW/D96K/Ins97aV,
Q38H/D60bT/F60eS/Y60gW/D96K/Ins97aV/G151H,
Q38H/D60bT/F60eS/Y60gW/D96K/F97G,
Q38H/D60bT/F60eS/Y60gW/D96K/F97G/G151H,
Q38H/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV,
Q38H/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/I41S,
Q38H/I41S/G151H, Q38H/I41S/Ins97aV, Q38H/I41S/Ins97aV/G151H, Q38H/I41S/F97G,
Q38H/I41S/F97G/G151H, Q38H/I41S/F97G/Ins97aV, Q38H/I41S/F97G/Ins97aV/G151H,
Q38H/I41S/D96K, Q38H/I41S/D96K/G151H, Q38H/I41S/D96K/Ins97aV,
Q38H/I41S/D96K/Ins97aV/G151H, Q38H/I41S/D96K/F97G,
Q38H/I41S/D96K/F97G/G151H, Q38H/I41S/D96K/F97G/Ins97aV,
Q38H/I41S/D96K/F97G/Ins97aV/G151H, Q38H/I41S/Y60gW, Q38H/I41S/Y60gW/G151H,
Q38H/I41S/Y60gW/Ins97aV, Q38H/I41S/Y60gW/Ins97aV/G151H,
Q38H/I41S/Y60gW/F97G, Q38H/I41S/Y60gW/F97G/G151H,
Q38H/I41S/Y60gW/F97G/Ins97aV, Q38H/I41S/Y60gW/F97G/Ins97aV/G151H,
Q38H/I41S/Y60gW/D96K, Q38H/I41S/Y60gW/D96K/G151H,
Q38H/I41S/Y60gW/D96K/Ins97aV, Q38H/I41S/Y60gW/D96K/Ins97aV/G151H,
Q38H/I41S/Y60gW/D96K/F97G, Q38H/I41S/Y60gW/D96K/F97G/G151H,

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Q38H/I41S/Y60gW/D96K/F97G/Ins97aV,
 Q38H/I41S/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/I41S/F60eS,
 Q38H/I41S/F60eS/G151H, Q38H/I41S/F60eS/Ins97aV, Q38H/I41S/F60eS/Ins97aV/G151H,
 Q38H/I41S/F60eS/F97G, Q38H/I41S/F60eS/F97G/G151H,
 Q38H/I41S/F60eS/F97G/Ins97aV, Q38H/I41S/F60eS/F97G/Ins97aV/G151H,
 Q38H/I41S/F60eS/D96K, Q38H/I41S/F60eS/D96K/G151H,
 Q38H/I41S/F60eS/D96K/Ins97aV, Q38H/I41S/F60eS/D96K/Ins97aV/G151H,
 Q38H/I41S/F60eS/D96K/F97G, Q38H/I41S/F60eS/D96K/F97G/G151H,
 Q38H/I41S/F60eS/D96K/F97G/Ins97aV, Q38H/I41S/F60eS/D96K/F97G/Ins97aV/G151H,
 Q38H/I41S/F60eS/Y60gW, Q38H/I41S/F60eS/Y60gW/G151H,
 Q38H/I41S/F60eS/Y60gW/Ins97aV, Q38H/I41S/F60eS/Y60gW/Ins97aV/G151H,
 Q38H/I41S/F60eS/Y60gW/F97G, Q38H/I41S/F60eS/Y60gW/F97G/G151H,
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 Q38H/I41S/F60eS/Y60gW/F97G/Ins97aV/G151H, Q38H/I41S/F60eS/Y60gW/D96K,
 Q38H/I41S/F60eS/Y60gW/D96K/G151H, Q38H/I41S/F60eS/Y60gW/D96K/Ins97aV,
 Q38H/I41S/F60eS/Y60gW/D96K/Ins97aV/G151H, Q38H/I41S/F60eS/Y60gW/D96K/F97G,
 Q38H/I41S/F60eS/Y60gW/D96K/F97G/G151H,
 Q38H/I41S/F60eS/Y60gW/D96K/F97G/Ins97aV,
 Q38H/I41S/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/I41S/D60bT,
 Q38H/I41S/D60bT/G151H, Q38H/I41S/D60bT/Ins97aV,
 Q38H/I41S/D60bT/Ins97aV/G151H, Q38H/I41S/D60bT/F97G,
 Q38H/I41S/D60bT/F97G/G151H, Q38H/I41S/D60bT/F97G/Ins97aV,
 Q38H/I41S/D60bT/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/D96K,
 Q38H/I41S/D60bT/D96K/G151H, Q38H/I41S/D60bT/D96K/Ins97aV,
 Q38H/I41S/D60bT/D96K/Ins97aV/G151H, Q38H/I41S/D60bT/D96K/F97G,
 Q38H/I41S/D60bT/D96K/F97G/G151H, Q38H/I41S/D60bT/D96K/F97G/Ins97aV,
 Q38H/I41S/D60bT/D96K/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/Y60gW,
 Q38H/I41S/D60bT/Y60gW/G151H, Q38H/I41S/D60bT/Y60gW/Ins97aV,
 Q38H/I41S/D60bT/Y60gW/Ins97aV/G151H, Q38H/I41S/D60bT/Y60gW/F97G,
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 Q38H/I41S/D60bT/Y60gW/D96K/G151H, Q38H/I41S/D60bT/Y60gW/D96K/Ins97aV,
 Q38H/I41S/D60bT/Y60gW/D96K/Ins97aV/G151H,

Q38H/I41S/D60bT/Y60gW/D96K/F97G, Q38H/I41S/D60bT/Y60gW/D96K/F97G/G151H, Q38H/I41S/D60bT/Y60gW/D96K/F97G/Ins97aV, Q38H/I41S/D60bT/Y60gW/D96K/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS, Q38H/I41S/D60bT/F60eS/G151H, Q38H/I41S/D60bT/F60eS/Ins97aV, Q38H/I41S/D60bT/F60eS/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS/F97G, Q38H/I41S/D60bT/F60eS/F97G/G151H, Q38H/I41S/D60bT/F60eS/F97G/Ins97aV, Q38H/I41S/D60bT/F60eS/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS/D96K, Q38H/I41S/D60bT/F60eS/D96K/G151H, Q38H/I41S/D60bT/F60eS/D96K/Ins97aV, Q38H/I41S/D60bT/F60eS/D96K/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS/D96K/F97G, Q38H/I41S/D60bT/F60eS/D96K/F97G/G151H, Q38H/I41S/D60bT/F60eS/D96K/F97G/Ins97aV, Q38H/I41S/D60bT/F60eS/D96K/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS/Y60gW, Q38H/I41S/D60bT/F60eS/Y60gW/G151H, Q38H/I41S/D60bT/F60eS/Y60gW/Ins97aV, Q38H/I41S/D60bT/F60eS/Y60gW/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS/Y60gW/F97G, Q38H/I41S/D60bT/F60eS/Y60gW/F97G/G151H, Q38H/I41S/D60bT/F60eS/Y60gW/F97G/Ins97aV, Q38H/I41S/D60bT/F60eS/Y60gW/F97G/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS/Y60gW/D96K, Q38H/I41S/D60bT/F60eS/Y60gW/D96K/G151H, Q38H/I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV, Q38H/I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV/G151H, Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G, Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/G151H, Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV, Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/G151H, and the same modifications except C122S is not modified and is C122C.

12. The modified MTSP-1 polypeptide of any of claims 1-6, further comprising modifications selected from among combinations that include T98P/F99L/Q175L/Q192D, optionally C122S, and one or more modifications selected from among: I41S, D60bT, F60eS, Y60gW, D96K, F97G, Ins97aV and G151H.

13. The modified MTSP-1 polypeptide of any of claims 1-6, further comprising modifications selected from among:

T98P/F99L/C122S/G151H/Q175L/Q192D, Ins97aV/T98P/F99L/C122S/Q175L/Q192D, Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,

F97G/T98P/F99L/C122S/Q175L/Q192D, F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D96K/T98P/F99L/C122S/Q175L/Q192D, D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/T98P/F99L/C122S/Q175L/Q192D, F60eS/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/F97G/T98P/F99L/C122S/Q175L/Q192D,
F60eS/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,

F60eS/D96K/T98P/F99L/C122S/Q175L/Q192D,
F60eS/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
F60eS/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/T98P/F99L/C122S/Q175L/Q192D,
D60bT/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/D96K/T98P/F99L/C122S/Q175L/Q192D,

D60bT/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
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D60bT/F60eS/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/D96K/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,

D60bT/F60eS/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/T98P/F99L/C122S/Q175L/Q192D, I41S/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,

I41S/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,

I41S/F60eS/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,

I41S/D60bT/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F60eS/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F60eS/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F60eS/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F60eS/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F60eS/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F60eS/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F60eS/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F60eS/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F60eS/D96K/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F60eS/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F60eS/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F60eS/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F60eS/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
I41S/D60bT/F60eS/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
I41S/D60bT/F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,

I41S/D60bT/F60eS/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
 I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D, and
 the same modifications except C122S is not modified and is C122C.

14. The modified MTSP-1 polypeptide of any of claims 1-6, comprising the modifications selected from among:

Q38H/T98P/F99L/C122S/Q175L/Q192D,
 Q38H/T98P/F99L/C122S/G151H/Q175L/Q192D,
 Q38H/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
 Q38H/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 Q38H/F97G/T98P/F99L/C122S/Q175L/Q192D,
 Q38H/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
 Q38H/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
 Q38H/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 Q38H/D96K/T98P/F99L/C122S/Q175L/Q192D,
 Q38H/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
 Q38H/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
 Q38H/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 Q38H/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,

Q38H/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Q38H/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/Y60gW/T98P/F99L/C122S/Q175L/Q192D,
Q38H/Y60gW/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/Y60gW/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Q38H/Y60gW/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/Y60gW/F97G/T98P/F99L/C122S/Q175L/Q192D,
Q38H/Y60gW/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Q38H/Y60gW/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/Y60gW/D96K/T98P/F99L/C122S/Q175L/Q192D,
Q38H/Y60gW/D96K/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Q38H/Y60gW/D96K/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/Y60gW/D96K/F97G/T98P/F99L/C122S/Q175L/Q192D,
Q38H/Y60gW/D96K/F97G/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Q38H/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/F60eS/T98P/F99L/C122S/Q175L/Q192D,
Q38H/F60eS/T98P/F99L/C122S/G151H/Q175L/Q192D,
Q38H/F60eS/Ins97aV/T98P/F99L/C122S/Q175L/Q192D,
Q38H/F60eS/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
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 Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/Ins97aV/T98P/F99L/C122S/G151H/Q175L/Q192D,
 and the same modifications except C122S is not modified and is C122C.

15. The modified MTSP-1 polypeptide of any of claims 1-6, 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 comprises the protease domain of SEQ ID
 NO:2 or SEQ ID NO:4.

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 any of SEQ ID NOs: 6, 8, 21-59, 63-81, 289, 294, 295, 301, 306-317, 320, 322, 328, 329, 337, 330, 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.

17. 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:35.

18. 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:35, except that the residue at position 122, by chymotrypsin numbering, is cysteine (C).

19. The modified MTSP-1 polypeptide of any of claims 1-18, wherein the unmodified MTSP-1 polypeptide consists of the sequence of amino acid residues set forth in SEQ ID NO:2 or 4.

20. The modified MTSP-1 polypeptide of any of claims 1-19 that is modified by a polymer to increase serum half-life or to reduce immunogenicity or both.

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

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

23. The modified MTSP-1 polypeptide of any of claims 20-22, comprising a PEG that has a molecular weight from about 3 kD to about 50 kD.

24. The modified MTSP-1 polypeptide of claim 23, comprising a PEG that has a molecular weight of 40 kD.

25. The modified MTSP-1 polypeptide of any of claims 20-24, comprising a branched PEG.

26. The modified MTSP-1 polypeptide of any of claims 21-25, wherein the PEG is linked via a cysteine residue in the modified MTSP-1 polypeptide.

27. The modified MTSP-1 polypeptide of any of claims 20-26, comprising a PEG-maleimide linked via a cysteine residue in the modified MTSP-1 polypeptide.

28. 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.

29. The modified MTSP-1 polypeptide of claim 28, wherein the PEG is a branched PEG.

30. The modified MTSP-1 polypeptide of claim 28 or claim 29, wherein the PEG is a PEG-maleimide.

31. The modified MTSP-1 polypeptide of any of claims 28-30, wherein the PEG has a molecular weight from about 3 kDa to about 50 kDa.

32. The modified MTSP-1 polypeptide of any of claims 28-31 that is a mature MTSP-1 polypeptide.

33. A fusion protein, comprising a modified MTSP-1 polypeptide or a catalytically active portion of a modified MTSP-1 polypeptide of any of claims 1-32 that is linked to a multimerization domain or a protein transduction domain (PTD).

34. The fusion protein of claim 33, wherein the polypeptide is linked to a multimerization domain that is an Fc domain.

35. A nucleic acid molecule, comprising a sequence of nucleotides encoding a modified MTSP-1 polypeptide of any of claims 1-32 or a fusion protein of claim 33 or claim 34.

36. A vector, comprising the nucleic acid molecule of claim 35.

37. The vector of claim 36 that is a eukaryotic vector.

38. The vector of claim 36 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.

39. An isolated cell or a cell culture, comprising the nucleic acid molecule of claim 35 or the vector of any of claims 36-38, wherein the isolated cell is not a human zygote.

40. A method of treating a disease or condition mediated by or involving complement activation, comprising administering the modified MTSP-1 polypeptide of any of claims 1-32, or a fusion protein of claim 33 or claim 34, or a nucleic acid molecule of claim 35, or a vector of any of claims 36-38, wherein inhibition of complement activation effects treatment or amelioration of the disease or condition.

41. The method of claim 40, 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.

42. The method of claim 40, wherein the disease or condition is an ocular disease or is rejection or inflammation due to a transplanted organ.

43. The method of claim 42, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.
44. The method of claim 43, wherein the disease or condition is a macular degeneration.
45. The method of claim 44, wherein the macular degeneration is age-related macular degeneration (AMD).
46. The method of any of claims 40-45, wherein:
the disease or condition is an ophthalmic disorder or ocular disorder; and
the modified MTSP-1 polypeptide is administered to the eye.
47. The method of claim 46, wherein the disorder is macular degeneration or diabetic retinopathy.
48. The method of claim 47, wherein the disorder is age-related macular degeneration (AMD).
49. The method of claim 40 and claim 42, wherein the disease or condition is delayed renal graft function (DGF).
50. The method of any of claims 40-49, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:35, or the sequence of amino acids set forth in SEQ ID NO:35 except that the residue at position 122 is cysteine (C).
51. The method of any of claims 40-50, wherein the modified MTSP-1 polypeptide comprises the modifications
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.
52. The method of any of claims 40-51, wherein the modified MTSP-1 polypeptide is PEGylated.
53. The modified MTSP-1 polypeptide of any of claims 1-32, or the fusion protein of claim 33 or claim 34, or the nucleic acid molecule of claim 35, or the vector of any of claims 36-38, for use for treatment of a disease or condition mediated by or involving

complement activation, wherein inhibition of complement activation effects treatment or amelioration of the disease or condition.

54. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of claim 53, 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.

55. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of claim 53, wherein the disease or condition is an ocular disease or is rejection or inflammation due to a transplanted organ.

56. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of claim 53, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.

57. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of claim 56, wherein the disease or condition is a macular degeneration.

58. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of claim 57, wherein the macular degeneration is age-related macular degeneration (AMD).

59. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of claim 53, wherein the disease or condition is delayed renal graft function (DGF).

60. The modified MTSP-1 polypeptide of any of claims 1-32, or a fusion protein of claim 33 or claim 34, wherein the modified MTSP-1 polypeptide is PEGylated.

61. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of any of claims 53-60, wherein the modified MTSP-1 polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:35 or the polypeptide that comprises the sequence of amino acid residues set forth in SEQ ID NO:35 except that the residue at position 122 is cysteine (C).

62. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of any of claims 53-61, 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.

63. The modified MTSP-1 polypeptide, fusion protein, nucleic acid, or vector of any of claims 53-62, wherein the modified MTSP-1 polypeptide is PEGylated.

64. A method of making a modified MTSP-1 polypeptide or fusion protein, comprising:

introducing a nucleic acid or vector encoding the modified MTSP-1 polypeptide of any of claims 1-32 or the fusion protein of claim 33 or claim 34 into a cell;

culturing the cell under conditions, whereby the polypeptide is expressed; and

isolating the expressed polypeptide.

65. The method of claim 64, wherein nucleic acid encoding the modified MTSP-1 polypeptide is operatively linked to a nucleic acid encoding a Small Ubiquitin-like Modifier (SUMO) tag.

66. A pharmaceutical composition, comprising the modified MTSP-1 polypeptide of any of claims 1-32, or the fusion protein of claim 33 or claim 34, or the nucleic acid of claim 35, or the vector of any of claims 36-38, in a pharmaceutically acceptable vehicle.

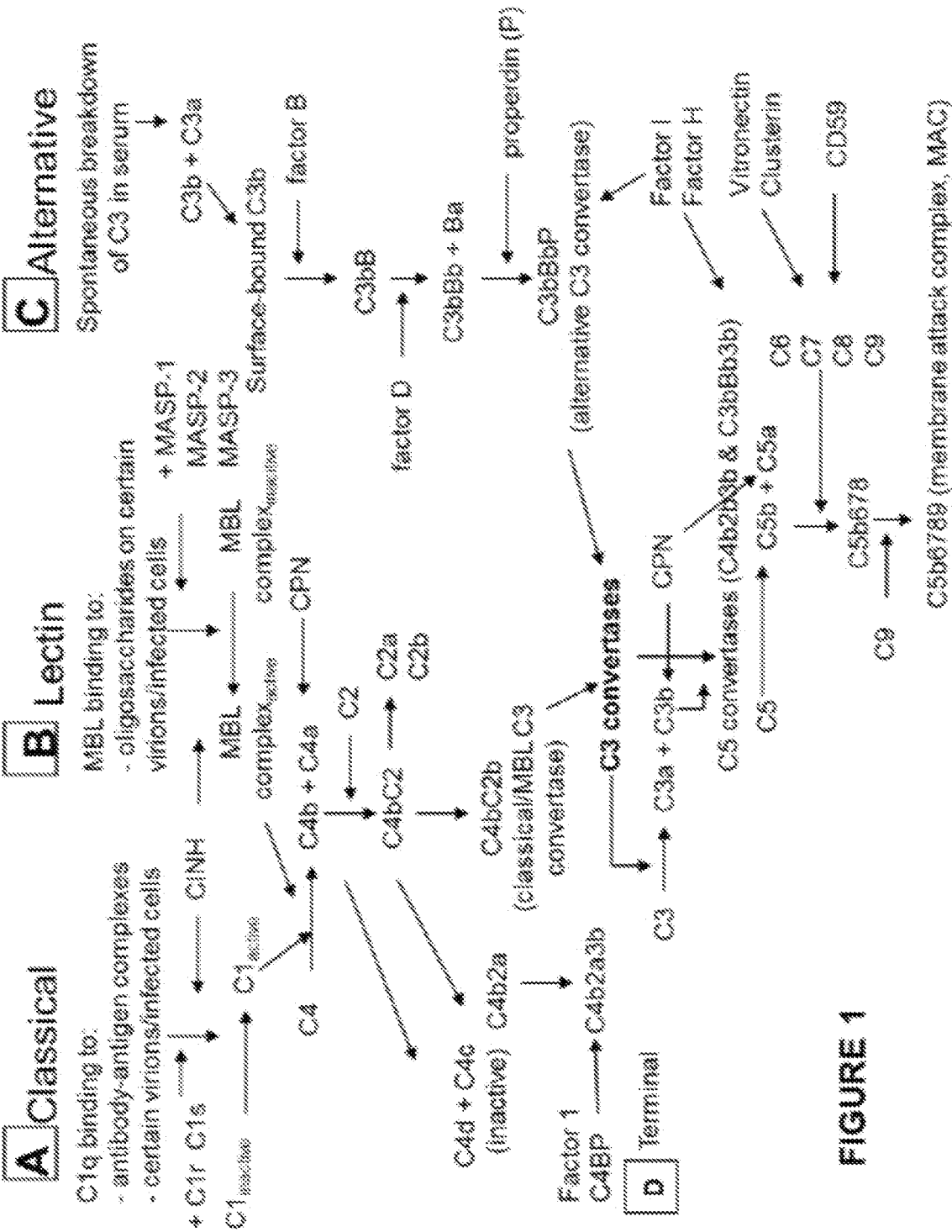


FIGURE 1

4939SEQ.PC2

SEQUENCE LISTING

<110> Madison, Edwin L.
Soros, Vanessa
Popkov, Mikhail

<120> MODIFIED MEMBRANE TYPE SERINE PROTEASE 1
(MTSP-1) POLYPEPTIDES AND METHODS OF USE

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pro-peptide C122S

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			20					25					30		
Glu	Glu	Gly	Val	Glu	Phe	Leu	Pro	Val	Asn	Asn	Val	Lys	Lys	Val	Glu
		35					40					45			
Lys	His	Gly	Pro	Gly	Arg	Trp	Val	Val	Leu	Ala	Ala	Val	Leu	Ile	Gly
	50					55				60					
Leu	Leu	Leu	Val	Leu	Leu	Gly	Ile	Gly	Phe	Leu	Val	Trp	His	Leu	Gln
65					70				75					80	
Tyr	Arg	Asp	Val	Arg	Val	Gln	Lys	Val	Phe	Asn	Gly	Tyr	Met	Arg	Ile

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				85					90				95				
Thr	Asn	Glu	Asn	Phe	Val	Asp	Ala	Tyr	Glu	Asn	Ser	Asn	Ser	Thr	Glu		
			100					105				110					
Phe	Val	Ser	Leu	Ala	Ser	Lys	Val	Lys	Asp	Ala	Leu	Lys	Leu	Leu	Tyr		
		115					120					125					
Ser	Gly	Val	Pro	Phe	Leu	Gly	Pro	Tyr	His	Lys	Glu	Ser	Ala	Val	Thr		
	130					135					140						
Ala	Phe	Ser	Glu	Gly	Ser	Val	Ile	Ala	Tyr	Tyr	Trp	Ser	Glu	Phe	Ser		
145					150					155					160		
Ile	Pro	Gln	His	Leu	Val	Glu	Glu	Ala	Glu	Arg	Val	Met	Ala	Glu	Glu		
				165					170					175			
Arg	Val	Val	Met	Leu	Pro	Pro	Arg	Ala	Arg	Ser	Leu	Lys	Ser	Phe	Val		
			180					185					190				
Val	Thr	Ser	Val	Val	Ala	Phe	Pro	Thr	Asp	Ser	Lys	Thr	Val	Gln	Arg		
	195						200					205					
Thr	Gln	Asp	Asn	Ser	Cys	Ser	Phe	Gly	Leu	His	Ala	Arg	Gly	Val	Glu		
	210					215					220						
Leu	Met	Arg	Phe	Thr	Thr	Pro	Gly	Phe	Pro	Asp	Ser	Pro	Tyr	Pro	Ala		
225					230					235					240		
His	Ala	Arg	Cys	Gln	Trp	Ala	Leu	Arg	Gly	Asp	Ala	Asp	Ser	Val	Leu		
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Ser	Leu	Thr	Phe	Arg	Ser	Phe	Asp	Leu	Ala	Ser	Cys	Asp	Glu	Arg	Gly		
			260				265					270					
Ser	Asp	Leu	Val	Thr	Val	Tyr	Asn	Thr	Leu	Ser	Pro	Met	Glu	Pro	His		
	275						280					285					
Ala	Leu	Val	Gln	Leu	Cys	Gly	Thr	Tyr	Pro	Pro	Ser	Tyr	Asn	Leu	Thr		
	290					295					300						
Phe	His	Ser	Ser	Gln	Asn	Val	Leu	Leu	Ile	Thr	Leu	Ile	Thr	Asn	Thr		
305					310					315					320		
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				325					330					335			
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			340					345					350				
Ser	Pro	Tyr	Tyr	Pro	Gly	His	Tyr	Pro	Pro	Asn	Ile	Asp	Cys	Thr	Trp		
	355						360					365					
Asn	Ile	Glu	Val	Pro	Asn	Asn	Gln	His	Val	Lys	Val	Arg	Phe	Lys	Phe		
	370					375					380						
Phe	Tyr	Leu	Leu	Glu	Pro	Gly	Val	Pro	Ala	Gly	Thr	Cys	Pro	Lys	Asp		
385					390					395					400		
Tyr	Val	Glu	Ile	Asn	Gly	Glu	Lys	Tyr	Cys	Gly	Glu	Arg	Ser	Gln	Phe		
				405					410					415			
Val	Val	Thr	Ser	Asn	Ser	Asn	Lys	Ile	Thr	Val	Arg	Phe	His	Ser	Asp		
			420					425					430				
Gln	Ser	Tyr	Thr	Asp	Thr	Gly	Phe	Leu	Ala	Glu	Tyr	Leu	Ser	Tyr	Asp		
	435					440						445					
Ser	Ser	Asp	Pro	Cys	Pro	Gly	Gln	Phe	Thr	Cys	Arg	Thr	Gly	Arg	Cys		
	450					455					460						
Ile	Arg	Lys	Glu	Leu	Arg	Cys	Asp	Gly	Trp	Ala	Asp	Cys	Thr	Asp	His		
465					470					475					480		
Ser	Asp	Glu	Leu	Asn	Cys	Ser	Cys	Asp	Ala	Gly	His	Gln	Phe	Thr	Cys		
				485					490					495			
Lys	Asn	Lys	Phe	Cys	Lys	Pro	Leu	Phe	Trp	Val	Cys	Asp	Ser	Val	Asn		

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			500				505				510					
Asp	Cys	Gly	Asp	Asn	Ser	Asp	Glu	Gln	Gly	Cys	Ser	Cys	Pro	Ala	Gln	
			515				520				525					
Thr	Phe	Arg	Cys	Ser	Asn	Gly	Lys	Cys	Leu	Ser	Lys	Ser	Gln	Gln	Cys	
			530				535				540					
Asn	Gly	Lys	Asp	Asp	Cys	Gly	Asp	Gly	Ser	Asp	Glu	Ala	Ser	Cys	Pro	
			545				550				555					
Lys	Val	Asn	Val	Val	Thr	Cys	Thr	Lys	His	Thr	Tyr	Arg	Cys	Leu	Asn	
			565				570				575					
Gly	Leu	Cys	Leu	Ser	Lys	Gly	Asn	Pro	Glu	Cys	Asp	Gly	Lys	Glu	Asp	
			580				585				590					
Cys	Ser	Asp	Gly	Ser	Asp	Glu	Lys	Asp	Cys	Asp	Cys	Gly	Leu	Arg	Ser	
			595				600				605					
Phe	Thr	Arg	Gln	Ala	Arg	Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	
			610				615				620					
Glu	Trp	Pro	Trp	Gln	Val	Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ile	
			625				630				635					
Cys	Gly	Ala	Ser	Leu	Ile	Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	
			645				650				655					
Cys	Tyr	Ile	Asp	Asp	Arg	Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	
			660				665				670					
Thr	Ala	Phe	Leu	Gly	Leu	His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	
			675				680				685					
Val	Gln	Glu	Arg	Arg	Leu	Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	
			690				695				700					
Asp	Phe	Thr	Phe	Asp	Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	
			705				710				715					
Ala	Glu	Tyr	Ser	Ser	Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	
			725				730				735					
His	Val	Phe	Pro	Ala	Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	
			740				745				750					
Thr	Gln	Tyr	Gly	Gly	Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	
			755				760				765					
Arg	Val	Ile	Asn	Gln	Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	
			770				775				780					
Thr	Pro	Arg	Met	Met	Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	
			785				790				795					
Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	
			805				810				815					
Arg	Ile	Phe	Gln	Ala	Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	
			820				825				830					
Arg	Asn	Lys	Pro	Gly	Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	
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Ile	Lys	Glu	Asn	Thr	Gly	Val										
			850				855									

$\langle 210 \rangle$ 4

<211> 241

<212> PRT

<213> Artificial Sequence

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<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain C1225

<400> 4

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Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ile	Cys	Gly	Ala	Ser	Leu	Ile
		20					25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Phe	Thr	Phe	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	Cys
				165					170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 5

<211> 3149

<212> DNA

<213> Homo sapiens

<400> 5

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tgaatggctt	ggaggaaggc	gtggagtcc	tgccagtcaa	caacgtcaag	aaggtggaaa	180
agcatggccc	ggggcgctgg	gtggtgctgg	cagccgtgct	gatcggcctc	ctcttgggtct	240
tgctggggat	cggcttcctg	gtgtggcatt	tgacgtaccg	ggacgtgcgt	gtccagaagg	300
tcttcaatgg	ctacatgagg	atcacaaatg	agaattttgt	ggatgcctac	gagaactcca	360
actccactga	gtttgtaagc	ctggccagca	aggtgaagga	cgcgctgaag	ctgctgtaca	420

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ccgagcgcgt	catggccgag	gagcgcgtag	tcatgctgcc	cccgcgggcg	cgctccctga	600
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<210> 6

<211> 241

<212> PRT

<213> Artificial Sequence

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<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41T/F97L/F99L/C122S/G151N/Q175S/Q192S/D217W

<400> 6

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			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Leu	Thr	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Ser	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ser	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Trp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 7

<211> 723

<212> DNA

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

<400> 7

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ctgggccagg gccacatctg cggtgcttcc ctcatctctc ccaactggct ggtctctgcc 120

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aagcgcatca tctccacacc cttcttcaat gacttcacct tcgactatga catcgcgctg 300
ctggagctgg agaaaccggc agagtacagc tccatgggtg gggccatctg cctgccggac 360
gcctcccatg tcttcctgc cggcaaggcc atctgggtca cgggctgggg acacaccag 420
tatggaggca ctggcgcgct gacctgcaa aagggtgaga tccgcgtcat caaccagacc 480
acctgcgaga acctcctgcc gcagcagatc acgccgcgca tgatgtgcgt gggcttcctc 540
agcggcggcg tggactcctg ccagggtgat tccgggggac ccctgtccag cgtggaggcg 600
gatgggcgga tcttcaggc cgggtgtggtg agctggggag acggctgcgc tcagagggaac 660
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gta 723

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<210> 8

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97T/F99M/C122S/Q192V/D217M

<400> 8

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      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Thr Met Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100         105         110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115         120         125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130         135         140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145         150         155         160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165         170         175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180         185         190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195         200         205
Val Val Ser Trp Gly Met Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210         215         220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly

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225 Val 230 235 240

<210> 9
 <211> 1663
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Complement Protein C3

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 Ile Leu Arg Leu Glu Ser Glu Glu Thr Met Val Leu Glu Ala His Asp
 35 40 45
 Ala Gln Gly Asp Val Pro Val Thr Val Thr Val His Asp Phe Pro Gly
 50 55 60
 Lys Lys Leu Val Leu Ser Ser Glu Lys Thr Val Leu Thr Pro Ala Thr
 65 70 75 80
 Asn His Met Gly Asn Val Thr Phe Thr Ile Pro Ala Asn Arg Glu Phe
 85 90 95
 Lys Ser Glu Lys Gly Arg Asn Lys Phe Val Thr Val Gln Ala Thr Phe
 100 105 110
 Gly Thr Gln Val Val Glu Lys Val Val Leu Val Ser Leu Gln Ser Gly
 115 120 125
 Tyr Leu Phe Ile Gln Thr Asp Lys Thr Ile Tyr Thr Pro Gly Ser Thr
 130 135 140
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 Arg Thr Val Met Val Asn Ile Glu Asn Pro Glu Gly Ile Pro Val Lys
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 Trp Asp Ile Pro Glu Leu Val Asn Met Gly Gln Trp Lys Ile Arg Ala
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 Tyr Tyr Glu Asn Ser Pro Gln Gln Val Phe Ser Thr Glu Phe Glu Val
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 Lys Glu Tyr Val Leu Pro Ser Phe Glu Val Ile Val Glu Pro Thr Glu
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 Ala Arg Phe Leu Tyr Gly Lys Lys Val Glu Gly Thr Ala Phe Val Ile
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 Lys Arg Ile Pro Ile Glu Asp Gly Ser Gly Glu Val Val Leu Ser Arg
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Gly	Lys	Ser	Leu	Tyr	Val	Ser	Ala	Thr	Val	Ile	Leu	His	Ser	Gly	Ser	325	330	335	
Asp	Met	Val	Gln	Ala	Glu	Arg	Ser	Gly	Ile	Pro	Ile	Val	Thr	Ser	Pro	340	345	350	
Tyr	Gln	Ile	His	Phe	Thr	Lys	Thr	Pro	Lys	Tyr	Phe	Lys	Pro	Gly	Met	355	360	365	
Pro	Phe	Asp	Leu	Met	Val	Phe	Val	Thr	Asn	Pro	Asp	Gly	Ser	Pro	Ala	370	375	380	
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Thr	Gln	Gly	Asp	Gly	Val	Ala	Lys	Leu	Ser	Ile	Asn	Thr	His	Pro	Ser	405	410	415	
Gln	Lys	Pro	Leu	Ser	Ile	Thr	Val	Arg	Thr	Lys	Lys	Gln	Glu	Leu	Ser	420	425	430	
Glu	Ala	Glu	Gln	Ala	Thr	Arg	Thr	Met	Gln	Ala	Leu	Pro	Tyr	Ser	Thr	435	440	445	
Val	Gly	Asn	Ser	Asn	Asn	Tyr	Leu	His	Leu	Ser	Val	Leu	Arg	Thr	Glu	450	455	460	
Leu	Arg	Pro	Gly	Glu	Thr	Leu	Asn	Val	Asn	Phe	Leu	Leu	Arg	Met	Asp	465	470	475	480
Arg	Ala	His	Glu	Ala	Lys	Ile	Arg	Tyr	Tyr	Thr	Tyr	Leu	Ile	Met	Asn	485	490	495	
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Asp	Leu	Val	Val	Leu	Pro	Leu	Ser	Ile	Thr	Thr	Asp	Phe	Ile	Pro	Ser	515	520	525	
Phe	Arg	Leu	Val	Ala	Tyr	Tyr	Thr	Leu	Ile	Gly	Ala	Ser	Gly	Gln	Arg	530	535	540	
Glu	Val	Val	Ala	Asp	Ser	Val	Trp	Val	Asp	Val	Lys	Asp	Ser	Cys	Val	545	550	555	560
Gly	Ser	Leu	Val	Val	Lys	Ser	Gly	Gln	Ser	Glu	Asp	Arg	Gln	Pro	Val	565	570	575	
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Val Thr Met Tyr His Ala Lys Ala Lys Asp Gln Leu Thr Cys Asn Lys
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Cys Glu Pro Gly Val Asp Tyr Val Tyr Lys Thr Arg Leu Val Lys Val
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Ser	Asp	Leu	Val	Thr	Val	Tyr	Asn	Thr	Leu	Ser	Pro	Met	Glu	Pro	His
		275					280					285			
Ala	Leu	Val	Gln	Leu	Cys	Gly	Thr	Tyr	Pro	Pro	Ser	Tyr	Asn	Leu	Thr
		290				295					300				
Phe	His	Ser	Ser	Gln	Asn	Val	Leu	Leu	Ile	Thr	Leu	Ile	Thr	Asn	Thr
305					310					315					320
Glu	Arg	Arg	His	Pro	Gly	Phe	Glu	Ala	Thr	Phe	Phe	Gln	Leu	Pro	Arg
				325					330					335	
Met	Ser	Ser	Cys	Gly	Gly	Arg	Leu	Arg	Lys	Ala	Gln	Gly	Thr	Phe	Asn
			340					345					350		
Ser	Pro	Tyr	Tyr	Pro	Gly	His	Tyr	Pro	Pro	Asn	Ile	Asp	Cys	Thr	Trp
		355					360					365			
Asn	Ile	Glu	Val	Pro	Asn	Asn	Gln	His	Val	Lys	Val	Arg	Phe	Lys	Phe
		370				375					380				
Phe	Tyr	Leu	Leu	Glu	Pro	Gly	Val	Pro	Ala	Gly	Thr	Cys	Pro	Lys	Asp
385					390					395					400
Tyr	Val	Glu	Ile	Asn	Gly	Glu	Lys	Tyr	Cys	Gly	Glu	Arg	Ser	Gln	Phe
				405					410					415	
Val	Val	Thr	Ser	Asn	Ser	Asn	Lys	Ile	Thr	Val	Arg	Phe	His	Ser	Asp
			420					425					430		
Gln	Ser	Tyr	Thr	Asp	Thr	Gly	Phe	Leu	Ala	Glu	Tyr	Leu	Ser	Tyr	Asp
		435					440					445			
Ser	Ser	Asp	Pro	Cys	Pro	Gly	Gln	Phe	Thr	Cys	Arg	Thr	Gly	Arg	Cys
		450				455					460				
Ile	Arg	Lys	Glu	Leu	Arg	Cys	Asp	Gly	Trp	Ala	Asp	Cys	Thr	Asp	His
465					470					475					480
Ser	Asp	Glu	Leu	Asn	Cys	Ser	Cys	Asp	Ala	Gly	His	Gln	Phe	Thr	Cys
				485					490					495	
Lys	Asn	Lys	Phe	Cys	Lys	Pro	Leu	Phe	Trp	Val	Cys	Asp	Ser	Val	Asn
			500					505					510		
Asp	Cys	Gly	Asp	Asn	Ser	Asp	Glu	Gln	Gly	Cys	Ser	Cys	Pro	Ala	Gln
		515					520					525			
Thr	Phe	Arg	Cys	Ser	Asn	Gly	Lys	Cys	Leu	Ser	Lys	Ser	Gln	Gln	Cys
		530				535					540				
Asn	Gly	Lys	Asp	Asp	Cys	Gly	Asp	Gly	Ser	Asp	Glu	Ala	Ser	Cys	Pro
545					550					555					560
Lys	Val	Asn	Val	Val	Thr	Cys	Thr	Lys	His	Thr	Tyr	Arg	Cys	Leu	Asn
				565					570					575	
Gly	Leu	Cys	Leu	Ser	Lys	Gly	Asn	Pro	Glu	Cys	Asp	Gly	Lys	Glu	Asp
			580					585					590		
Cys	Ser	Asp	Gly	Ser	Asp	Glu	Lys	Asp	Cys	Asp	Cys	Gly	Leu	Arg	Ser
		595					600					605			
Phe	Thr	Arg	Gln	Ala											

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Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
    675                                680                685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                                695                700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                                710                715                720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
    725                                730                735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
    740                                745                750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
    755                                760                765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                                775                780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                                790                795                800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
    805                                810                815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
    820                                825                830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
    835                                840                845
Ile Lys Glu Asn Thr Gly Val
    850                                855

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<210> 12

<211> 855

<212> PRT

<213> Mus musculus

<400> 12

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Gly Ala Gly Leu Lys Tyr Asn Ser Arg Leu Glu Asn Met Asn Gly Phe
    20                                25                30
Glu Glu Gly Val Glu Phe Leu Pro Ala Asn Asn Ala Lys Lys Val Glu
    35                                40                45
Lys Arg Gly Pro Arg Arg Trp Val Val Leu Val Ala Val Leu Phe Ser
    50                                55                60
Phe Leu Leu Leu Ser Leu Met Ala Gly Leu Leu Val Trp His Phe His
65                                70                75                80
Tyr Arg Asn Val Arg Val Gln Lys Val Phe Asn Gly His Leu Arg Ile
    85                                90                95
Thr Asn Glu Ile Phe Leu Asp Ala Tyr Glu Asn Ser Thr Ser Thr Glu
    100                                105                110
Phe Ile Ser Leu Ala Ser Gln Val Lys Glu Ala Leu Lys Leu Leu Tyr
    115                                120                125
Asn Glu Val Pro Val Leu Gly Pro Tyr His Lys Lys Ser Ala Val Thr
    130                                135                140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                                150                155                160

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Ile	Pro	Pro	His	Leu	Ala	Glu	Glu	Val	Asp	Arg	Ala	Met	Ala	Val	Glu
				165					170					175	
Arg	Val	Val	Thr	Leu	Pro	Pro	Arg	Ala	Arg	Ala	Leu	Lys	Ser	Phe	Val
			180					185				190			
Leu	Thr	Ser	Val	Val	Ala	Phe	Pro	Ile	Asp	Pro	Arg	Met	Leu	Gln	Arg
		195					200				205				
Thr	Gln	Asp	Asn	Ser	Cys	Ser	Phe	Ala	Leu	His	Ala	His	Gly	Ala	Ala
	210					215				220					
Val	Thr	Arg	Phe	Thr	Thr	Pro	Gly	Phe	Pro	Asn	Ser	Pro	Tyr	Pro	Ala
225				230					235					240	
His	Ala	Arg	Cys	Gln	Trp	Val	Leu	Arg	Gly	Asp	Ala	Asp	Ser	Val	Leu
			245						250					255	
Ser	Leu	Thr	Phe	Arg	Ser	Phe	Asp	Val	Ala	Pro	Cys	Asp	Glu	His	Gly
			260					265					270		
Ser	Asp	Leu	Val	Thr	Val	Tyr	Asp	Ser	Leu	Ser	Pro	Met	Glu	Pro	His
		275					280					285			
Ala	Val	Val	Arg	Leu	Cys	Gly	Thr	Phe	Ser	Pro	Ser	Tyr	Asn	Leu	Thr
	290					295				300					
Phe	Leu	Ser	Ser	Gln	Asn	Val	Phe	Leu	Val	Thr	Leu	Ile	Thr	Asn	Thr
305				310						315					320
Asp	Arg	Arg	His	Pro	Gly	Phe	Glu	Ala	Thr	Phe	Phe	Gln	Leu	Pro	Lys
			325						330					335	
Met	Ser	Ser	Cys	Gly	Gly	Phe	Leu	Ser	Asp	Thr	Gln	Gly	Thr	Phe	Ser
		340						345					350		
Ser	Pro	Tyr	Tyr	Pro	Gly	His	Tyr	Pro	Pro	Asn	Ile	Asn	Cys	Thr	Trp
		355					360					365			
Asn	Ile	Lys	Val	Pro	Asn	Asn	Arg	Asn	Val	Lys	Val	Arg	Phe	Lys	Leu
	370					375					380				
Phe	Tyr	Leu	Val	Asp	Pro	Asn	Val	Pro	Val	Gly	Ser	Cys	Thr	Lys	Asp
385				390						395					400
Tyr	Val	Glu	Ile	Asn	Gly	Glu	Lys	Tyr	Cys	Gly	Glu	Arg	Ser	Gln	Phe
			405						410					415	
Val	Val	Ser	Ser	Asn	Ser	Ser	Lys	Ile	Thr	Val	His	Phe	His	Ser	Asp
		420						425					430		
His	Ser	Tyr	Thr	Asp	Thr	Gly	Phe	Leu	Ala	Glu	Tyr	Leu	Ser	Tyr	Asp
		435				440						445			
Ser	Asn	Asp	Pro	Cys	Pro	Gly	Met	Phe	Met	Cys	Lys	Thr	Gly	Arg	Cys
	450					455					460				
Ile	Arg	Lys	Glu	Leu	Arg	Cys	Asp	Gly	Trp	Ala	Asp	Cys	Pro	Asp	Tyr
465				470						475					480
Ser	Asp	Glu	Arg	Tyr	Cys	Arg	Cys	Asn	Ala	Thr	His	Gln	Phe	Thr	Cys
			485						490					495	
Lys	Asn	Gln	Phe	Cys	Lys	Pro	Leu	Phe	Trp	Val	Cys	Asp	Ser	Val	Asn
		500						505					510		
Asp	Cys	Gly	Asp	Gly											

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Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Thr Asp
 580 585 590
 Cys Ser Asp Gly Ser Asp Glu Lys Asn Cys Asp Cys Gly Leu Arg Ser
 595 600 605
 Phe Thr Lys Gln Ala Arg Val Val Gly Gly Thr Asn Ala Asp Glu Gly
 610 615 620
 Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Leu
 625 630 635 640
 Cys Gly Ala Ser Leu Ile Ser Pro Asp Trp Leu Val Ser Ala Ala His
 645 650 655
 Cys Phe Gln Asp Asp Lys Asn Phe Lys Tyr Ser Asp Tyr Thr Met Trp
 660 665 670
 Thr Ala Phe Leu Gly Leu Leu Asp Gln Ser Lys Arg Ser Ala Ser Gly
 675 680 685
 Val Gln Glu Leu Lys Leu Lys Arg Ile Ile Thr His Pro Ser Phe Asn
 690 695 700
 Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Ser
 705 710 715 720
 Val Glu Tyr Ser Thr Val Val Arg Pro Ile Cys Leu Pro Asp Ala Thr
 725 730 735
 His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
 740 745 750
 Thr Lys Glu Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
 755 760 765
 Arg Val Ile Asn Gln Thr Thr Cys Glu Asp Leu Met Pro Gln Gln Ile
 770 775 780
 Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
 785 790 795 800
 Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Ala Glu Lys Asp Gly
 805 810 815
 Arg Met Phe Gln Ala Gly Val Val Ser Trp Gly Glu Gly Cys Ala Gln
 820 825 830
 Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Val Val Arg Asp Trp
 835 840 845
 Ile Lys Glu His Thr Gly Val
 850 855

<210> 13

<211> 855

<212> PRT

<213> Rattus norvegicus

<400> 13

Met Gly Asn Asn Arg Gly Arg Lys Ala Gly Gly Gly Ser Gln Asp Phe
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 Gly Ala Gly Leu Lys Tyr Asn Ser Arg Leu Glu Asn Met Asn Gly Phe
 20 25 30
 Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Ala Lys Gln Val Glu
 35 40 45
 Lys Arg Gly Pro Arg Arg Trp Val Val Met Val Ala Val Val Phe Ser
 50 55 60

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Phe 65	Leu	Leu	Leu	Ser 70	Leu	Met	Ala	Gly	Leu	Leu	Val	Trp	His	Phe	His 80
Tyr	Arg	Asn	Val	Arg 85	Ile	Gln	Lys	Val	Phe 90	Asn	Gly	His	Leu	Arg 95	Ile
Thr	Asn	Glu	Asn 100	Phe	Leu	Asp	Ala	Tyr 105	Glu	Asn	Ser	Thr	Ser	Thr	Glu
Phe	Ile	Ser 115	Leu	Ala	Ser	Gln	Val 120	Lys	Glu	Ala	Leu	Lys 125	Leu	Met	Tyr
Ser 130	Glu	Val	Pro	Val	Leu	Gly 135	Pro	Tyr	His	Lys	Lys 140	Ser	Thr	Val	Thr
Ala 145	Phe	Ser	Glu	Gly	Ser	Val 150	Ile	Ala	Tyr	Tyr	Trp	Ser	Glu	Phe	Ser 160
Ile	Pro	Pro	His	Leu	Glu	Glu	Glu	Val	Asp 170	Arg	Ala	Met	Ala	Val	Glu 175
Arg	Val	Val	Thr 180	Leu	Pro	Pro	Arg	Ala 185	Arg	Ala	Leu	Lys	Ser	Phe	Val
Leu	Thr	Ser 195	Val	Val	Ala	Phe	Pro 200	Ile	Asp	Pro	Arg	Met	Leu	Gln	Arg
Thr 210	Gln	Asp	Asn	Ser	Cys	Ser 215	Phe	Ala	Leu	His	Ala 220	Arg	Gly	Arg	Thr
Val 225	Thr	Arg	Phe	Thr	Thr	Pro 230	Gly	Phe	Pro	Asn	Ser 235	Pro	Tyr	Pro	Ala 240
His	Ala	Arg	Cys	Gln	Trp	Val	Leu	Arg	Gly 250	Asp	Ala	Asp	Ser	Val	Leu 255
Ser	Leu	Thr	Phe 260	Arg	Ser	Phe	Asp 265	Val	Ala	Pro	Cys	Asp	Gly	His	Asp
Ser	Asp	Leu	Val	Thr	Val	Tyr	Asp 280	Ser	Leu	Ser	Pro	Met	Glu	Pro	His
Ala 290	Val	Val	Arg	Leu	Cys	Gly 295	Thr	Phe	Ser	Pro	Ser 300	Tyr	Asn	Leu	Thr
Phe 305	Leu	Ser	Ser	Gln	Asn	Val 310	Phe	Leu	Val	Thr	Leu 315	Ile	Thr	Asn	Thr 320
Asp	Arg	Arg	His	Pro	Gly	Phe	Glu	Ala	Thr	Phe	Phe	Gln	Leu	Pro	Lys 335
Met	Ser	Ser	Cys 340	Gly	Gly	Leu	Leu	Ser	Glu	Ala	Gln	Gly	Thr	Phe	Ser
Ser	Pro	Tyr 355	Tyr	Pro	Gly	His	Tyr 360	Pro	Pro	Asn	Ile	Asn	Cys	Thr	Trp
Asn 370	Ile	Lys	Val	Pro	Asn	Asn 375	Arg	Asn	Val	Lys	Val 380	Arg	Phe	Lys	Leu
Phe 385	Tyr	Leu	Val	Asp	Pro	Asn 390	Ile	Pro	Val	Gly	Ser 395	Cys	Thr	Lys	Asp 400
Tyr	Val	Glu	Ile	Asn	Gly	Glu	Lys	Phe	Cys	Gly	Glu	Arg	Ser	Gln	Phe 415
Val	Val	Ser	Ser	Asn	Ser	Ser	Lys	Ile	Thr	Val	His	Phe	His	Ser	Asp 430
His	Ser	Tyr 435	Thr	Asp	Thr	Gly	Phe 440	Leu	Ala	Glu	Tyr	Leu	Ser	Tyr	Asp
Ser	Asn	Asp	Pro	Cys	Pro	Gly 455	Met	Phe	Met	Cys	Lys 460	Thr	Gly	Arg	Cys
Ile 465	Arg	Lys	Asp	Leu	Arg	Cys 470	Asp	Gly	Trp	Ala	Asp 475	Cys	Pro	Asp	Tyr 480

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Ser Asp Glu Arg His Cys Arg Cys Asn Ala Thr His Gln Phe Met Cys
 485 490 495
 Lys Asn Gln Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
 500 505 510
 Asp Cys Gly Asp Gly Ser Asp Glu Glu Gly Cys Ser Cys Pro Ala Gly
 515 520 525
 Ser Phe Lys Cys Ser Asn Gly Lys Cys Leu Pro Gln Ser Gln Gln Cys
 530 535 540
 Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Asp
 545 550 555 560
 Asn Val Asn Ala Val Ser Cys Thr Lys Tyr Thr Tyr Arg Cys Gln Asn
 565 570 575
 Gly Leu Cys Leu Asn Lys Gly Asn Pro Glu Cys Asp Gly Lys Lys Asp
 580 585 590
 Cys Ser Asp Gly Ser Asp Glu Lys Asn Cys Asp Cys Gly Leu Arg Ser
 595 600 605
 Phe Thr Lys Gln Ala Arg Val Val Gly Gly Thr Asn Ala Asp Glu Gly
 610 615 620
 Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Leu
 625 630 635 640
 Cys Gly Ala Ser Leu Ile Ser Pro Asp Trp Leu Val Ser Ala Ala His
 645 650 655
 Cys Phe Gln Asp Glu Thr Ile Phe Lys Tyr Ser Asp His Thr Met Trp
 660 665 670
 Thr Ala Phe Leu Gly Leu Leu Asp Gln Ser Lys Arg Ser Ala Ser Gly
 675 680 685
 Val Gln Glu His Lys Leu Lys Arg Ile Ile Thr His Pro Ser Phe Asn
 690 695 700
 Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
 705 710 715 720
 Ala Glu Tyr Ser Thr Val Val Arg Pro Ile Cys Leu Pro Asp Asn Thr
 725 730 735
 His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
 740 745 750
 Thr Lys Glu Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
 755 760 765
 Arg Val Ile Asn Gln Thr Thr Cys Glu Glu Leu Leu Pro Gln Gln Ile
 770 775 780
 Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
 785 790 795 800
 Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Lys Asp Gly
 805 810 815
 Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Glu Gly Cys Ala Gln
 820 825 830
 Arg Asn Lys Pro Gly Val Tyr Thr Arg Ile Pro Glu Val Arg Asp Trp
 835 840 845
 Ile Lys Glu Gln Thr Gly Val
 850 855

<210> 14

<211> 263

<212> PRT

<213> Artificial Sequence

<220>

<223> chymotrypsin B

<400> 14

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Met Ala Phe Leu Trp Leu Leu Ser Cys Trp Ala Leu Leu Gly Thr Thr
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           20           25           30
Arg Ile Val Asn Gly Glu Asp Ala Val Pro Gly Ser Trp Pro Trp Gln
           35           40           45
Val Ser Leu Gln Asp Lys Thr Gly Phe His Phe Cys Gly Gly Ser Leu
 50           55           60
Ile Ser Glu Asp Trp Val Val Thr Ala Ala His Cys Gly Val Arg Thr
65           70           75           80
Ser Asp Val Val Val Ala Gly Glu Phe Asp Gln Gly Ser Asp Glu Glu
           85           90           95
Asn Ile Gln Val Leu Lys Ile Ala Lys Val Phe Lys Asn Pro Lys Phe
          100          105          110
Ser Ile Leu Thr Val Asn Asn Asp Ile Thr Leu Leu Lys Leu Ala Thr
          115          120          125
Pro Ala Arg Phe Ser Gln Thr Val Ser Ala Val Cys Leu Pro Ser Ala
          130          135          140
Asp Asp Asp Phe Pro Ala Gly Thr Leu Cys Ala Thr Thr Gly Trp Gly
145          150          155          160
Lys Thr Lys Tyr Asn Ala Asn Lys Thr Pro Asp Lys Leu Gln Gln Ala
          165          170          175
Ala Leu Pro Leu Leu Ser Asn Ala Glu Cys Lys Lys Ser Trp Gly Arg
          180          185          190
Arg Ile Thr Asp Val Met Ile Cys Ala Gly Ala Ser Gly Val Ser Ser
          195          200          205
Cys Met Gly Asp Ser Gly Gly Pro Leu Val Cys Gln Lys Asp Gly Ala
          210          215          220
Trp Thr Leu Val Gly Ile Val Ser Trp Gly Ser Asp Thr Cys Ser Thr
225          230          235          240
Ser Ser Pro Gly Val Tyr Ala Arg Val Thr Lys Leu Ile Pro Trp Val
          245          250          255
Gln Lys Ile Leu Ala Ala Asn
          260

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<210> 15

<211> 865

<212> DNA

<213> Artificial Sequence

<220>

<223> chymotrypsin B

<400> 15

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gaatgggggag gacgccgtcc ccggctcctg gccctggcag gtgtccctgc aggacaaaac 180
cggcttccac ttctgcgggg gctccctcat cagcgaggac tgggtgggtca ccgtgccca 240
ctgcgggggtc aggacctccg acgtgggtcgt ggctggggag tttgaccagg gctctgacga 300
ggagaacatc caggtcctga agatcgccaa ggtcttcaag aacccaagt tcagcattct 360
gaccgtgaac aatgacatca cctgctgaa gctggccaca cctgcccgt tctcccagac 420
agtgtccgcc gtgtgcctgc ccagcgccga cgacgacttc cccgcgggga cactgtgtgc 480
caccacaggc tggggcaaga ccaagtacaa cgccaacaag acccctgaca agctgcagca 540
ggcagccctg cccctcctgt ccaatgccga atgcaagaag tcctggggca ggaggatcac 600
cgacgtgatg atctgtgccg gggccagtgg cgtctcctcc tgcattggcg actctggcgg 660
tcccctggtc tgccaaaagg atggagcctg gaccctgggtg ggcatgtgt cctggggcag 720
cgacacctgc tccacctcca gccctggcgt gtacgcccg gtcaccaagc tcatacctg 780
gggtgcagaag atcctggctg ccaactgagc ccgcggctcc ctccgaccct gctccccaca 840
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<210> 16

<211> 1637

<212> PRT

<213> Artificial Sequence

<220>

<223> Complement Protein C3: mature 2 chain

<400> 16

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Ser Pro Met Tyr Ser Ile Ile Thr Pro Asn Ile Leu Arg Leu Glu Ser
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          20           25           30
Val Thr Val Thr Val His Asp Phe Pro Gly Lys Lys Leu Val Leu Ser
          35           40           45
Ser Glu Lys Thr Val Leu Thr Pro Ala Thr Asn His Met Gly Asn Val
          50           55           60
Thr Phe Thr Ile Pro Ala Asn Arg Glu Phe Lys Ser Glu Lys Gly Arg
65           70           75           80
Asn Lys Phe Val Thr Val Gln Ala Thr Phe Gly Thr Gln Val Val Glu
          85           90           95
Lys Val Val Leu Val Ser Leu Gln Ser Gly Tyr Leu Phe Ile Gln Thr
          100          105          110
Asp Lys Thr Ile Tyr Thr Pro Gly Ser Thr Val Leu Tyr Arg Ile Phe
          115          120          125
Thr Val Asn His Lys Leu Leu Pro Val Gly Arg Thr Val Met Val Asn
          130          135          140
Ile Glu Asn Pro Glu Gly Ile Pro Val Lys Gln Asp Ser Leu Ser Ser
145          150          155          160
Gln Asn Gln Leu Gly Val Leu Pro Leu Ser Trp Asp Ile Pro Glu Leu
          165          170          175
Val Asn Met Gly Gln Trp Lys Ile Arg Ala Tyr Tyr Glu Asn Ser Pro
          180          185          190
Gln Gln Val Phe Ser Thr Glu Phe Glu Val Lys Glu Tyr Val Leu Pro
          195          200          205
Ser Phe Glu Val Ile Val Glu Pro Thr Glu Lys Phe Tyr Tyr Ile Tyr

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Asn	Glu	Lys	Gly	Leu	Glu	Val	Thr	Ile	Thr	Ala	Arg	Phe	Leu	Tyr	Gly
225	230					235					240				
Lys	Lys	Val	Glu	Gly	Thr	Ala	Phe	Val	Ile	Phe	Gly	Ile	Gln	Asp	Gly
	245					250					255				
Glu	Gln	Arg	Ile	Ser	Leu	Pro	Glu	Ser	Leu	Lys	Arg	Ile	Pro	Ile	Glu
	260					265					270				
Asp	Gly	Ser	Gly	Glu	Val	Val	Leu	Ser	Arg	Lys	Val	Leu	Leu	Asp	Gly
	275					280					285				
Val	Gln	Asn	Pro	Arg	Ala	Glu	Asp	Leu	Val	Gly	Lys	Ser	Leu	Tyr	Val
	290					295					300				
Ser	Ala	Thr	Val	Ile	Leu	His	Ser	Gly	Ser	Asp	Met	Val	Gln	Ala	Glu
305	310					315					320				
Arg	Ser	Gly	Ile	Pro	Ile	Val	Thr	Ser	Pro	Tyr	Gln	Ile	His	Phe	Thr
	325					330					335				
Lys	Thr	Pro	Lys	Tyr	Phe	Lys	Pro	Gly	Met	Pro	Phe	Asp	Leu	Met	Val
	340					345					350				
Phe	Val	Thr	Asn	Pro	Asp	Gly	Ser	Pro	Ala	Tyr	Arg	Val	Pro	Val	Ala
	355					360					365				
Val	Gln	Gly	Glu	Asp	Thr	Val	Gln	Ser	Leu	Thr	Gln	Gly	Asp	Gly	Val
	370					375					380				
Ala	Lys	Leu	Ser	Ile	Asn	Thr	His	Pro	Ser	Gln	Lys	Pro	Leu	Ser	Ile
385	390					395					400				
Thr	Val	Arg	Thr	Lys	Lys	Gln	Glu	Leu	Ser	Glu	Ala	Glu	Gln	Ala	Thr
	405					410					415				
Arg	Thr	Met	Gln	Ala	Leu	Pro	Tyr	Ser	Thr	Val	Gly	Asn	Ser	Asn	Asn
	420					425					430				
Tyr	Leu	His	Leu	Ser	Val	Leu	Arg	Thr	Glu	Leu	Arg	Pro	Gly	Glu	Thr
	435					440					445				
Leu	Asn	Val	Asn	Phe	Leu	Leu	Arg	Met	Asp	Arg	Ala	His	Glu	Ala	Lys
	450					455					460				
Ile	Arg	Tyr	Tyr	Thr	Tyr	Leu	Ile	Met	Asn	Lys	Gly	Arg	Leu	Leu	Lys
465	470					475					480				
Ala	Gly	Arg	Gln	Val	Arg	Glu	Pro	Gly	Gln	Asp	Leu	Val	Val	Leu	Pro
	485					490					495				
Leu	Ser	Ile	Thr	Thr	Asp	Phe	Ile	Pro	Ser	Phe	Arg	Leu	Val	Ala	Tyr
	500					505					510				
Tyr	Thr	Leu	Ile	Gly	Ala	Ser	Gly	Gln	Arg	Glu	Val	Val	Ala	Asp	Ser
	515					520					525				
Val	Trp	Val	Asp	Val	Lys	Asp	Ser	Cys	Val	Gly	Ser	Leu	Val	Val	Lys
	530					535					540				
Ser	Gly	Gln	Ser	Glu	Asp	Arg	Gln	Pro	Val	Pro	Gly	Gln	Gln	Met	Thr
545	550					555					560				
Leu	Lys	Ile	Glu	Gly	Asp	His	Gly	Ala	Arg	Val	Val	Leu	Val	Ala	Val
	565					570					575				
Asp	Lys	Gly	Val	Phe	Val	Leu	Asn	Lys	Lys	Asn	Lys	Leu	Thr	Gln	Ser
	580					585					590				
Lys	Ile	Trp	Asp	Val	Val	Glu	Lys	Ala	Asp	Ile	Gly	Cys	Thr	Pro	Gly
	595					600					605				
Ser	Gly	Lys	Asp	Tyr	Ala	Gly	Val	Phe	Ser	Asp	Ala	Gly	Leu	Thr	Phe
	610					615					620				
Thr	Ser	Ser	Ser	Gly	Gln	Gln	Thr	Ala	Gln	Arg	Ala	Glu	Leu	Gln	Cys

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625	Pro	Gln	Pro	Ala	Ala	Ser	Val	Gln	Leu	Thr	Glu	Lys	Arg	Met	Asp	Lys	640
					645						650					655	
Val	Gly	Lys	Tyr	Pro	Lys	Glu	Leu	Arg	Lys	Cys	Cys	Glu	Asp	Gly	Met		
			660					665					670				
Arg	Glu	Asn	Pro	Met	Arg	Phe	Ser	Cys	Gln	Arg	Arg	Thr	Arg	Phe	Ile		
		675					680					685					
Ser	Leu	Gly	Glu	Ala	Cys	Lys	Lys	Val	Phe	Leu	Asp	Cys	Cys	Asn	Tyr		
	690					695					700						
Ile	Thr	Glu	Leu	Arg	Arg	Gln	His	Ala	Arg	Ala	Ser	His	Leu	Gly	Leu		
705					710					715					720		
Ala	Arg	Ser	Asn	Leu	Asp	Glu	Asp	Ile	Ile	Ala	Glu	Glu	Asn	Ile	Val		
				725					730					735			
Ser	Arg	Ser	Glu	Phe	Pro	Glu	Ser	Trp	Leu	Trp	Asn	Val	Glu	Asp	Leu		
			740					745					750				
Lys	Glu	Pro	Pro	Lys	Asn	Gly	Ile	Ser	Thr	Lys	Leu	Met	Asn	Ile	Phe		
		755				760						765					
Leu	Lys	Asp	Ser	Ile	Thr	Thr	Trp	Glu	Ile	Leu	Ala	Val	Ser	Met	Ser		
	770					775					780						
Asp	Lys	Lys	Gly	Ile	Cys	Val	Ala	Asp	Pro	Phe	Glu	Val	Thr	Val	Met		
785					790					795					800		
Gln	Asp	Phe	Phe	Ile	Asp	Leu	Arg	Leu	Pro	Tyr	Ser	Val	Val	Arg	Asn		
				805					810					815			
Glu	Gln	Val	Glu	Ile	Arg	Ala	Val	Leu	Tyr	Asn	Tyr	Arg	Gln	Asn	Gln		
			820					825					830				
Glu	Leu	Lys	Val	Arg	Val	Glu	Leu	Leu	His	Asn	Pro	Ala	Phe	Cys	Ser		
		835					840					845					
Leu	Ala	Thr	Thr	Lys	Arg	Arg	His	Gln	Gln	Thr	Val	Thr	Ile	Pro	Pro		
	850					855					860						
Lys	Ser	Ser	Leu	Ser	Val	Pro	Tyr	Val	Ile	Val	Pro	Leu	Lys	Thr	Gly		
865					870					875					880		
Leu	Gln	Glu	Val	Glu	Val	Lys	Ala	Ala	Val	Tyr	His	His	Phe	Ile	Ser		
				885					890					895			
Asp	Gly	Val	Arg	Lys	Ser	Leu	Lys	Val	Val	Pro	Glu	Gly	Ile	Arg	Met		
			900					905					910				
Asn	Lys	Thr	Val	Ala	Val	Arg	Thr	Leu	Asp	Pro	Glu	Arg	Leu	Gly	Arg		
		915					920					925					
Glu	Gly	Val	Gln	Lys	Glu	Asp	Ile	Pro	Pro	Ala	Asp	Leu	Ser	Asp	Gln		
	930					935					940						
Val	Pro	Asp	Thr	Glu	Ser	Glu	Thr	Arg	Ile	Leu	Leu	Gln	Gly	Thr	Pro		
945					950					955					960		
Val	Ala	Gln	Met	Thr	Glu	Asp	Ala	Val	Asp	Ala	Glu	Arg	Leu	Lys	His		
				965					970					975			
Leu	Ile	Val	Thr	Pro	Ser	Gly	Cys	Gly	Glu	Gln	Asn	Met	Ile	Gly	Met		
			980					985					990				
Thr	Pro	Thr	Val	Ile	Ala	Val	His	Tyr	Leu	Asp	Glu	Thr	Glu	Gln	Trp		
			995				1000						1005				
Glu	Lys	Phe	Gly	Leu	Glu	Lys	Arg	Gln	Gly	Ala	Leu	Glu	Leu	Ile	Lys		
	1010					1015					1020						
Lys	Gly	Tyr	Thr	Gln	Gln	Leu	Ala	Phe	Arg	Gln	Pro	Ser	Ser	Ala	Phe		
1025					1030					1035					1040		
Ala	Ala	Phe	Val	Lys	Arg	Ala	Pro	Ser	Thr	Trp	Leu	Thr	Ala	Tyr	Val		

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				1045				1050				1055			
Val	Lys	Val	Phe	Ser	Leu	Ala	Val	Asn	Leu	Ile	Ala	Ile	Asp	Ser	Gln
			1060					1065				1070			
Val	Leu	Cys	Gly	Ala	Val	Lys	Trp	Leu	Ile	Leu	Glu	Lys	Gln	Lys	Pro
		1075					1080					1085			
Asp	Gly	Val	Phe	Gln	Glu	Asp	Ala	Pro	Val	Ile	His	Gln	Glu	Met	Ile
	1090					1095					1100				
Gly	Gly	Leu	Arg	Asn	Asn	Glu	Lys	Asp	Met	Ala	Leu	Thr	Ala	Phe	
1105				1110					1115					1120	
Val	Leu	Ile	Ser	Leu	Gln	Glu	Ala	Lys	Asp	Ile	Cys	Glu	Glu	Gln	Val
			1125						1130					1135	
Asn	Ser	Leu	Pro	Gly	Ser	Ile	Thr	Lys	Ala	Gly	Asp	Phe	Leu	Glu	Ala
		1140							1145				1150		
Asn	Tyr	Met	Asn	Leu	Gln	Arg	Ser	Tyr	Thr	Val	Ala	Ile	Ala	Gly	Tyr
	1155						1160					1165			
Ala	Leu	Ala	Gln	Met	Gly	Arg	Leu	Lys	Gly	Pro	Leu	Leu	Asn	Lys	Phe
	1170				1175					1180					
Leu	Thr	Thr	Ala	Lys	Asp	Lys	Asn	Arg	Trp	Glu	Asp	Pro	Gly	Lys	Gln
1185				1190						1195					1200
Leu	Tyr	Asn	Val	Glu	Ala	Thr	Ser	Tyr	Ala	Leu	Leu	Ala	Leu	Leu	Gln
			1205						1210						1215
Leu	Lys	Asp	Phe	Asp	Phe	Val	Pro	Pro	Val	Val	Arg	Trp	Leu	Asn	Glu
		1220						1225				1230			
Gln	Arg	Tyr	Tyr	Gly	Gly	Gly	Tyr	Gly	Ser	Thr	Gln	Ala	Thr	Phe	Met
	1235						1240					1245			
Val	Phe	Gln	Ala	Leu	Ala	Gln	Tyr	Gln	Lys	Asp	Ala	Pro	Asp	His	Gln
	1250					1255					1260				
Glu	Leu	Asn	Leu	Asp	Val	Ser	Leu	Gln	Leu	Pro	Ser	Arg	Ser	Ser	Lys
1265				1270						1275					1280
Ile	Thr	His	Arg	Ile	His	Trp	Glu	Ser	Ala	Ser	Leu	Leu	Arg	Ser	Glu
			1285						1290					1295	
Glu	Thr	Lys	Glu	Asn	Glu	Gly	Phe	Thr	Val	Thr	Ala	Glu	Gly	Lys	Gly
		1300					1305					1310			
Gln	Gly	Thr	Leu	Ser	Val	Val	Thr	Met	Tyr	His	Ala	Lys	Ala	Lys	Asp
	1315						1320					1325			
Gln	Leu	Thr	Cys	Asn	Lys	Phe	Asp	Leu	Lys	Val	Thr	Ile	Lys	Pro	Ala
	1330				1335					1340					
Pro	Glu	Thr	Glu	Lys	Arg	Pro	Gln	Asp	Ala	Lys	Asn	Thr	Met	Ile	Leu
1345				1350						1355				1360	
Glu	Ile	Cys	Thr	Arg	Tyr	Arg	Gly	Asp	Gln	Asp	Ala	Thr	Met	Ser	Ile
			1365						1370					1375	
Leu	Asp	Ile	Ser	Met	Met	Thr	Gly	Phe	Ala	Pro	Asp	Thr	Asp	Asp	Leu
		1380						1385					1390		
Lys	Gln	Leu	Ala	Asn	Gly	Val	Asp	Arg	Tyr	Ile	Ser	Lys	Tyr	Glu	Leu
	1395					1400						1405			
Asp	Lys	Ala	Phe	Ser	Asp	Arg	Asn	Thr	Leu	Ile	Ile	Tyr	Leu	Asp	Lys
	1410					1415					1420				
Val	Ser	His	Ser	Glu	Asp	Asp	Cys	Leu	Ala	Phe	Lys	Val	His	Gln	Tyr
1425				1430						1435					1440
Phe	Asn	Val	Glu	Leu	Ile	Gln	Pro	Gly	Ala	Val	Lys	Val	Tyr	Ala	Tyr
			1445						1450					1455	
Tyr	Asn	Leu	Glu	Glu	Ser	Cys	Thr	Arg	Phe	Tyr	His	Pro	Glu	Lys	Glu

23 Nov 2021

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<210> 17
<211> 4
<212> PRT
<213> Artificial Sequence
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<220>
<223> C3 convertase cleavage site 748-749

<400> 17
Gly Leu Ala Arg
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<210> 18
<211> 4
<212> PRT
<213> Artificial Sequence
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<220>
<223> Factor I cleavage site 954-955

<400> 18
Arg Leu Gly Arg
1

<210> 19

<211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Factor I cleavage site 1303-1304

<400> 19
 Leu Pro Ser Arg
 1

<210> 20
 <211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Factor I cleavage site 1320-1321

<400> 20
 Ser Leu Leu Arg
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<210> 21
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41R/F97T/Ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192
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<400> 21
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

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      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 22
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41A/D60bV/F60eR/Y60gW/F97T/ins97aE/T98G/F99L
 /C122S/G151N/Q175L/Q192D

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<400> 22
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met

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				165				170					175				
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser		
			180					185					190				
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala		
		195					200					205					
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly		
	210				215						220						
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr		
225				230						235					240		
Gly	Val																

<210> 23

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 23

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
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Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile		
		20					25					30					
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg		
	35					40						45					
Gly	Lys	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55					60							
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu		
65				70					75						80		
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp		
			85					90					95				
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser		
	100					105						110					
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala		
	115					120						125					
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly		
	130				135						140						
Thr	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln		
145				150						155					160		
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met		
			165					170						175			
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser		
			180					185					190				
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala		
	195					200						205					
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly		

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210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 24
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L
 /C122S/G151H/Q175L/Q192E

<400> 24
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 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

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<210> 25
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L
 /C122S/G151H/Q175L/Q192D

<400> 25
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 26
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

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<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L
 /C122S/G151H/Q175L/Q192D

<400> 26

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
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Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Lys	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 27

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L
 /C122S/G151N/Q175L/Q192D

<400> 27

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
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Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 28

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 28

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45

```


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Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 29

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

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

<400> 29

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ile Tyr Asn Gly Leu Asp
 85 90 95

4939SEQ.PC2

```

Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 30

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 30

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Asp Ala Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140

```

4939SEQ.PC2

```

Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

```

<210> 31

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 31

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
          20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
          35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Trp Asn Gly Leu Asp
          85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180      185      190

```

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Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 32

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C1
 22S/G151N/Q175L/Q192D

<400> 32

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ile Asn Gly Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240

Val

<210> 33
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97E/ins97aV/T98G
 /F99L/C122S/G151H/Q175L/Q192D

<400> 33
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Tyr Glu Val Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 34
 <211> 242

23 Nov 2021

4939SEQ.PC2

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F60eS/Y60gW/D96L/F97D/ins97aG/T98N
/F99L/C122S/G151H/Q175L/Q192E

<400> 34

[illegible]

<210> 35

$\langle 211 \rangle$ 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

4939SEQ.PC2

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

<400> 35

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Ser	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
			180					185				190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 36

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainQ38H/I41S/D60bT/F60eS/Y60gW/D96V/F97G/ins97aV/T98P
/F99L/C122S/G151H/Q175L/Q192D

<400> 36

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	

4939SEQ.PC2

```

Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Val Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 37

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97D/ins97aA/T98P
/F99L/C122S/G151N/Q175L/Q192D

<400> 37

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60

```


4939SEQ.PC2

```

His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Asp Ala Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 38

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 38

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110

```

4939SEQ.PC2

```

Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
   115                               120                               125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130                               135                               140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145                               150                               155                               160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
   165                               170                               175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
   180                               185                               190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
   195                               200                               205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
   210                               215                               220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
  225                               230                               235                               240
Gly Val

```

<210> 39

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 39

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                               5                               10                               15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
   20                               25                               30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
   35                               40                               45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                               55                               60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65                               70                               75                               80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Phe Val Pro Leu Asp
   85                               90                               95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
  100                               105                               110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
  115                               120                               125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
  130                               135                               140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145                               150                               155                               160

```

4939SEQ.PC2

```

Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 40

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 40

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205

```

4939SEQ.PC2

Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 41
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41E/F99L/C122S/G151N/Q192T

<400> 41
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

4939SEQ.PC2

<210> 42
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41D/C122S/G151N/Q192T

<400> 42

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225          230          235          240
Val

```

<210> 43
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/F99L/C122S/G151N/Q192V

4939SEQ.PC2

<400> 43

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225          230          235          240
Val

```

<210> 44

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

```

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain          I41E/F99L/C122S/G151N/Q192T

```

<400> 44

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45

```

4939SEQ.PC2

```

Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100        105        110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115        120        125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130        135        140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150        155        160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165        170        175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
          180        185        190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195        200        205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210        215        220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230        235          240
Val

```

<210> 45

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/Y59F/D96E/F99L/C122S/G151N/Q192T

<400> 45

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Glu Phe Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100        105        110

```

4939SEQ.PC2

```

Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 46

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/Y59F/C122S/G151N/Q192T

<400> 46

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175

```


4939SEQ.PC2

Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 47

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

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

<400> 47

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220

4939SEQ.PC2

Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 48

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

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

<400> 48

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 49
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/F60eS/Y60gW/D96K/F97G/ins97aV/T98P/F99L/
 C122S/G151H/Q175L/Q192D

<400> 49
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 50
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

4939SEQ.PC2

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41S/D60bT/Y60gW/D96K/F97G/ins97aV/T98P/F99L/
C122S/G151H/Q175L/Q192D

<400> 50

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Phe	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 51

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41S/D60bT/F60eS/D96K/F97G/ins97aV/T98P/F99L/
C122S/G151H/Q175L/Q192D

<400> 51

4939SEQ.PC2

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Ser	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
		180					185					190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 52

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/T98P/F99L/C1

22S/G151H/Q175L/Q192D

<400> 52

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			

4939SEQ.PC2

Gly	Ser	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
50					55						60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Pro	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met	
			100				105					110			
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 53

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 53

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Ser	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55						60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Val	Thr	Leu	Asp
				85					90					95	

4939SEQ.PC2

Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 54

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

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

<400> 54

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140

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Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

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<210> 55

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 55

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
          35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
          85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100     105     110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115     120     125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130     135     140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190

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Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 56

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 56

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr

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225	230	235	240
Gly Val			

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<210> 57
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D

<400> 57															
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ser	Cys	Gly	Ala 30	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Lys	Gly	Val	Pro	Leu	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu 105	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp 120	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr 140	Gln	Tyr	Gly	Gly
Thr 145	Gly	Ala	Leu	Ile	Leu	Gln 150	Lys	Gly	Glu	Ile 155	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Gln	Ile 170	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val 185	Asp	Ser	Cys	Asp	Gly	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile 205	Phe	Gln	Ala
Gly	Val 210	Val	Ser	Trp	Gly	Asp 215	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
Val 225	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
Gly	Val				230					235					240

<210> 58

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<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D

<400> 58
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
85 90 95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
100 105 110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
115 120 125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130 135 140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145 150 155 160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
165 170 175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
180 185 190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
195 200 205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
210 215 220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225 230 235 240
Gly Val

<210> 59
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/
Q192D

<400> 59

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 60

<211> 855

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1)

pro-peptide 381S 674V

<400> 60

Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe

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1				5					10				15				
Gly	Ala	Gly	Leu	Lys	Tyr	Asn	Ser	Arg	His	Glu	Lys	Val	Asn	Gly	Leu		
			20					25					30				
Glu	Glu	Gly	Val	Glu	Phe	Leu	Pro	Val	Asn	Asn	Val	Lys	Lys	Val	Glu		
		35					40					45					
Lys	His	Gly	Pro	Gly	Arg	Trp	Val	Val	Leu	Ala	Ala	Val	Leu	Ile	Gly		
	50					55					60						
Leu	Leu	Leu	Val	Leu	Leu	Gly	Ile	Gly	Phe	Leu	Val	Trp	His	Leu	Gln		
65				70					75					80			
Tyr	Arg	Asp	Val	Arg	Val	Gln	Lys	Val	Phe	Asn	Gly	Tyr	Met	Arg	Ile		
				85					90					95			
Thr	Asn	Glu	Asn	Phe	Val	Asp	Ala	Tyr	Glu	Asn	Ser	Asn	Ser	Thr	Glu		
			100					105						110			
Phe	Val	Ser	Leu	Ala	Ser	Lys	Val	Lys	Asp	Ala	Leu	Lys	Leu	Leu	Tyr		
		115					120					125					
Ser	Gly	Val	Pro	Phe	Leu	Gly	Pro	Tyr	His	Lys	Glu	Ser	Ala	Val	Thr		
	130					135					140						
Ala	Phe	Ser	Glu	Gly	Ser	Val	Ile	Ala	Tyr	Tyr	Trp	Ser	Glu	Phe	Ser		
145					150				155						160		
Ile	Pro	Gln	His	Leu	Val	Glu	Glu	Ala	Glu	Arg	Val	Met	Ala	Glu	Glu		
				165					170					175			
Arg	Val	Val	Met	Leu	Pro	Pro	Arg	Ala	Arg	Ser	Leu	Lys	Ser	Phe	Val		
			180					185					190				
Val	Thr	Ser	Val	Val	Ala	Phe	Pro	Thr	Asp	Ser	Lys	Thr	Val	Gln	Arg		
		195					200					205					
Thr	Gln	Asp	Asn	Ser	Cys	Ser	Phe	Gly	Leu	His	Ala	Arg	Gly	Val	Glu		
	210					215					220						
Leu	Met	Arg	Phe	Thr	Thr	Pro	Gly	Phe	Pro	Asp	Ser	Pro	Tyr	Pro	Ala		
225					230					235					240		
His	Ala	Arg	Cys	Gln	Trp	Ala	Leu	Arg	Gly	Asp	Ala	Asp	Ser	Val	Leu		
				245					250					255			
Ser	Leu	Thr	Phe	Arg	Ser	Phe	Asp	Leu	Ala	Ser	Cys	Asp	Glu	Arg	Gly		
			260					265					270				
Ser	Asp	Leu	Val	Thr	Val	Tyr	Asn	Thr	Leu	Ser	Pro	Met	Glu	Pro	His		
		275					280					285					
Ala	Leu	Val	Gln	Leu	Cys	Gly	Thr	Tyr	Pro	Pro	Ser	Tyr	Asn	Leu	Thr		
	290					295					300						
Phe	His	Ser	Ser	Gln	Asn	Val	Leu	Leu	Ile	Thr	Leu	Ile	Thr	Asn	Thr		
305					310					315					320		
Glu	Arg	Arg	His	Pro	Gly	Phe	Glu	Ala	Thr	Phe	Phe	Gln	Leu	Pro	Arg		
				325					330					335			
Met	Ser	Ser	Cys	Gly	Gly	Arg	Leu	Arg	Lys	Ala	Gln	Gly	Thr	Phe	Asn		
			340					345					350				
Ser	Pro	Tyr	Tyr	Pro	Gly	His	Tyr	Pro	Pro	Asn	Ile	Asp	Cys	Thr	Trp		
		355					360					365					
Asn	Ile	Glu	Val	Pro	Asn	Asn	Gln	His	Val	Lys	Val	Arg	Phe	Lys	Phe		
	370					375					380						
Phe	Tyr	Leu	Leu	Glu	Pro	Gly	Val	Pro	Ala	Gly	Thr	Cys	Pro	Lys	Asp		
385					390					395					400		
Tyr	Val	Glu	Ile	Asn	Gly	Glu	Lys	Tyr	Cys	Gly	Glu	Arg	Ser	Gln	Phe		
				405					410					415			
Val	Val	Thr	Ser	Asn	Ser	Asn	Lys	Ile	Thr	Val	Arg	Phe	His	Ser	Asp		

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			420					425					430					
Gln	Ser	Tyr	Thr	Asp	Thr	Gly	Phe	Leu	Ala	Glu	Tyr	Leu	Ser	Tyr	Asp			
			435					440					445					
Ser	Ser	Asp	Pro	Cys	Pro	Gly	Gln	Phe	Thr	Cys	Arg	Thr	Gly	Arg	Cys			
			450					455					460					
Ile	Arg	Lys	Glu	Leu	Arg	Cys	Asp	Gly	Trp	Ala	Asp	Cys	Thr	Asp	His			
465				470					475					480				
Ser	Asp	Glu	Leu	Asn	Cys	Ser	Cys	Asp	Ala	Gly	His	Gln	Phe	Thr	Cys			
			485					490					495					
Lys	Asn	Lys	Phe	Cys	Lys	Pro	Leu	Phe	Trp	Val	Cys	Asp	Ser	Val	Asn			
			500					505					510					
Asp	Cys	Gly	Asp	Asn	Ser	Asp	Glu	Gln	Gly	Cys	Ser	Cys	Pro	Ala	Gln			
			515					520					525					
Thr	Phe	Arg	Cys	Ser	Asn	Gly	Lys	Cys	Leu	Ser	Lys	Ser	Gln	Gln	Cys			
			530					535					540					
Asn	Gly	Lys	Asp	Asp	Cys	Gly	Asp	Gly	Ser	Asp	Glu	Ala	Ser	Cys	Pro			
545				550					555					560				
Lys	Val	Asn	Val	Val	Thr	Cys	Thr	Lys	His	Thr	Tyr	Arg	Cys	Leu	Asn			
			565					570					575					
Gly	Leu	Cys	Leu	Ser	Lys	Gly	Asn	Pro	Glu	Cys	Asp	Gly	Lys	Glu	Asp			
			580					585					590					
Cys	Ser	Asp	Gly	Ser	Asp	Glu	Lys	Asp	Cys	Asp	Cys	Gly	Leu	Arg	Ser			
			595					600					605					
Phe	Thr	Arg	Gln	Ala	Arg	Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly			
			610					615					620					
Glu	Trp	Pro	Trp	Gln	Val	Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ile			
625				630					635					640				
Cys	Gly	Ala	Ser	Leu	Ile	Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His			
			645					650					655					
Cys	Tyr	Ile	Asp	Asp	Arg	Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp			
			660					665					670					
Thr	Ala	Phe	Leu	Gly	Leu	His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly			
			675					680					685					
Val	Gln	Glu	Arg	Arg	Leu	Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn			
			690					695					700					
Asp	Phe	Thr	Phe	Asp	Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro			
705				710					715					720				
Ala	Glu	Tyr	Ser	Ser	Met	Val	Arg	Pro	Ile	Cys	Leu	Pro	Asp	Ala	Ser			
			725					730					735					
His	Val	Phe	Pro	Ala	Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His			
			740					745					750					
Thr	Gln	Tyr	Gly	Gly	Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile			
			755					760					765					
Arg	Val	Ile	Asn	Gln	Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile			
			770					775					780					
Thr	Pro	Arg	Met	Met	Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser			
785				790					795					800				
Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly			
			805					810					815					
Arg	Ile	Phe	Gln	Ala	Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln			
			820					825					830					
Arg	Asn	Lys	Pro	Gly	Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp			

Ile Lys Glu Asn Thr Gly Val
 850 835 840 845

<210> 61
 <211> 330
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IgG1; FC 99-330

<400> 61
 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 225 230 235 240
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn

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290 295 300
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 325 330

<210> 62
 <211> 231
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> hIgG1 Fc

<400> 62
 Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 1 5 10 15
 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 20 25 30
 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 35 40 45
 Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
 50 55 60
 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 65 70 75 80
 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 85 90 95
 Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
 100 105 110
 Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 115 120 125
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
 130 135 140
 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 145 150 155 160
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 165 170 175
 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 180 185 190
 Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 195 200 205
 Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 210 215 220
 Leu Ser Leu Ser Pro Gly Lys
 225 230

<210> 63
 <211> 242
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D

<400> 63

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25						30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100				105					110			
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115				120					125				
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130				135					140					
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155				160	
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
		180					185					190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195				200						205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215					220					
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225				230					235					240	
Gly	Val														

<210> 64

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/
Q192D

4939SEQ.PC2

<400> 64

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
          65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
          145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
          225          230          235          240
Gly Val

```

<210> 65

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/
Q192D/D217V

<400> 65

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30

```

4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
   35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
           85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
           100        105        110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
           115        120        125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
           130        135        140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
           145        150        155        160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
           165        170        175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
           180        185        190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
           195        200        205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
           210        215        220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
           225        230        235        240
Gly Val

```

<210> 66

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V

<400> 66

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
   1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
           20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
           35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
           50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
           65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp

```

4939SEQ.PC2

```

      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 67

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192D/D217V

<400> 67

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly

```

4939SEQ.PC2

```

      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 68

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41S/D96M/F97G/ins97aV/T98P/F99L/C122S/Q192G/D217V

<400> 68

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190

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4939SEQ.PC2

Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 69

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192V/D217I

<400> 69

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 70
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192H

<400> 70
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 71
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192N/D217V

<400> 71

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asn	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Val	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 72

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41S/D60bY/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192D

4939SEQ.PC2

<400> 72

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

```

<210> 73

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/
D217V

<400> 73

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg

```

4939SEQ.PC2

```

      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 74

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192V

<400> 74

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp

```

4939SEQ.PC2

```

      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 75

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41S/P49S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192G/
D217V

<400> 75

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Ser Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly

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4939SEQ.PC2

130					135					140					
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
165					170					175					
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ser	Gly	Asp	Ser
180					185					190					
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
195					200					205					
Gly	Val	Val	Ser	Trp	Gly	Val	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
210					215					220					
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					
Gly	Val														

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<210> 76
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175L/Q192N
      /D217V
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<400>	76														
Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Lys	Gly	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asn	Gly	Asp	Ser

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180 185 190															
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
195 200 205															
Gly	Val	Val	Ser	Trp	Gly	Val	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
210 215 220															
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225 230 235 240															
Gly	Val														

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<210> 77
<211> 241
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
I41T/F97W/F99L/C122S/G151N/O175M/O192G/D217L

<400>	77														
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Gln	Gly	His 25	Thr	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu 80
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Trp	Thr	Leu	Asp	Tyr 95
Asp	Ile	Ala	Leu 100	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser	Met
Val	Arg	Pro 115	Ile	Ser	Leu	Pro	Asp 120	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
Lys	Ala 130	Ile	Trp	Val	Thr	Gly 135	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
Asn 145	Ala	Leu	Ile	Leu	Gln 150	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr 160
Thr	Cys	Glu	Asn	Leu 165	Leu	Pro	Gln	Met	Ile 170	Thr	Pro	Arg	Met	Met	Cys
Val	Gly	Phe	Leu 180	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Gly	Gly	Asp	Ser	Gly
Gly	Pro	Leu	Ser 195	Ser	Val	Glu	Ala	Asp 200	Gly	Arg	Ile	Phe	Gln	Ala	Gly
Val	Val 210	Ser	Trp	Gly	Leu	Gly 215	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
Tyr 225	Thr	Arg	Leu	Pro	Leu 230	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly 240

Val

<210> 78

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41G/F97L/F99L/C122S/Q175A/Q192T/D217V

<400> 78

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Gly	Cys	Gly	Ala	Ser	Leu	Ile
			20				25						30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Leu	Thr	Leu	Asp	Tyr
			85						90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Pro	Gln	Ala	Ile	Thr	Pro	Arg	Met	Met	Cys	
			165					170					175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Thr	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Val	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 79

<211> 241

<212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41G/F97V/F99L/C122S/G151Q/Q175M/Q192A/D217L

<400> 79

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Gly	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55						60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Val	Thr	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
	115						120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gln	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Met	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
	195						200					205			
Val	Val	Ser	Trp	Gly	Leu	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 80

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41G/F97I/F99L/C122S/G151L/Q175M/Q192S/D217V

4939SEQ.PC2

<400> 80

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ile Thr Leu Asp Tyr
      85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Leu Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225          230          235          240
Val

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<210> 81

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

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<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      I41G/F97S/F99L/C122S/G151N/Q175L/Q192G/D217I

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<400> 81

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45

```


4939SEQ.PC2

Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 82
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Buforin II

<400> 82
Thr Arg Ser Ser Arg Ala Gly Leu Gln Phe Pro Val Gly Arg Val His
1 5 10 15
Arg Leu Leu Arg Lys
20

<210> 83
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> DPV3

<400> 83

4939SEQ.PC2

Arg Lys Lys Arg Arg Arg Glu Ser Arg Lys Lys Arg Arg Arg Glu Ser
1 5 10 15

<210> 84
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> DPV6

<400> 84
Gly Arg Pro Arg Glu Ser Gly Lys Lys Arg Lys Arg Lys Arg Leu Lys
1 5 10 15
Pro

<210> 85
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> DPV7

<400> 85
Gly Lys Arg Lys Lys Lys Gly Lys Leu Gly Lys Lys Arg Asp Pro
1 5 10 15

<210> 86
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> DPV7b

<400> 86
Gly Lys Arg Lys Lys Lys Gly Lys Leu Gly Lys Lys Arg Pro Arg Ser
1 5 10 15
Arg

<210> 87
<211> 18
<212> PRT
<213> Artificial Sequence

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4939SEQ.PC2

<220>

<223> DPV3/10

<400> 87

Arg Lys Lys Arg Arg Arg Glu Ser Arg Arg Ala Arg Arg Ser Pro Arg
1 5 10 15
His Leu

<210> 88

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> DPV10/6

<400> 88

Ser Arg Arg Ala Arg Arg Ser Pro Arg Glu Ser Gly Lys Lys Arg Lys
1 5 10 15
Arg Lys Arg

<210> 89

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> DPV1047

<400> 89

Val Lys Arg Gly Leu Lys Leu Arg His Val Arg Pro Arg Val Thr Arg
1 5 10 15
Met Asp Val

<210> 90

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> DPV1048

<400> 90

Val Lys Arg Gly Leu Lys Leu Arg His Val Arg Pro Arg Val Thr Arg
1 5 10 15
Asp Val

<210> 91
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> DPV10

<400> 91
Ser Arg Arg Ala Arg Arg Ser Pro Arg His Leu Gly Ser Gly
1 5 10

<210> 92
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> DPV15

<400> 92
Leu Arg Arg Glu Arg Gln Ser Arg Leu Arg Arg Glu Arg Gln Ser Arg
1 5 10 15

<210> 93
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> DPV15b

<400> 93
Gly Ala Tyr Asp Leu Arg Arg Arg Glu Arg Gln Ser Arg Leu Arg Arg
1 5 10 15
Arg Glu Arg Gln Ser Arg
20

<210> 94
<211> 30
<212> PRT
<213> Artificial Sequence

<220>

4939SEQ.PC2

<223> GALA

<400> 94

Trp	Glu	Ala	Ala	Leu	Ala	Glu	Ala	Leu	Ala	Glu	Ala	Leu	Ala	Glu	His
1				5				10						15	
Leu	Ala	Glu	Ala	Leu	Ala	Glu	Ala	Leu	Glu	Ala	Leu	Ala	Ala		
			20					25					30		

<210> 95

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Fibrinogen beta chain

<400> 95

Lys	Gly	Ser	Trp	Tyr	Ser	Met	Arg	Lys	Met	Ser	Met	Lys	Ile	Arg	Pro
1				5				10						15	
Phe	Phe	Pro	Gln	Gln											
			20												

<210> 96

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Fibrinogen gamma chain precursor

<400> 96

Lys	Thr	Arg	Tyr	Tyr	Ser	Met	Lys	Lys	Thr	Thr	Met	Lys	Ile	Ile	Pro
1				5				10						15	
Phe	Asn	Arg	Leu												
			20												

<210> 97

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Fibrinogen alpha chain

<400> 97

Arg	Gly	Ala	Asp	Tyr	Ser	Leu	Arg	Ala	Val	Arg	Met	Lys	Ile	Arg	Pro
1				5				10						15	

Leu Val Thr Gln
20

<210> 98
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> hCT(9-32)

<400> 98
Leu Gly Thr Tyr Thr Gln Asp Phe Asn Lys Phe His Thr Phe Pro Gln
1 5 10 15
Thr Ala Ile Gly Val Gly Ala Pro
20

<210> 99
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> HN-1

<400> 99
Thr Ser Pro Leu Asn Ile His Asn Gly Gln Lys Leu
1 5 10

<210> 100
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Influenza virus nucleoprotein (NLS)

<400> 100
Asn Ser Ala Ala Phe Glu Asp Leu Arg Val Leu Ser
1 5 10

<210> 101
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> KALA

4939SEQ.PC2

<400> 101

Trp	Glu	Ala	Lys	Leu	Ala	Lys	Ala	Leu	Ala	Lys	Ala	Leu	Ala	Lys	His
1				5				10						15	
Leu	Ala	Lys	Ala	Leu	Ala	Lys	Ala	Leu	Lys	Ala	Cys	Glu	Ala		
			20					25					30		

<210> 102

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Ku70

<400> 102

Val	Pro	Met	Leu	Lys	Pro	Met	Leu	Lys	Glu
1				5				10	

<210> 103

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> MAP

<400> 103

Lys	Leu	Ala	Leu	Lys	Leu	Ala	Leu	Lys	Ala	Leu	Lys	Ala	Ala	Leu	Lys
1				5				10						15	
Leu	Ala														

<210> 104

<211> 27

<212> PRT

<213> Artificial Sequence

<220>

<223> MPG

<400> 104

Gly	Ala	Leu	Phe	Leu	Gly	Phe	Leu	Gly	Ala	Ala	Gly	Ser	Thr	Met	Gly
1				5				10						15	
Ala	Trp	Ser	Gln	Pro	Lys	Lys	Lys	Arg	Lys	Val					
			20					25							

<210> 105

4939SEQ.PC2

<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Human Fibroblast growth factor 4 (Kaposi
Fibroblast growth
factor)

<400> 105
Ala Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Leu Ala Pro
1 5 10 15

<210> 106
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> N50 (NLS of NF-kB P50)

<400> 106
Val Gln Arg Lys Arg Gln Lys Leu Met
1 5

<210> 107
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Pep-1

<400> 107
Lys Glu Thr Trp Trp Glu Thr Trp Trp Thr Glu Trp Ser Gln Pro Lys
1 5 10 15
Lys Lys Arg Lys Val
20

<210> 108
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Pep-7

<400> 108

4939SEQ.PC2

Ser Asp Leu Trp Glu Met Met Met Val Ser Leu Ala Cys Gln Tyr
1 5 10 15

<210> 109
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Penetratin

<400> 109
Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> 110
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Penetratin variant

<400> 110
Gly Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys
1 5 10 15
Lys

<210> 111
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Short Penetratin

<400> 111
Arg Arg Met Lys Trp Lys Lys
1 5

<210> 112
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Penetratin 42-58

<400> 112

Glu Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys
1 5 10 15
Lys

<210> 113

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Poly Arginine - R7

<400> 113

Arg Arg Arg Arg Arg Arg Arg
1 5

<210> 114

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Poly Arginine - R9

<400> 114

Arg Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> 115

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> pISL

<400> 115

Arg Val Ile Arg Val Trp Phe Gln Asn Lys Arg Cys Lys Asp Lys Lys
1 5 10 15

<210> 116

<211> 28

<212> PRT

<213> Artificial Sequence

4939SEQ.PC2

<220>

<223> Prion mouse PrPc1-28

<400> 116

Met	Ala	Asn	Leu	Gly	Tyr	Trp	Leu	Leu	Ala	Leu	Phe	Val	Thr	Met	Trp
1				5				10						15	
Thr	Asp	Val	Gly	Leu	Cys	Lys	Lys	Arg	Pro	Lys	Pro				
			20				25								

<210> 117

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> pVEC

<400> 117

Leu	Leu	Ile	Ile	Leu	Arg	Arg	Arg	Ile	Arg	Lys	Gln	Ala	His	Ala	His
1				5				10						15	
Ser	Lys														

<210> 118

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> pVEC variant

<400> 118

Leu	Leu	Ile	Ile	Leu	Arg	Arg	Arg	Ile	Arg	Lys	Gln	Ala	His	Ala	His
1				5				10						15	

<210> 119

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> SAP

<400> 119

Val	Arg	Leu	Pro	Pro	Pro	Val	Arg	Leu	Pro	Pro	Pro	Val	Arg	Leu	Pro
1				5				10						15	
Pro	Pro														

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4939SEQ.PC2

<210> 120
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> SV-40 (NLS)

<400> 120
Pro Lys Lys Lys Arg Lys Val
1 5

<210> 121
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> SynB1

<400> 121
Arg Gly Gly Arg Leu Ser Tyr Ser Arg Arg Arg Phe Ser Thr Ser Thr
1 5 10 15
Gly Arg

<210> 122
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> SynB3

<400> 122
Arg Arg Leu Ser Tyr Ser Arg Arg Arg Phe
1 5 10

<210> 123
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> SynB4

<400> 123
Ala Trp Ser Phe Arg Val Ser Tyr Arg Gly Ile Ser Tyr Arg Arg Ser

4939SEQ.PC2
10

15

1
Arg

5

<210> 124
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 47-60

<400> 124
Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
1 5 10

<210> 125
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 47-57

<400> 125
Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5 10

<210> 126
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 47-56

<400> 126
Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg
1 5 10

<210> 127
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 48-56

<400> 127
Gly Arg Lys Lys Arg Arg Gln Arg Arg
1 5

<210> 128
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 48-57

<400> 128
Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5 10

<210> 129
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 49-57

<400> 129
Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5

<210> 130
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 49-56

<400> 130
Arg Lys Lys Arg Arg Gln Arg Arg
1 5

<210> 131
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 48-60

<400> 131

Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
 1 5 10

<210> 132

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Tat 48-52

<400> 132

Gly Arg Lys Lys Arg
 1 5

<210> 133

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> Tat 37-72

<400> 133

Cys Phe Ile Thr Lys Ala Leu Gly Ile Ser Tyr Gly Arg Lys Lys Arg
 1 5 10 15
 Arg Gln Arg Arg Arg Pro Pro Gln Phe Ser Gln Thr His Gln Val Ser
 20 25 30
 Leu Ser Lys Gln
 35

<210> 134

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Tat 38-72

<400> 134

Phe Ile Thr Lys Ala Leu Gly Ile Ser Tyr Gly Arg Lys Lys Arg Arg
 1 5 10 15
 Gln Arg Arg Arg Pro Gln Phe Ser Gln Thr His Gln Val Ser Leu Ser
 20 25 30

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Lys Gln

<210> 135
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Tat 47-59

<400> 135
Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro
1 5 10

<210> 136
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Transportan

<400> 136
Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Lys Ile Asn Leu
1 5 10 15
Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25

<210> 137
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Transportan 10

<400> 137
Ala Gly Tyr Leu Leu Gly Lys Ile Asn Leu Lys Ala Leu Ala Ala Leu
1 5 10 15
Ala Lys Lys Ile Leu
20

<210> 138
<211> 12
<212> PRT
<213> Artificial Sequence

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<220>

<223> Transportan derivative

<400> 138

Gly	Trp	Thr	Leu	Asn	Ser	Ala	Gly	Tyr	Leu	Leu	Gly
1				5					10		

<210> 139

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Transportan derivative 2

<400> 139

Ile	Asn	Leu	Lys	Ala	Leu	Ala	Ala	Leu	Ala	Lys	Lys	Ile	Leu
1				5					10				

<210> 140

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> VP22

<400> 140

Asp	Ala	Ala	Thr	Ala	Thr	Arg	Gly	Arg	Ser	Ala	Ala	Ser	Arg	Pro	Thr
1				5					10					15	
Glu	Arg	Pro	Arg	Ala	Pro	Ala	Arg	Ser	Ala	Ser	Arg	Pro	Arg	Arg	Pro
			20					25					30		
Val	Asp														

<210> 141

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> VT5

<400> 141

Asp	Pro	Lys	Gly	Asp	Pro	Lys	Gly	Val	Thr	Val	Thr	Val	Thr	Val	Thr
1				5					10					15	

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Val Thr Gly Lys Gly Asp Pro Lys Pro Asp
20 25

<210> 142
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Signal Sequence-based peptide

<400> 142
Gly Ala Leu Phe Leu Gly Trp Leu Gly Ala Ala Gly Ser Thr Met Gly
1 5 10 15
Ala Trp Ser Gln Pro Lys Lys Lys Arg Lys Val
20 25

<210> 143
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Amphiphilic model peptide

<400> 143
Lys Leu Ala Leu Lys Leu Ala Leu Lys Ala Leu Lys Ala Ala Leu Lys
1 5 10 15
Leu Ala

<210> 144
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Bacterial cell wall permeating

<400> 144
Lys Phe Phe Lys Phe Phe Lys Phe Phe Lys
1 5 10

<210> 145
<211> 37

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<212> PRT

<213> Artificial Sequence

<220>

<223> LL- 37

<400> 145

Leu	Leu	Gly	Asp	Phe	Phe	Arg	Lys	Ser	Lys	Glu	Lys	Ile	Gly	Lys	Glu
1				5				10					15		
Phe	Lys	Arg	Ile	Val	Gln	Arg	Ile	Lys	Asp	Phe	Leu	Arg	Asn	Leu	Val
			20					25					30		
Pro	Arg	Thr	Glu	Ser											
			35												

<210> 146

<211> 31

<212> PRT

<213> Artificial Sequence

<220>

<223> Cecropin P1

<400> 146

Ser	Trp	Leu	Ser	Lys	Thr	Ala	Lys	Lys	Leu	Glu	Asn	Ser	Ala	Lys	Lys
1				5				10					15		
Arg	Ile	Ser	Glu	Gly	Ile	Ala	Ile	Ala	Ile	Gln	Gly	Gly	Pro	Arg	
			20					25					30		

<210> 147

<211> 30

<212> PRT

<213> Artificial Sequence

<220>

<223> alpha defensin

<400> 147

Ala	Cys	Tyr	Cys	Arg	Ile	Pro	Ala	Cys	Ile	Ala	Gly	Glu	Arg	Arg	Tyr
1				5				10					15		
Gly	Thr	Cys	Ile	Tyr	Gln	Gly	Arg	Leu	Trp	Ala	Phe	Cys	Cys		
			20					25					30		

<210> 148

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> beta defensin

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<400> 148

Asp	His	Tyr	Asn	Cys	Val	Ser	Ser	Gly	Gly	Gln	Cys	Leu	Tyr	Ser	Ala
1				5					10					15	
Cys	Pro	Ile	Phe	Thr	Lys	Ile	Gln	Gly	Thr	Cys	Tyr	Arg	Gly	Lys	Ala
			20					25					30		
Lys	Cys	Cys	Lys												
		35													

<210> 149

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Bactenecin

<400> 149

Arg	Lys	Cys	Arg	Ile	Trp	Ile	Arg	Val	Cys	Arg
1				5					10	

<210> 150

<211> 42

<212> PRT

<213> Artificial Sequence

<220>

<223> PR- 39

<400> 150

Arg	Arg	Arg	Pro	Arg	Pro	Pro	Tyr	Leu	Pro	Arg	Pro	Arg	Pro	Pro	Pro
1				5					10					15	
Phe	Phe	Pro	Pro	Arg	Leu	Pro	Pro	Arg	Ile	Pro	Pro	Gly	Phe	Pro	Pro
			20					25					30		
Arg	Phe	Pro	Pro	Arg	Phe	Pro	Gly	Lys	Arg						
		35					40								

<210> 151

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Indolicidin

<400> 151

Ile	Leu	Pro	Trp	Lys	Trp	Pro	Trp	Trp	Pro	Trp	Arg	Arg
1				5					10			

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<210> 152
 <211> 27
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MPS

<400> 152
 Gly Ala Leu Phe Leu Gly Trp Leu Gly Ala Ala Gly Ser Thr Met Gly
 1 5 10 15
 Ala Trp Ser Gln Pro Lys Lys Lys Arg Lys Val
 20 25

<210> 153
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> pIs1

<400> 153
 Pro Val Ile Arg Arg Val Trp Phe Gln Asn Lys Arg Cys Lys Asp Lys
 1 5 10 15
 Lys

<210> 154
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97E/F99L/C122S/D217I/K224N

<400> 154
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80

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Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Glu Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Asn Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 155

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain C122S/G193A

<400> 155

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr

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      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Ala Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 156

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain C122S/G193E

<400> 156

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Glu Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly

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		195					200				205								
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val				
	210					215					220								
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly				
225					230					235					240				
Val																			

<210> 157

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain D96_F97delinsWYY/T98P/F99L/C122S

<400> 157

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val				
1				5					10					15					
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ile	Cys	Gly	Ala	Ser	Leu	Ile				
		20					25					30							
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg				
		35					40					45							
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu				
	50					55					60								
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu				
65					70					75					80				
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Trp	Tyr	Tyr	Pro	Leu	Asp				
				85					90					95					
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser				
			100					105					110						
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala				
		115					120					125							
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly				
	130					135					140								
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln				
145					150					155					160				
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met				
				165					170					175					
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser				
			180					185				190							
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala				
		195					200					205							
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly				
	210					215					220								
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr				
225					230					235					240				
Gly	Val																		

<210> 158
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97D/F99L/C122S/Q192G

<400> 158
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 159
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

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domain H40R/I41H/F97D/F99L/C122S/Q192G

<400> 159

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 160

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain C122S/G151N/G193A

<400> 160

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg

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```

      35              40              45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
      85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100              105              110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115              120              125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130              135              140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145              150              155              160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165              170              175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Ala Asp Ser Gly
      180              185              190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195              200              205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210              215              220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225              230              235              240
Val

```

<210> 161

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/C122S/G151N

<400> 161

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1              5              10              15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20              25              30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35              40              45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
      85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met

```

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```

      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 162

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/C122S/G151N

<400> 162

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys

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4939SEQ.PC2

				165				170					175				
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly		
			180					185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		
		195					200					205					
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val		
	210					215					220						
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly		
225					230					235					240		
Val																	

<210> 163

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97E/C122S

<400> 163

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
1				5				10						15			
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	Arg	His	Cys	Gly	Ala	Ser	Leu	Ile		
		20					25					30					
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg		
		35				40						45					
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55					60							
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu		
65				70					75						80		
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Glu	Thr	Phe	Asp	Tyr		
			85					90					95				
Asp	Ile	Ala	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met			
		100				105						110					
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly		
	115					120					125						
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr		
	130				135					140							
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr		
145				150					155						160		
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	Cys		
			165					170					175				
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly		
		180					185					190					
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		
	195					200						205					
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val		
	210					215					220						
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly		

225 Val 230 235 240

<210> 164
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E

<400> 164
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 165
 <211> 241
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/Y60gL/F97D/F99L/C122S/G151N/Q175M/D217I/K224S

<400> 165

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	Arg	Ile	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Leu	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55						60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Leu	Asp	Tyr
			85						90					95	
Asp	Ile	Ala	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met	
			100				105					110			
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
	115						120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Met	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
	195						200					205			
Val	Val	Ser	Trp	Gly	Ile	Gly	Cys	Ala	Gln	Arg	Asn	Ser	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 166

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain H40R/I41H/F97D/F99L/C122S/G151D/Q192G

4939SEQ.PC2

<400> 166

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225          230          235          240
Val

```

<210> 167

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/F99L/Q192G

<400> 167

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```


4939SEQ.PC2

```

      50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100              105              110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115              120              125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130              135              140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145              150              155              160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165              170              175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180              185              190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195              200              205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210              215              220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225              230              235              240
Val

```

<210> 168

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/Y60gH/F97D/F99L/C122S/G151N/Q175A/Q192H/
D217I/K224R

<400> 168

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg His Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met

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4939SEQ.PC2

```

      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Ala Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 169

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

```

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      H40R/I41H/Y60gF/F97D/F99L/C122S/Q192G/D217M/K224R

```

<400> 169

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160

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4939SEQ.PC2

```

Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Met Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 170

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

H40R/I41H/Y60gF/F97D/F99L/C122S/Q192G/D217R/K224A

<400> 170

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Arg Gly Cys Ala Gln Arg Asn Ala Pro Gly Val

```

4939SEQ.PC2

210	215	220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly		
225	230	235
Val		240

<210> 171

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/F97D/F99L/C122S/Q175L/Q192G/D217K/K224A

<400> 171

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val	
1 5 10 15	
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile	
20 25 30	
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg	
35 40 45	
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu	
50 55 60	
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu	
65 70 75 80	
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr	
85 90 95	
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met	
100 105 110	
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly	
115 120 125	
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr	
130 135 140	
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr	
145 150 155 160	
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys	
165 170 175	
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly	
180 185 190	
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly	
195 200 205	
Val Val Ser Trp Gly Lys Gly Cys Ala Gln Arg Asn Ala Pro Gly Val	
210 215 220	
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly	
225 230 235 240	
Val	

4939SEQ.PC2

<210> 172
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 H40R/I41H/F97D/F99L/C122S/Q175M/Q192G/D217V/K224Y

<400> 172
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Tyr Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 173
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

H40R/I41H/F97D/F99L/C122S/Q175K/Q192G/D217I/K224H

<400> 173

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Lys Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn His Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 174

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/F99L/C122S/Q175M/Q192G/D217S

<400> 174

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30

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4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
           85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
           100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
           115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
           130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
           145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
           165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
           180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
           195          200          205
Val Val Ser Trp Gly Ser Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
           210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
           225          230          235          240
Val

```

<210> 175

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/Y60gF/F97D/F99L/C122S/Q175M/Q192G/D217W/
K224R

<400> 175

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
           20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
           35          40          45
Gly Phe Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
           50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
           65          70          75          80

```

4939SEQ.PC2

Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Trp Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 176

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

H40R/I41H/Y60gN/F97D/F99L/C122S/G151N/Q175K/Q192S/
 D217S/K224L

<400> 176

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Asn Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125

4939SEQ.PC2

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Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Lys Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Ser Gly Cys Ala Gln Arg Asn Leu Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

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<210> 177

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/Y60gH/F97D/F99L/C122S/Q175M/Q192G/D217I/K224L

<400> 177

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg His Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
          165          170          175

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4939SEQ.PC2

Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Leu Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 178

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain H40K/I41L/Y60gF/F97D/F99L/C122S/G151N/Q175R

<400> 178

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Lys Leu Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240

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4939SEQ.PC2

Val

<210> 179
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/Y60gL/F97D/F99L/C122S/G151N

<400> 179
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Leu Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 180
<211> 241
<212> PRT
<213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40K/I41M/Y60gG/F97D/F99L/C122S/G151N/Q175R/Q192R/D217V/K224S

<400> 180

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	Lys	Met	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Gly	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
		130				135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Arg	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Arg	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Val	Gly	Cys	Ala	Gln	Arg	Asn	Ser	Pro	Gly	Val
		210				215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 181

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40K/I41M/Y60gF/F97D/F99L/C122S/G151N/Q175L/Q192D

4939SEQ.PC2

<400> 181

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly Lys Met Cys Gly Ala Ser Leu Ile
          20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35           40           45
Gly Phe Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
          85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
          145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
          225          230          235          240
Val

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<210> 182

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

H40R/I41H/F97D/C122S/G151N/Q175M/Q192A/D217S/K224R

<400> 182

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
          20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35           40           45

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4939SEQ.PC2

Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Phe Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Ser Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 183

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

 H40R/I41H/Y60gH/F97D/F99L/C122S/Q175M/Q192G/D217I/
 K224R

<400> 183

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg His Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95

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Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

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<210> 184

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/F97D/F99L/C122S/G151D/Q175M/Q192G/D217V

<400> 184

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

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145	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Met	Ile	Thr	Pro	Arg	Met	Met	Cys	160
					165					170						175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser	Gly		
			180					185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		
		195					200					205					
Val	Val	Ser	Trp	Gly	Val	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val		
	210					215					220						
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly		
225					230					235					240		
Val																	

<210> 185

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/F97D/F99L/C122S/G151N/Q175M/Q192A/D217N/

K224R

<400> 185

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
1				5				10						15			
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	Arg	His	Cys	Gly	Ala	Ser	Leu	Ile		
			20				25					30					
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg		
		35				40						45					
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55					60							
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu		
65				70					75					80			
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Leu	Asp	Tyr		
			85					90					95				
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met		
		100				105						110					
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly		
	115					120						125					
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr		
	130					135					140						
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr		
145				150				155						160			
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Met	Ile	Thr	Pro	Arg	Met	Met	Cys		
			165					170						175			
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser	Gly		
		180						185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		

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195 200 205
 Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 186
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 H40R/I41H/F97D/F99L/C122S/G151N/Q175L/Q192A/D217N/
 K224R

<400> 186
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 187
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 H40K/I41M/F97D/F99L/C122S/G151N/Q175M/Q192D/D217N/
 K224R

<400> 187
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Lys Met Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 188
 <211> 241
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
H40K/I41M/F97D/F99L/C122S/G151N/Q175L/Q192A/D217N/
K224R

<400> 188

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	Lys	Met	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55						60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met	
			100				105					110			
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
				165					170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Asn	Gly	Cys	Ala	Gln	Arg	Asn	Arg	Pro	Gly	Val
	210				215						220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 189

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
H40R/I41H/F97D/F99L/C122S/Q175M/Q192D/D217N/K224R

4939SEQ.PC2

<400> 189

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
          65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
          145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
          225          230          235          240
Val

```

<210> 190

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/F99L/C122S/Q175M/D217N/K224R

<400> 190

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45

```

4939SEQ.PC2

Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 191

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40K/I41M/F97D/F99L/C122S/Q175M/Q192D/D217N/K224R

<400> 191

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Lys Met Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met

4939SEQ.PC2

```

      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 192

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

```

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      H40K/I41M/F97D/F99L/C122S/G151N/Q175M/Q192A/D217N/
      K224R

```

<400> 192

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Lys Met Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

```

4939SEQ.PC2

```

145              150              155              160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
              165              170              175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
              180              185              190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
              195              200              205
Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
              210              215              220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225              230              235              240
Val

```

<210> 193

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40K/I41M/F97D/F99L/C122S/Q175M/D217N/K224R

<400> 193

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Lys Met Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Arg Pro Gly Val

```

4939SEQ.PC2

210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 194
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 H40R/I41H/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E

<400> 194
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 195
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 H40R/I41H/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G

<400> 195
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 196
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

H40R/I41H/F97E/ins97aE/T98G/F99L/C122S/Q175L/Q192G

<400> 196

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Glu Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 197

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain H40R/I41H/F97D/F99L/C122S/G151N/Q192H

<400> 197

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30

```

4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
           85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
           100        105        110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
           115        120        125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
           130        135        140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
   145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
           165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser Gly
           180        185        190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
           195        200        205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
   210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
   225          230          235          240
Val

```

<210> 198

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/F99L/C122S/G151N/L153R

<400> 198

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
   1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
           20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
           35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
           50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
           85          90          95

```

4939SEQ.PC2

```

Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Arg Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 199

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/C122S/G151N/L153R/V202M

<400> 199

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Arg Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160

```

4939SEQ.PC2

```

Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Met Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 200

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/F99L/C122S/G151N/Q192H/P232S

<400> 200

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220

```

4939SEQ.PC2

Tyr Thr Arg Leu Ser Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 201
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 H40R/I41H/F97D/ins97aE/T98G/F99L/C122S/Q175L/Q192G

<400> 201
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 202

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain H40R/I41H/F97D/C122S/G151N/L153R

<400> 202
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Phe Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Arg Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 203
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain H40K/I41M/F99L/C122S/T150A/G151R/Q192G

4939SEQ.PC2

<400> 203

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly Lys Met Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Ala
 130          135          140
Arg Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145          150          155          160
Thr Cys Glu Asn Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225          230          235          240
Val

```

<210> 204

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/C122S/G133D/G151N

<400> 204

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```


4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Asp
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 205

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41R/F99L/C122S/Q192G

<400> 205

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly

```

4939SEQ.PC2

```

      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225      230      235      240
Val

```

<210> 206

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F99L/C122S/G151K/Q192G

<400> 206

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Lys Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly

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180 185 190															
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
195 200 205															
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
210 215 220															
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225 230 235 240															
Val															

<210> 207
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
I41R/ins97aE/F97T/T98G/F99L/C122S/G151E/Q175L/Q192E

<400> 207															
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Gln	Gly	His 25	Arg	Cys	Gly	Ala 30	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu 80
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Thr	Glu	Gly	Leu 95	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala 120	Ser	His	Val 125	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr 135	Gly	Trp	Gly	His 140	Thr	Gln	Tyr	Gly	Gly
Thr 145	Glu	Ala	Leu	Ile	Leu 150	Gln	Lys	Gly	Glu	Ile 155	Arg	Val	Ile	Asn	Gln 160
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu 170	Ile	Thr	Pro	Arg	Met 175	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val 185	Asp	Ser	Cys	Glu	Gly	Asp	Ser
Gly	Gly 195	Pro	Leu	Ser	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile 205	Phe	Gln	Ala
Gly	Val 210	Val	Ser	Trp	Gly	Asp 215	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr

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4939SEQ.PC2

225	230	235	240
Gly Val			

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<210> 208
<211> 241
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain K86R/K110R/C122S/K134R/K157R/K224R/K239R

<400>	208														
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Gln	Gly	His 25	Ile	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
Arg	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Phe	Thr	Phe	Asp	Tyr
Asp	Ile	Ala	Leu 100	Leu	Glu	Leu	Glu	Arg 105	Pro	Ala	Glu	Tyr	Ser	Ser	Met
Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp 120	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
Arg	Ala 130	Ile	Trp	Val	Thr	Gly 135	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
Gly 145	Ala	Leu	Ile	Leu	Gln 150	Arg	Gly	Glu	Ile	Arg 155	Val	Ile	Asn	Gln	Thr
Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Gln	Ile 170	Thr	Pro	Arg	Met	Met	Cys
Val	Gly	Phe	Leu 180	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Gln	Gly	Asp	Ser	Gly
Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
Val	Val 210	Ser	Trp	Gly	Asp	Gly 215	Cys	Ala	Gln	Arg	Asn 220	Arg	Pro	Gly	Val
Tyr 225	Thr	Arg	Leu	Pro	Leu 230	Phe	Arg	Asp	Trp	Ile 235	Arg	Glu	Asn	Thr	Gly
Val															

<210>	209
<211>	241
<212>	PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/K86R/F97D/K110R/C122S/K134R/G151N/K157R/
K224R/K239R

<400> 209

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val	1		5		10		15
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	Arg	His	Cys	Gly	Ala	Ser	Leu	Ile	20		25		30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg	35		40		45		
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu	50		55		60		
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu	65		70		75		80
Arg	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Phe	Asp	Tyr	85		90		95		
Asp	Ile	Ala	Leu	Glu	Leu	Glu	Arg	Pro	Ala	Glu	Tyr	Ser	Ser	Met		100		105		110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly	115		120		125		
Arg	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr	130		135		140		
Asn	Ala	Leu	Ile	Leu	Gln	Arg	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr	145		150		155		160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	Cys	165		170		175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly	180		185		190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly	195		200		205		
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Arg	Pro	Gly	Val	210		215		220		
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Arg	Glu	Asn	Thr	Gly	225		230		235		240
Val																						

<210> 210

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

K86R/F97T/ins97aE/T98G/F99L/K110R/C122S/K134R/K157

4939SEQ.PC2

R/Q175L/Q192E/K224R/K239R

<400> 210

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Arg Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Arg Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Arg Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Arg Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Arg Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Arg Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 211

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

H40R/I41H/F97D/F99L/C122S/Q175R/Q192G/D217H/K224S

<400> 211

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30

```

4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35              40              45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100             105             110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115             120             125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130             135             140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145             150             155             160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
      165             170             175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180             185             190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195             200             205
Val Val Ser Trp Gly His Gly Cys Ala Gln Arg Asn Ser Pro Gly Val
      210             215             220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225             230             235             240
Val

```

<210> 212

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/F99L/C122S/Q192G/D217I/K224S

<400> 212

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1              5              10              15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20              25              30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35              40              45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85              90              95

```

4939SEQ.PC2

```

Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Ser Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 213

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/F99L/C122S/Q192G/D217K/K224A

<400> 213

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160

```


4939SEQ.PC2

```

Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Lys Gly Cys Ala Gln Arg Asn Ala Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 214

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

H40R/I41H/F97D/F99L/C122S/Q175R/Q192G/D217E/K224R

<400> 214

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Glu Gly Cys Ala Gln Arg Asn Arg Pro Gly Val

```

4939SEQ.PC2

210	215	220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly		
225	230	235
Val		240

<210> 215

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
H40R/I41H/F97D/C122S/Q175R/Q192G/D217I/K224Q

<400> 215

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val	
1 5 10 15	
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile	
20 25 30	
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg	
35 40 45	
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu	
50 55 60	
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu	
65 70 75 80	
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Phe Asp Tyr	
85 90 95	
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met	
100 105 110	
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly	
115 120 125	
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr	
130 135 140	
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr	
145 150 155 160	
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys	
165 170 175	
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly	
180 185 190	
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly	
195 200 205	
Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Gln Pro Gly Val	
210 215 220	
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly	
225 230 235 240	
Val	

4939SEQ.PC2

<210> 216
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40P/I41R/F99L/C122S/Q192G

<400> 216
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly Pro Arg Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 217
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40P/I41R/F99L/C122S/G151K/Q192G

4939SEQ.PC2

<400> 217

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly Pro Arg Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Lys Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225          230          235          240
Val

```

<210> 218

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F99L/C122S/G151E/Q192G

<400> 218

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45

```

4939SEQ.PC2

Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Glu Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 219

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

 I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175L/Q192
 E

<400> 219

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95

4939SEQ.PC2

```

Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 220

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175T/Q192

E

<400> 220

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140

```

4939SEQ.PC2

```

Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

```

<210> 221

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175T/Q192

D

<400> 221

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
          20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100     105     110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115     120     125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130     135     140
Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145     150     155     160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met
          165     170     175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180     185     190

```

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4939SEQ.PC2

Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 222
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41R/ins97aE/F97T/T98G/F99L/C122S/G151E/Q175T/Q192
 D

<400> 222
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Glu Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240

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4939SEQ.PC2

Gly Val

<210> 223

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

H40P/I41R/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E

<400> 223

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	Pro	Arg	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55				60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75				80	
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 224

<211> 242

<212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
H40P/I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175L
/Q192E

<400> 224

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Pro Arg Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
          145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
          225          230          235          240
Gly Val

```

<210> 225

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192

4939SEQ.PC2

E

<400> 225

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 226

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192
D

<400> 226

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile

```

4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 227

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175T/Q192

E

<400> 227

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

```

4939SEQ.PC2

```

65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met
      165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

```

<210> 228

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175T/Q192

D

<400> 228

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

```

4939SEQ.PC2

```

      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
  130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 229
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41R/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E

```

<400> 229
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175

```

4939SEQ.PC2

Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 230

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain H40P/I41R/F99L/C122S/G151E/Q192G

<400> 230

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly Pro Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Glu Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240

Val

<210> 231
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41R/F97T/ins97aE/T98G/F99L/C122S/G151E/Q175T/Q192
E

<400> 231
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
85 90 95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
100 105 110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
115 120 125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130 135 140
Thr Glu Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145 150 155 160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met
165 170 175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
180 185 190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
195 200 205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
210 215 220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225 230 235 240
Gly Val

<210> 232
<211> 242

4939SEQ.PC2

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175S/Q192E

<400> 232

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 233

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

4939SEQ.PC2

I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175I/Q192
E

<400> 233

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Arg	Cys	Gly	Ala	Ser	Leu	Ile
		20					25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Ile	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 234

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainH40R/I41H/Y60gF/F97D/F99L/C122S/Q175K/Q192G/D217R/
K224Q

<400> 234

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	

4939SEQ.PC2

```

Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
   20                               25                               30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35                               40                               45
Gly Phe Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                               55                               60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65                               70                               75                               80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
   85                               90                               95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
  100                               105                               110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
  115                               120                               125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
  130                               135                               140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145                               150                               155                               160
Thr Cys Glu Asn Leu Leu Pro Gln Lys Ile Thr Pro Arg Met Met Cys
  165                               170                               175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
  180                               185                               190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
  195                               200                               205
Val Val Ser Trp Gly Arg Gly Cys Ala Gln Arg Asn Gln Pro Gly Val
  210                               215                               220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225                               230                               235                               240
Val

```

<210> 235

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

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<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      H40R/I41H/F97D/F99L/C122S/Q175L/Q192G/D217Q/K224R

```

<400> 235

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                               5                               10                               15
Ser Leu His Ala Leu Gly Gln Gly Arg Ile Cys Gly Ala Ser Leu Ile
   20                               25                               30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35                               40                               45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                               55                               60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

```

4939SEQ.PC2

```

65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100        105        110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115        120        125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130        135        140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145        150        155        160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165        170        175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180        185        190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195        200        205
Val Val Ser Trp Gly Gln Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
      210        215        220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225        230        235        240
Val

```

<210> 236

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

```

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      H40R/I41H/F97D/F99L/C122S/G151N/Q192N/D217L/K224R

```

<400> 236

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20        25        30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35        40        45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50        55        60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100        105        110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115        120        125

```

4939SEQ.PC2

```

Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asn Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 237

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/F97D/F99L/C122S/G151N/Q192H/D217K/K224A

<400> 237

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser Gly

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185

180 185 190															
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
195 200 205															
Val	Val	Ser	Trp	Gly	Lys	Gly	Cys	Ala	Gln	Arg	Asn	Ala	Pro	Gly	Val
210 215 220															
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225 230 235 240															
Val															

```
<210> 238
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain ins97aV/F97D/T98P/F99L/C122S/O192G

<400> 238

[illegible]

<210> 239
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97N/ins97aT/T98Y/F99N/C122S

<400> 239
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asn Thr Tyr Asn Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 240
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain F97M/ins97aD/T98D/F99L/C122S/Q192T

<400> 240

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Met Asp Asp Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 241

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain ins97aV/F97Q/T98P/F99L/C122S/Q175F/Q192D

<400> 241

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile

```


4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gln Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Phe Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 242

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
ins97aD/F97T/T98S/F99L/C122S/Q192E/D217Y/K224R

<400> 242

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80

```

4939SEQ.PC2

Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Asp Ser Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Tyr Gly Cys Ala Gln Arg Asn Arg Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 243

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

ins97aN/F97H/T98D/F99L/C122S/Q192E/D217Q/K224S

<400> 243

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp His Asn Asp Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly

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130					135					140					
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
165					170					175					
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
180					185					190					
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
195					200					205					
Gly	Val	Val	Ser	Trp	Gly	Gln	Gly	Cys	Ala	Gln	Arg	Asn	Ser	Pro	Gly
210					215					220					
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					
Gly	Val														

<210> 244

<211> 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain F970/ins97aT/T98M/C122S/Q192E/D217R/K224L

<400> 244

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Gln	Gly	His	Ile	Cys	Gly	Ala	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Gln	Thr	Met	Phe	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
Thr 145	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala

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195 200 205
 Gly Val Val Ser Trp Gly Arg Gly Cys Ala Gln Arg Asn Leu Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 245

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

ins97aD/F97Q/T98G/F99L/C122S/Q175L/Q192E/D217F/K22
4S

<400> 245

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gln Asp Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Phe Gly Cys Ala Gln Arg Asn Ser Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 246
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 ins97aD/F97G/T98N/F99L/C122S/Q192E/D217Y/K224R

<400> 246
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gly Asp Asn Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Tyr Gly Cys Ala Gln Arg Asn Arg Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 247
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
ins97aE/F97Y/T98S/F99L/C122S/Q192T/D217Q/K224R

<400> 247

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ile	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Tyr	Glu	Ser	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Thr	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Gln	Gly	Cys	Ala	Gln	Arg	Asn	Arg	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 248

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
ins97aG/F97N/T98D/F99L/C122S/Q192E/D217H/K224A

<400> 248

4939SEQ.PC2

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asn Gly Asp Leu Asp
 85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
195      200      205
Gly Val Val Ser Trp Gly His Gly Cys Ala Gln Arg Asn Ala Pro Gly
210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235
Gly Val

```

<210> 249

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

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<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      ins97aA/F97G/T98N/F99L/C122S/Q175M/Q192T/K224A

```

<400> 249

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

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4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gly Ala Asn Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Ala Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 250

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175S/Q192

D

<400> 250

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser

```


4939SEQ.PC2

```

      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 251

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175I/Q192

D

<400> 251

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln

```

4939SEQ.PC2

```

145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

```

<210> 252

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/F97T/ins97aE/T98G/F99L/C122S/G151D/Q175I/Q192

E

<400> 252

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala

```

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195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 253
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41R/ins97aE/F97T/T98G/F99L/C122S/G151D/Q175I/Q192
 D

<400> 253
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 254
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 S90T/D96A/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D

<400> 254
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Thr His Pro Phe Phe Asn Ala Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 255
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Y59F/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E

<400> 255

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ile	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Phe	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55						60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 256

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E/Q209L

<400> 256

4939SEQ.PC2

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Leu Ala
195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235
Gly Val

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<210> 257

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Y59F/D96V/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E

<400> 257

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```

4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Val Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 258

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
D96V/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D

<400> 258

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Val Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110

```

4939SEQ.PC2

```

Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
   115                               120               125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130                               135               140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145                               150               155               160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
   165                               170               175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
   180                               185               190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
   195                               200               205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
   210                               215               220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
  225                               230               235               240
Gly Val

```

<210> 259

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/ins97aE/F97T/T98G/F99L/C122S/G151S/Q175L/Q192
E

<400> 259

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
   20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
   85           90           95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
  100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
   115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130          135          140
Thr Ser Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145          150          155          160

```


4939SEQ.PC2

```

Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 260

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

E24K/ins97aE/F97T/T98G/F99L/C122S/A152S/Q175L/Q192

D

<400> 260

```

Val Val Gly Gly Thr Asp Ala Asp Lys Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ser Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205

```

4939SEQ.PC2

Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 261
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 ins97aE/F97T/T98G/F99L/C122S/L153Q/Q175L/Q192D

<400> 261
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Gln Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 262
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 ins97aE/F97T/T98G/F99L/C122S/I136M/L155M/N170D/Q17
 5L/Q192E

<400> 262
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Met Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Met Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asp Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 263
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41R/ins97aE/F97T/T98G/F99L/A112V/C122S/Q175L/Q192
E

<400> 263

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val	1		5		10		15
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Arg	Cys	Gly	Ala	Ser	Leu	Ile	20		25		30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg	35		40		45		
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu	50		55		60		
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu	65		70		75		80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp	85		90		95		
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Val	Glu	Tyr	Ser	Ser	100		105		110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	115		120		125		
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	130		135		140		
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	145		150		155		160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	165		170		175		
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser	180		185		190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	195		200		205		
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	210		215		220		
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	225		230		235		240
Gly	Val																					

<210> 264

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Y59F/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192D

<400> 264

4939SEQ.PC2

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 265

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Y59F/G60dS/R84H/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E/V212I

<400> 265

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
      35      40      45

```

4939SEQ.PC2

```

Ser Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg His Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
          145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Ile Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
          225          230          235          240
Gly Val

```

<210> 266

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Y59F/ins97aE/F97T/T98G/F99L/C122S/L153Q/Q175L/Q192E

<400> 266

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
          65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95

```

4939SEQ.PC2

```

Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Gln Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 267

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/Y59F/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192D

<400> 267

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln

```

4939SEQ.PC2

145	Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	
				165						170					175		
	Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	
				180					185					190			
	Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	
			195					200					205				
	Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	
		210				215						220					
	Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	
225					230						235					240	
	Gly	Val															

<210> 268

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41R/Y59F/G60dS/R84H/ins97aE/F97T/T98G/F99L/C122S/

Q175L/Q192E/V212I

<400> 268

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
1				5				10						15			
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Arg	Cys	Gly	Ala	Ser	Leu	Ile		
			20				25					30					
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Phe	Ile	Asp	Asp	Arg		
		35				40						45					
Ser	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55						60						
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	His	Leu		
65				70					75					80			
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp		
			85					90					95				
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser		
			100			105						110					
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala		
		115				120						125					
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly		
	130				135						140						
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln		
145				150					155					160			
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met		
				165					170					175			
	Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser	
				180				185					190				
	Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	

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4939SEQ.PC2

195 200 205
 Gly Ile Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 269

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41R/Y59F/ins97aE/F97T/T98G/F99L/C122S/L153Q/Q175L
/Q192E

<400> 269

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Gln Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 270
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41R/F97W/F99L/C122S/G151N/Q192G

<400> 270
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Trp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 271
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain F97D/ins97aV/T98P/F99L/C122S/G151N/Q192G

<400> 271

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 272

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41D/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192E

<400> 272

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15

```

4939SEQ.PC2

```

Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 273

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41D/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192

E

<400> 273

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60

```

4939SEQ.PC2

```

His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 274

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38E/H40R/I41H/F97D/F99L/C122S/Q192G

<400> 274

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Glu Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125

```

4939SEQ.PC2

Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
130						135					140				
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	Cys
				165						170				175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser	Gly
		180						185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
	195						200						205		
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 275

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain H40R/I41H/F97D/F99L/Q175R/Q192G/D217E/K224R

<400> 275

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	Arg	His	Cys	Gly	Ala	Ser	Leu	Ile
			20					25				30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
		100						105					110		
Val	Arg	Pro	Ile	Cys	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Arg	Ile	Thr	Pro	Arg	Met	Met	Cys
				165						170				175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser	Gly
		180						185					190		

4939SEQ.PC2

Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Glu Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 276

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41R/ins97aV/F97D/T98P/F99L/C122S/G151N/Q192G

<400> 276

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 277
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain ins97aV/F97D/T98P/F99L/C122S/Q175L/Q192E

<400> 277
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 278
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41R/ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192
E

<400> 278

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Arg	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215						220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 279

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38E/H40R/I41H/D60bE/F97D/F99L/C122S/Q192G

<400> 279

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val

4939SEQ.PC2

```

1           5           10           15
Ser Leu His Ala Leu Gly Glu Gly Arg His Cys Gly Ala Ser Leu Ile
20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Glu Arg
35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 280

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38E/H40R/I41H/D60bN/F97D/F99L/C122S/Q192G

<400> 280

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1           5           10           15
Ser Leu His Ala Leu Gly Glu Gly Arg His Cys Gly Ala Ser Leu Ile
20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asn Arg
35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

```

4939SEQ.PC2

```

65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100        105        110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115        120        125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130        135        140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145        150        155        160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165        170        175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180        185        190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195        200        205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210        215        220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225        230        235        240
Val

```

<210> 281

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38E/H40R/I41H/D60bK/F97D/F99L/C122S/Q175L/Q192G

<400> 281

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1          5          10          15
Ser Leu His Ala Leu Gly Glu Gly Arg His Cys Gly Ala Ser Leu Ile
      20        25        30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Lys Arg
      35        40        45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50        55        60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65        70        75        80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100        105        110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115        120        125

```

4939SEQ.PC2

```

Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 282

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38E/H40R/I41H/D60bN/F60eT/F97D/F99L/C122S/Q175L/Q192G

<400> 282

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Glu Gly Arg His Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asn Arg
          35          40          45
Gly Thr Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175

```

4939SEQ.PC2

Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 283

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

Q38R/I41S/D60bH/F60eV/F97T/ins97aE/T98G/F99L/C122S

/Q175L/Q192E

<400> 283

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Arg Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
 35 40 45
 Gly Val Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220

4939SEQ.PC2

Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 284
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38G/H40R/I41H/D60bK/F97D/F99L/C122S/Q175L/Q192G

<400> 284
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gly Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Lys Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 285

4939SEQ.PC2

<211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41D/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L/Q192
 E/Q209L

<400> 285
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Leu Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 286
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

2018290281 23 Nov 2021

4939SEQ.PC2

domain

Q38G/H40R/I41H/D60bN/F97D/F99L/C122S/Q175L/Q192G

<400> 286

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gly Gly Arg His Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asn Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100     105     110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115     120     125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130     135     140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145     150     155     160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165     170     175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180     185     190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195     200     205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210     215     220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225     230     235     240
Val

```

<210> 287

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

Q38R/I41S/D60bH/F60eV/ins97aE/F97T/T98G/F99L/C122S

/G151N/Q175L/Q192E

<400> 287

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15

```


4939SEQ.PC2

```

Ser Leu His Ala Leu Gly Arg Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
      35      40      45
Gly Val Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 288

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

H40R/I41H/F97D/ins97aV/T98P/F99L/C122S/Q175R/Q192G/D217E/K224R

<400> 288

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60

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4939SEQ.PC2

```

His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Glu Gly Cys Ala Gln Arg Asn Arg Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 289

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bA/F60eV/Y60gF/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192T

<400> 289

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ala Arg
      35      40      45
Gly Val Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110

```

4939SEQ.PC2

```

Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
   115                               120                               125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130                               135                               140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145                               150                               155                               160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
   165                               170                               175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
   180                               185                               190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
   195                               200                               205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
   210                               215                               220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
  225                               230                               235                               240
Gly Val

```

<210> 290

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38E/I41S/D60bH/F60eI/F97T/ins97aE/T98G/F99L/C122S
/Q175L/Q192V

<400> 290

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                               5                               10                               15
Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile
   20                               25                               30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
   35                               40                               45
Gly Ile Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                               55                               60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65                               70                               75                               80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
   85                               90                               95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
  100                               105                               110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
  115                               120                               125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
  130                               135                               140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145                               150                               155                               160

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4939SEQ.PC2

```

Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 291

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38R/I41S/D60bH/F60eI/ins97aE/F97T/T98G/F99L/C122S
/Q175L/Q192E

<400> 291

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Arg Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
      35      40      45
Gly Ile Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205

```

4939SEQ.PC2

Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 292
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38E/I41S/D60bV/F60eK/F97T/ins97aE/T98G/F99L/C122S
 /Q175L/Q192I

<400> 292
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Lys Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ile Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 293
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38R/I41E/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192T

<400> 293
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Arg Gly His Glu Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 294
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41A/D60bV/F60eR/Y60gW/ins97aE/F97T/T98G/F99L
/C122S/Q175L/Q192D

<400> 294

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Val	Arg
		35					40					45			
Gly	Arg	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165				170						175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 295

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41A/D60bA/F60eR/F97T/ins97aE/T98G/F99L/C122S
/Q175L/Q192E

4939SEQ.PC2

<400> 295

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ala Arg
          35          40          45
Gly Arg Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

```

<210> 296

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

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<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      F97D/ins97aV/T98P/F99L/C122S/G151N/Q175L/Q192E

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<400> 296

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45

```


4939SEQ.PC2

Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 297

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

ins97aV/F97D/T98P/F99L/C122S/G151N/Q175L/Q192G

<400> 297

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser

4939SEQ.PC2

```

      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 298

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38G/H40R/I41H/D60bN/F60eT/F97D/F99L/C122S/Q175L/Q

192G

<400> 298

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gly Gly Arg His Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asn Arg
      35      40      45
Gly Thr Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

```

4939SEQ.PC2

145	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys	160
				165						170						175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser	Gly		
			180					185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		
		195					200					205					
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val		
	210				215						220						
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly		
225					230					235					240		
Val																	

<210> 299

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38G/H40R/I41H/D60bK/F60eT/F97D/F99L/C122S/Q175L/Q

192G

<400> 299

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
1				5				10						15			
Ser	Leu	His	Ala	Leu	Gly	Gly	Gly	Arg	His	Cys	Gly	Ala	Ser	Leu	Ile		
		20					25					30					
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Lys	Arg		
		35				40						45					
Gly	Thr	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55						60						
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu		
65				70					75					80			
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Leu	Asp	Tyr		
			85					90					95				
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met		
		100					105					110					
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly		
	115					120						125					
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr		
	130					135					140						
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr		
145				150				155						160			
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys		
			165					170						175			
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser	Gly		
		180						185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		

4939SEQ.PC2

195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 300
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38E/H40R/I41H/D60bK/F60eT/F97D/F99L/C122S/Q175L/Q
 192G

<400> 300
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Glu Gly Arg His Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Lys Arg
 35 40 45
 Gly Thr Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 301
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bA/F60eV/Y60gF/ins97aE/F97T/T98G/F99L
 /C122S/G151N/Q175L/Q192T

<400> 301
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ala Arg
 35 40 45
 Gly Val Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 302
 <211> 242
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38E/I41S/D60bH/F60eI/ins97aE/F97T/T98G/F99L/C122S
 /G151N/Q175L/Q192V

<400> 302

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
          35          40          45
Gly Ile Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
          145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
          225          230          235          240
Gly Val

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<210> 303

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38R/I41S/D60bH/F60eI/ins97aE/F97T/T98G/F99L/C122S

4939SEQ.PC2

/G151N/Q175L/Q192E

<400> 303

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Arg Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
 35 40 45
 Gly Ile Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 304

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

Q38E/I41S/D60bV/F60eK/ins97aE/F97T/T98G/F99L/C122S
 /G151N/Q175L/Q192I

<400> 304

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile

4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Lys Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ile Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 305

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

Q38R/I41E/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L

/Q192T

<400> 305

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Arg Gly His Glu Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

```


4939SEQ.PC2

```

65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 306

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 306

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

```

4939SEQ.PC2

```

      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 307
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41A/D60bA/F60eR/ins97aE/F97T/T98G/F99L/C122S
 /G151N/Q175L/Q192E

```

<400> 307
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ala Arg
      35      40      45
Gly Arg Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met

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4939SEQ.PC2

				165					170					175					
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser				
			180						185				190						
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala				
		195					200					205							
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly				
	210				215						220								
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr				
225				230						235					240				
Gly	Val																		

<210> 308

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 308

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val				
1				5				10						15					
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile				
		20					25					30							
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg				
	35					40					45								
Gly	Ser	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu				
	50				55					60									
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu				
65				70					75						80				
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp				
			85					90				95							
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser				
	100					105					110								
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala				
	115					120					125								
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly				
	130				135					140									
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln				
145				150					155					160					
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met				
			165			170					175								
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser				
		180				185						190							
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala				
	195					200					205								
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly				

4939SEQ.PC2

210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 309
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bV/F60eQ/Y60gF/ins97aE/F97T/T98G/F99L
 /C122S/Q175L/Q192I

<400> 309
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Gln Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ile Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 310
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41A/D60bV/F60eI/ins97aE/F97T/T98G/F99L/C122S
 /Q175L/Q192E

<400> 310
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Ile Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 311
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41A/D60bV/F60eT/Y60gW/ins97aE/F97T/T98G/F99L
/C122S/Q175L/Q192E

<400> 311

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Val	Arg
		35					40					45			
Gly	Thr	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 312

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41A/F60eA/Y60gW/ins97aE/F97T/T98G/F99L/C122S
/Q175L/Q192E

4939SEQ.PC2

<400> 312

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Ala Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

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<210> 313

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41A/D60bE/F60eH/Y60gW/ins97aE/F97T/T98G/F99L
/C122S/Q175L/Q192D

<400> 313

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Glu Arg

```

4939SEQ.PC2

```

      35      40      45
Gly His Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
  50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
  225      230      235      240
Gly Val

```

<210> 314

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 314

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Lys Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
  50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp

```


4939SEQ.PC2

```

      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 315

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bT/F60eH/Y60gW/ins97aE/F97T/T98G/F99L
/C122S/Q175L/Q192D

<400> 315

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly His Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly

```

4939SEQ.PC2

```

      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 316

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bS/F60eR/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192E

<400> 316

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ser Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser

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180 185 190															
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
195 200 205															
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
210 215 220															
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225 230 235 240															
Gly	Val														

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<210> 317
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41S/D60bT/F60eS/F97D/ins97aV/T98P/F99L/C122S
/G151H/Q175L/Q192D

<400>	317														
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ser	Cys	Gly	Ala 30	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Thr	Arg
Gly 50	Ser	Arg	Tyr	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu 80
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Asp	Val	Pro	Leu	Asp 95
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala 120	Ser	His	Val	Phe	Pro	Ala
Gly 130	Lys	Ala	Ile	Trp	Val	Thr 135	Gly	Trp	Gly	His	Thr 140	Gln	Tyr	Gly	Gly
Thr 145	His	Ala	Leu	Ile	Leu	Gln 150	Lys	Gly	Glu	Ile 155	Arg	Val	Ile	Asn	Gln 160
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu 170	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val 185	Asp	Ser	Cys	Asp	Gly 190	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile 205	Phe	Gln	Ala
Gly 210	Val	Val	Ser	Trp	Gly	Asp 215	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr

2018290281

4939SEQ.PC2

225	230	235	240
Gly Val			

<210> 318
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38R/I41T/ins97aE/F97T/T98G/F99L/C122S/G151N/Q175L
/Q192G

[illegible]

<210> 319

4939SEQ.PC2

<211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38S/I41S/F60eR/F97T/ins97aE/T98G/F99L/C122S/G151N
 /Q175L/Q192S

<400> 319
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Ser Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Arg Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 320
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

Q38H/I41T/D60bV/F60eQ/F97T/ins97aE/T98G/F99L/C122S
/Q175L/Q192G

<400> 320

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Thr Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35      40      45
Gly Gln Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 321

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainQ38G/H40R/I41H/D60bH/F60eK/F97T/ins97aE/T98G/F99L/
C122S/Q175L/V183A/Q192G

<400> 321

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val

4939SEQ.PC2

```

      1             5             10             15
Ser Leu His Ala Leu Gly Gly Gly Arg His Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
      35             40             45
Gly Lys Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50             55             60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65             70             75             80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85             90             95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100            105            110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115            120            125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130            135            140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145            150            155            160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165            170            175
Cys Ala Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180            185            190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195            200            205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210            215            220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225            230            235            240
Gly Val

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<210> 322

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41A/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G

<400> 322

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
      1             5             10             15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35             40             45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50             55             60

```

4939SEQ.PC2

```

His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 323

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38L/I41T/D60bR/F60eL/Y60gM/F97T/ins97aE/T98G/F99L
/C122S/G151N/Q175L/Q192G

<400> 323

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Leu Gly His Thr Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Arg Arg
      35      40      45
Gly Leu Arg Met Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110

```


4939SEQ.PC2

```

Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
    115                      120                      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
    130                      135                      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
    145                      150                      155                      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
    165                      170                      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
    180                      185                      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
    195                      200                      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
    210                      215                      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
    225                      230                      235                      240
Gly Val

```

<210> 324

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38F/I41S/D60bF/F60eR/Y60gF/F97T/ins97aE/T98G/F99L
/C122S/G151N/Q175L/Q192V

<400> 324

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                      5                      10                      15
Ser Leu His Ala Leu Gly Phe Gly His Ser Cys Gly Ala Ser Leu Ile
    20                      25                      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Phe Arg
    35                      40                      45
Gly Arg Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                      55                      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
    65                      70                      75                      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
    85                      90                      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
    100                      105                      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
    115                      120                      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
    130                      135                      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
    145                      150                      155                      160

```

4939SEQ.PC2

```

Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 325

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38V/I41S/D60bT/F60eT/F97D/ins97aV/T98P/F99L/C122S
/G151N/Q175H/Q192S

<400> 325

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Val Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Thr Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln His Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205

```

4939SEQ.PC2

Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 326
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38W/I41A/ins97aV/F97D/T98P/F99L/C122S/G151T/Q175S
 /Q192D

<400> 326
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Trp Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Thr Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 327
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38T/I41S/D60bV/F60eR/ins97aV/F97D/T98P/F99L/C122S
 /G151N/Q175R/Q192V

<400> 327
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Thr Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Arg Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 328
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D60bT/F60eS/ins97aV/F97D/T98P/F99L/C122S
/G151H/Q175A/Q192D

<400> 328

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Ser	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100				105					110			
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115				120					125				
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130				135					140					
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155				160	
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Ala	Ile	Thr	Pro	Arg	Met	Met
				165				170						175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
		180				185						190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195				200						205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215					220					
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225				230					235					240	
Gly	Val														

<210> 329

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D60bT/F60eT/F97D/ins97aV/T98P/F99L/C122S
/G151N/Q175L/Q192V

4939SEQ.PC2

<400> 329

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
          35          40          45
Gly Thr Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

```

<210> 330

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38Y/I41A/D60bL/F60eQ/ins97aV/F97D/T98P/F99L/C122S
/G151N/Q175M/Q192A

<400> 330

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Tyr Gly His Ala Cys Gly Ala Ser Leu Ile
          20          25          30

```

4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Leu Arg
   35                               40           45
Gly Gln Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                               55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65                               70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
   85                               90           95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
  100                               105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
  115                               120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
  130                               135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145                               150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
  165                               170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
  180                               185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
  195                               200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
  210                               215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
  225                               230          235          240
Gly Val

```

<210> 331

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38L/I41T/D60bA/F60eL/ins97aV/F97D/T98P/F99L/C122S/G151H/Q175M/Q192T

<400> 331

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                               5           10           15
Ser Leu His Ala Leu Gly Leu Gly His Thr Cys Gly Ala Ser Leu Ile
  20                               25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ala Arg
  35                               40           45
Gly Leu Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
  50                               55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65                               70           75           80

```

4939SEQ.PC2

```

Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85                      90                      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100                      105                      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115                      120                      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130                      135                      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145                      150                      155                      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
      165                      170                      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
      180                      185                      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195                      200                      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210                      215                      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225                      230                      235                      240
Gly Val

```

<210> 332

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38R/I41S/D60bY/F60eD/ins97aV/F97D/T98P/F99L/C122S
/G151N/Q175M/Q192A

<400> 332

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                      5                      10                      15
Ser Leu His Ala Leu Gly Arg Gly His Ser Cys Gly Ala Ser Leu Ile
      20                      25                      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
      35                      40                      45
Gly Asp Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50                      55                      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65                      70                      75                      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85                      90                      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100                      105                      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115                      120                      125

```


4939SEQ.PC2

Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 333

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

Q38W/I41S/D60bG/F60eI/F97D/ins97aV/T98P/F99L/C122S
 /G151N/Q175A/Q192D

<400> 333

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Trp Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Gly Arg
 35 40 45
 Gly Ile Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Ala Ile Thr Pro Arg Met Met
 165 170 175

4939SEQ.PC2

Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 334

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

Q38T/I41S/D60bG/F60eM/ins97aV/F97D/T98P/F99L/C122S
 /G151N/Q175S/Q192S

<400> 334

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Thr Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Gly Arg
 35 40 45
 Gly Met Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220

4939SEQ.PC2

Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 335

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

I41T/D60bW/F60eH/F97D/ins97aV/T98P/F99L/C122S/G151
 N/Q175L/Q192G

<400> 335

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Trp Arg
 35 40 45
 Gly His Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 336
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38D/I41S/D60bT/F60eR/ins97aV/F97D/T98P/F99L/C122S
 /G151K/Q175S/Q192V

<400> 336
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Asp Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Arg Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Lys Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 337
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

4939SEQ.PC2

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D60bF/F60eV/F97D/ins97aV/T98P/F99L/C122S
/G151N/Q175L/Q192A

<400> 337

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Phe	Arg
		35					40					45			
Gly	Val	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 338

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38L/I41A/D60bH/F60eT/ins97aV/F97D/T98P/F99L/C122S
/G151Q/Q175A/Q192G

<400> 338

4939SEQ.PC2

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Leu Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
      35      40      45
Gly Thr Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130      135      140
Thr Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Ala Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 339

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bE/F60eH/Y60gW/F97T/ins97aE/T98G/F99L
/C122S/G151N/Q175L/Q192D

<400> 339

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Glu Arg
      35      40      45

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4939SEQ.PC2

Gly His Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 340

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

Q38H/I41A/D60bV/F60eI/Y60gW/F97T/ins97aE/T98G/F99L
 /C122S/G151N/Q175L/Q192D

<400> 340

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Ile Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95

4939SEQ.PC2

Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 341

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

Q38E/I41S/D60bV/F60eK/Y60gW/F97T/ins97aE/T98G/F99L
 /C122S/G151N/Q175L/Q192D

<400> 341

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Lys Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140

4939SEQ.PC2

```

Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

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<210> 342

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 342

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
          35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
          85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180      185      190

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4939SEQ.PC2

Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 343
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L
 /C122S/G151H/Q175A/Q192D

<400> 343
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Ala Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240

Gly Val

<210> 344

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainQ38H/I41A/D60bV/F60eR/ins97aE/F97T/T98G/F99L/C122S
/G151N/Q175L/Q192D

<400> 344

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Val	Arg
		35					40					45			
Gly	Arg	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55				60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
		180					185					190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 345

<211> 242

4939SEQ.PC2

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bT/F60eH/Y60gW/F97T/ins97aE/T98G/F99L/C122S/G151N/Q175L/Q192D

<400> 345

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40						45		
Gly	His	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215						220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 346

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

4939SEQ.PC2

D60bY/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G

<400> 346

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 347

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41T/D60bY/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192
G

<400> 347

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile

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4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 348

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38E/I41S/D60bT/F60eR/F97T/ins97aE/T98G/F99L/C122S
/Q175L/Q192V

<400> 348

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Arg Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

```

4939SEQ.PC2

```

65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

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<210> 349

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bK/F60eK/Y60gW/F97T/ins97aE/T98G/F99L
/C122S/Q175L/Q192D

<400> 349

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Lys Arg
      35      40      45
Gly Lys Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

```

4939SEQ.PC2

```

      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
  130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 350

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bA/F60eV/ins97aE/F97T/T98G/F99L/C122S
/Q175L/Q192E/Q209L

<400> 350

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ala Arg
      35      40      45
Gly Val Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met

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4939SEQ.PC2

[illegible]

<210> 351

<211> 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bT/F60eR/F97T/ins97aE/T98G/F99L/C122S
/Q175L/Q192V

<400> 351

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ala	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Thr	Arg
Gly	Arg 50	Arg	Tyr	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Thr	Glu	Gly	Leu	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
Thr 145	Gly	Ala	Leu	Ile	Leu 150	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Val	Gly	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly

4939SEQ.PC2

210	215	220
Val Tyr Thr Arg Leu Pro	Leu Phe Arg Asp Trp	Ile Lys Glu Asn Thr
225	230	235
Gly Val		

<210> 352

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38K/I41S/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V

<400> 352

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val	1	5	10	15
Ser Leu His Ala Leu Gly Lys Gly His Ser Cys Gly Ala Ser Leu Ile	20	25	30	
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg	35	40	45	
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu	50	55	60	
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu	65	70	75	80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp	85	90	95	
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser	100	105	110	
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala	115	120	125	
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly	130	135	140	
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln	145	150	155	160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met	165	170	175	
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser	180	185	190	
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala	195	200	205	
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly	210	215	220	
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr	225	230	235	240
Gly Val				

4939SEQ.PC2

<210> 353
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38F/I41A/D60bT/F60eG/Y60gW/ins97aE/F97T/T98G/F99L
 /C122S/Q175L/Q192E

<400> 353

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Phe	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35				40						45			
Gly	Gly	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55						60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75					80	
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
			85					90					95		
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
		100				105						110			
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
	115					120						125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130				135						140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145				150					155					160	
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
			165					170						175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
		180				185						190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
	195					200						205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215					220					
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225				230						235				240	
Gly	Val														

<210> 354
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

4939SEQ.PC2

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41A/F60eH/Y60gW/ins97aE/F97T/T98G/F99L/C122S
/Q175L/Q192A

<400> 354

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
		20					25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	His	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 355

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41A/D60bT/F60eK/Y60gW/F97T/ins97aE/T98G/F99L
/C122S/Q175L/Q192A

<400> 355

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Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Lys	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 356

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bV/F60eA/Y60gW/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192V

<400> 356

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Val	Arg
		35					40					45			

4939SEQ.PC2

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Gly Ala Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

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<210> 357

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38E/I41V/D60bF/F60eK/Y60gF/F97T/ins97aE/T98G/F99L/C122S/Q175L/Q192G

<400> 357

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Glu Gly His Val Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Phe Arg
      35      40      45
Gly Lys Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85          90          95

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4939SEQ.PC2

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Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 358

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/H40P/I41A/F60eQ/Y60gW/F97T/ins97aE/T98G/F99L/
C122S/Q175L/Q192D

<400> 358

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly Pro Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Gln Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140

```

4939SEQ.PC2

```

Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

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<210> 359

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38R/I41V/D60bV/F60eV/Y60gF/ins97aE/F97T/T98G/F99L
/C122S/Q175L/Q192G

<400> 359

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Arg Gly His Val Cys Gly Ala Ser Leu Ile
          20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
          35      40      45
Gly Val Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100     105     110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115     120     125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130     135     140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145     150     155     160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165     170     175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
          180     185     190

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Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 360

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38L/H40P/I41T/D60bV/F60eH/Y60gL/ins97aE/F97T/T98G
 /F99L/C122S/Q175L/Q192A

<400> 360

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Leu Gly Pro Thr Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly His Arg Leu Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240

Gly Val

<210> 361

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bV/F60eH/ins97aE/F97T/T98G/F99L/C122S
/Q175L/Q192D

<400> 361

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Val	Arg
		35					40					45			
Gly	His	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
			85						90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
			165						170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
		180					185					190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215						220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 362

<211> 242

4939SEQ.PC2

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bA/F60eV/ins97aE/F97T/T98G/F99L/C122S
/Q175L/Q192V

<400> 362

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Ala	Arg
		35					40					45			
Gly	Val	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Val	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215						220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 363

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

2018290281 23 Nov 2021

4939SEQ.PC2

Q38R/I41T/D60bH/ins97aE/F97T/T98G/F99L/C122S/Q175L
/Q192G

<400> 363

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Arg	Gly	His	Thr	Cys	Gly	Ala	Ser	Leu	Ile
		20					25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	His	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 364

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bT/F60eR/ins97aE/F97T/T98G/F99L/C122S
/Q175L/Q192E

<400> 364

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	

4939SEQ.PC2

```

Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Arg Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 365

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38K/I41T/ins97aE/F97T/T98G/F99L/C122S/Q175L/Q192A

<400> 365

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Lys Gly His Thr Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

```

4939SEQ.PC2

```

65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
      180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

```

<210> 366

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

Q38H/I41A/D60bT/F60eK/ins97aE/F97T/T98G/F99L/C122S

/Q175L/Q192E

<400> 366

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Lys Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

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4939SEQ.PC2

```

      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
   195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
   210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 367
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38L/I41T/D60bV/F60eH/Y60gL/ins97aE/F97T/T98G/F99L
 /C122S/Q175L/Q192S

```

<400> 367
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Leu Gly His Thr Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
   35      40      45
Gly His Arg Leu Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met

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2018290281

4939SEQ.PC2

[illegible]

<210> 368

$\langle 211 \rangle$ 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
ins97aA/F97G/T98L/C122S/O175M/O192A/D217I/K224R

<400> 368

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Gln	Gly	His 25	Ile	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Gly	Ala	Leu	Phe	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr 135	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
Thr 145	Gly	Ala	Leu	Ile	Leu 150	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Met 170	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Ala	Gly	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala	Asp 200	Gly	Arg	Ile	Phe	Gln	Ala
Gly	Val 210	Val	Ser	Trp	Gly	Ile 215	Gly	Cys	Ala	Gln	Arg	Asn	Arg	Pro	Gly

4939SEQ.PC2

Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 369

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

Q38H/I41A/D60bY/F60eT/ins97aE/F97T/T98G/F99L/C122S
 /Q175L/Q192D

<400> 369

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
 35 40 45
 Gly Thr Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 370
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain ins97aY/F97H/F99L/C122S/Q175M/Q192A/D217V

<400> 370
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp His Tyr Thr Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 371
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

4939SEQ.PC2

ins97aL/F97Q/T98G/F99L/C122S/Q175M/Q192S/D217I

<400> 371

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gln Leu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 372

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain ins97aY/F97G/T98V/C122S/Q175M/Q192S/D217V

<400> 372

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg

```

4939SEQ.PC2

```

      35              40              45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65              70              75
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gly Tyr Val Phe Asp
      85              90              95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100             105             110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115             120             125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130             135             140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145             150             155
Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
      165             170             175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
      180             185             190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195             200             205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210             215             220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225             230             235
Gly Val

```

<210> 373

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38Y/I41S/D60bR/F60eE/Y60gF/ins97aE/F97T/T98G/F99L
/C122S/Q175L/Q192V

<400> 373

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1              5              10              15
Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
      20              25              30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Arg Arg
      35              40              45
Gly Glu Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65              70              75
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp

```

4939SEQ.PC2

```

      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 374

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F60eS/ins97aV/F97D/T98P/F99L/C122S
/G151H/Q175L/Q192V

<400> 374

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly

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130						135						140					
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln		
145						150						155					
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met		
					165						170						
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Val	Gly	Asp	Ser		
					180						185						
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala		
					195						200						
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly		
					210						215						
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr		
225						230						235					
Gly	Val																

<210> 375

$\langle 211 \rangle$ 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L
/C122S/G151H/Q175L/Q192V

<400> 375

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
Gly	Ser 50	Arg	Trp	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Asp	Val	Pro	Leu	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
Thr 145	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Val	Gly	Asp	Ser

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180 185 190															
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
195 200 205															
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
210 215 220															
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225 230 235 240															
Gly	Val														

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<210> 376
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L
/C122S/G151N/Q175A/Q192D

<400> 376															
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ser	Cys	Gly	Ala 30	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Thr	Arg
Gly 50	Ser	Arg	Trp	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg	Ser	Ala 70	Pro	Gly	Val	Gln 75	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Asp	Val	Pro	Leu	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala 120	Ser	His	Val	Phe	Pro	Ala
Gly 130	Lys	Ala	Ile	Trp	Val	Thr	Gly 135	Trp	Gly	His	Thr 140	Gln	Tyr	Gly	Gly
Thr 145	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile 155	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Ala 170	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Asp	Gly	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala	Asp 200	Gly	Arg	Ile	Phe	Gln	Ala
Gly 210	Val	Val	Ser	Trp	Gly	Asp	Gly 215	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr

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4939SEQ.PC2

225	230	235	240
Gly Val			

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<210> 377
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L
/C122S/G151N/Q175L/Q192E

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<210> 378

4939SEQ.PC2

<211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41A/D60bE/F60eH/Y60gW/ins97aE/F97T/T98G/F99L
 /C122S/G151H/Q175L/Q192D

<400> 378

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Glu	Arg
		35					40					45			
Gly	His	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
		50				55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Thr	Glu	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
		130				135					140				
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
		210				215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 379
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

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

<400> 379

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Lys Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 380

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainQ38H/I41A/D60bV/F60eI/Y60gW/ins97aE/F97T/T98G/F99L
/C122S/G151H/Q175L/Q192D

<400> 380

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val

4939SEQ.PC2

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      1             5             10             15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35             40             45
Gly Ile Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50             55             60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65             70             75             80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85             90             95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100            105            110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115            120            125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130            135            140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145            150            155            160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165            170            175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180            185            190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195            200            205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210            215            220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225            230            235            240
Gly Val

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<210> 381

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38E/I41S/D60bV/F60eK/Y60gW/ins97aE/F97T/T98G/F99L/C122S/G151H/Q175L/Q192D

<400> 381

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
      1             5             10             15
Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35             40             45
Gly Lys Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

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4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 382

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/L52M/D60bG/ins97aV/F97D/T98P/F99L/M117K/
C122S/I136L/Q192G/D217A

<400> 382

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Met Val Ser Ala Ala His Cys Tyr Ile Asp Gly Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser

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4939SEQ.PC2

```

      100      105      110
Lys Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Leu Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 383

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38E/I41A/D60bH/ins97aV/F97D/T98P/F99L/C122S/Q192G

/Q209L/D217H

<400> 383

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Glu Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln

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4939SEQ.PC2

145	Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	160
				165						170							175
	Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser	
				180					185						190		
	Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Leu	Ala	
			195					200					205				
	Gly	Val	Val	Ser	Trp	Gly	His	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	
		210				215						220					
	Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	
225						230					235					240	
	Gly	Val															

<210> 384

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41S/D60bT/F93L/ins97aV/F97D/T98P/F99L/C122S/Q192G

/D217H

<400> 384

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
1				5				10						15			
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile		
			20				25						30				
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg		
		35				40						45					
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55						60						
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu		
65				70					75						80		
Lys	Arg	Ile	Ile	Ser	His	Pro	Leu	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp		
			85					90					95				
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser		
		100				105						110					
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala		
		115				120						125					
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly		
	130				135						140						
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln		
145				150					155						160		
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met		
				165					170						175		
	Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser	
				180				185						190			
	Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	

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195 200 205
 Gly Val Val Ser Trp Gly His Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 385

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41T/D60bH/ins97aV/F97D/T98P/F99L/C122S/Q192G/D217

I

<400> 385

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 386
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/M117L/C122S
 /I136T/Q192G/D217I

<400> 386
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ser Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Leu Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Thr Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 387
 <211> 242
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38R/I41T/D60bT/ins97aV/F97D/T98P/F99L/C122S/I136V
/Q192G/D217N/L233Q

<400> 387

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Arg	Gly	His	Thr	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35				40					45				
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75					80	
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp
			85						90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105				110			
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115				120						125			
Gly	Lys	Ala	Val	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145				150						155				160	
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
			165					170						175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser
		180					185					190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195				200						205			
Gly	Val	Val	Ser	Trp	Gly	Asn	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215					220					
Val	Tyr	Thr	Arg	Leu	Pro	Gln	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225				230						235				240	
Gly	Val														

<210> 388

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bW/ins97aV/F97D/T98P/F99L/C122S/I136M

4939SEQ.PC2

/Q192G/D217N

<400> 388

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Trp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Met Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 389

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/P49Q/D60bS/F93L/ins97aV/F97D/T98P/F99L/C
122S/Q192G/D217Q

<400> 389

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile

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4939SEQ.PC2

```

      20      25      30
Ser  Gln  Asn  Trp  Leu  Val  Ser  Ala  Ala  His  Cys  Tyr  Ile  Asp  Ser  Arg
      35      40      45
Gly  Phe  Arg  Tyr  Ser  Asp  Pro  Thr  Gln  Trp  Thr  Ala  Phe  Leu  Gly  Leu
      50      55      60
His  Asp  Gln  Ser  Gln  Arg  Ser  Ala  Pro  Gly  Val  Gln  Glu  Arg  Arg  Leu
      65      70      75      80
Lys  Arg  Ile  Ile  Ser  His  Pro  Leu  Phe  Asn  Asp  Asp  Val  Pro  Leu  Asp
      85      90      95
Tyr  Asp  Ile  Ala  Leu  Leu  Glu  Leu  Glu  Lys  Pro  Ala  Glu  Tyr  Ser  Ser
      100     105     110
Met  Val  Arg  Pro  Ile  Ser  Leu  Pro  Asp  Ala  Ser  His  Val  Phe  Pro  Ala
      115     120     125
Gly  Lys  Ala  Ile  Trp  Val  Thr  Gly  Trp  Gly  His  Thr  Gln  Tyr  Gly  Gly
      130     135     140
Thr  Gly  Ala  Leu  Ile  Leu  Gln  Lys  Gly  Glu  Ile  Arg  Val  Ile  Asn  Gln
      145     150     155     160
Thr  Thr  Cys  Glu  Asn  Leu  Leu  Pro  Gln  Gln  Ile  Thr  Pro  Arg  Met  Met
      165     170     175
Cys  Val  Gly  Phe  Leu  Ser  Gly  Gly  Val  Asp  Ser  Cys  Gly  Gly  Asp  Ser
      180     185     190
Gly  Gly  Pro  Leu  Ser  Ser  Val  Glu  Ala  Asp  Gly  Arg  Ile  Phe  Gln  Ala
      195     200     205
Gly  Val  Val  Ser  Trp  Gly  Gln  Gly  Cys  Ala  Gln  Arg  Asn  Lys  Pro  Gly
      210     215     220
Val  Tyr  Thr  Arg  Leu  Pro  Leu  Phe  Arg  Asp  Trp  Ile  Lys  Glu  Asn  Thr
      225     230     235     240
Gly  Val

```

<210> 390

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bT/ins97aV/F97D/T98P/F99L/C122S/I136V
/Q192G/D217S

<400> 390

```

Val  Val  Gly  Gly  Thr  Asp  Ala  Asp  Glu  Gly  Glu  Trp  Pro  Trp  Gln  Val
  1      5      10      15
Ser  Leu  His  Ala  Leu  Gly  His  Gly  His  Ser  Cys  Gly  Ala  Ser  Leu  Ile
      20      25      30
Ser  Pro  Asn  Trp  Leu  Val  Ser  Ala  Ala  His  Cys  Tyr  Ile  Asp  Thr  Arg
      35      40      45
Gly  Phe  Arg  Tyr  Ser  Asp  Pro  Thr  Gln  Trp  Thr  Ala  Phe  Leu  Gly  Leu
      50      55      60
His  Asp  Gln  Ser  Gln  Arg  Ser  Ala  Pro  Gly  Val  Gln  Glu  Arg  Arg  Leu

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4939SEQ.PC2

```

65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100        105        110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115        120        125
Gly Lys Ala Val Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130        135        140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150        155        160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165        170        175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180        185        190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195        200        205
Gly Val Val Ser Trp Gly Ser Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210        215        220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230        235        240
Gly Val

```

<210> 391

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bS/F93L/D96Y/ins97aV/F97D/T98P/F99L/C

122S/I136F/Q192G/D217V

<400> 391

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ser Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Leu Phe Asn Tyr Asp Val Pro Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100        105        110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

```

4939SEQ.PC2

```

      115      120      125
Gly Lys Ala Phe Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
   195      200      205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
   210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 392

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41T/D60bH/ins97aV/F97D/T98P/F99L/C122S/I136F
/L153P/Q192G/D217Y

<400> 392

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Thr Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
   35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Phe Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Gly Ala Pro Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met

```

4939SEQ.PC2

				165					170					175					
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser				
			180						185				190						
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala				
		195					200					205							
Gly	Val	Val	Ser	Trp	Gly	Tyr	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly				
	210				215						220								
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr				
225				230						235					240				
Gly	Val																		

<210> 393

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F93L/ins97aV/F97D/T98P/F99L/S115N/C122S/Q192V/F208L/D217Q

<400> 393

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val				
1				5				10						15					
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile				
		20					25					30							
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg				
	35					40					45								
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu				
	50				55					60									
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu				
65				70					75						80				
Lys	Arg	Ile	Ile	Ser	His	Pro	Leu	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp				
			85						90					95					
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Asn	Ser				
	100					105					110								
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala				
	115					120					125								
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly				
	130					135					140								
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln				
145				150					155					160					
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met				
			165					170						175					
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Val	Gly	Asp	Ser				
		180					185						190						
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Leu	Gln	Ala				
	195					200					205								
Gly	Val	Val	Ser	Trp	Gly	Gln	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly				

4939SEQ.PC2

210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 394
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38K/I41T/D60bY/ins97aV/F97D/T98P/F99L/C122S/I136T
 /Q192G/F208V/D217R

<400> 394
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Lys Gly His Thr Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Thr Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Val Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Arg Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 395
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bS/ins97aV/F97D/T98P/F99L/C122S/I136V
 /Q192G/D217V

<400> 395
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ser Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Val Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 396
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D60bG/ins97aV/F97D/T98P/F99L/M117T/C122S
/N164D/Q192G/D217E

<400> 396

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Gly	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Thr	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asp	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Glu	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 397

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38K/I41S/D60bV/ins97aV/F97D/T98P/F99L/M117T/C122S
/Q145E/Q175L/Q192G

4939SEQ.PC2

<400> 397

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Lys Gly His Ser Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Thr Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Glu Tyr Gly Gly
 130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

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<210> 398

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bT/F60eT/Y60gW/ins97aV/F97D/T98P/F99L
/C122S/G151H/Q175L/Q192V

<400> 398

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg

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4939SEQ.PC2

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      35              40              45
Gly Thr Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
  50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65              70              75
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85              90              95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100             105             110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115             120             125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130             135             140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145             150             155
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165             170             175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180             185             190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195             200             205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210             215             220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
  225             230             235
Gly Val

```

<210> 399

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 399

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1              5              10              15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20              25              30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35              40              45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
  50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65              70              75
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp

```

4939SEQ.PC2

```

      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 400

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 400

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly

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4939SEQ.PC2

130						135						140					
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln		
145						150						155					
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met		
					165						170						
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser		
					180						185						
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala		
					195						200						
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly		
					210						215						
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr		
225						230						235					
Gly	Val																

$\langle 210 \rangle$ 401

$\langle 211 \rangle$ 242

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/L52M/D60bH/D96V/ins97aV/F97D/T98P/F99L/C
122S/T150A/Q192G/Q209L/D217T

<400> 401

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Met	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile	Asp	His	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Val	Asp	Val	Pro	Leu	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
Ala 145	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser

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			180					185				190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Leu	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Thr	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 402

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainI41S/D60bS/D96V/ins97aV/F97D/T98P/F99L/C122S/Q192G
/F208L/D217N

<400> 402

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Ser	Arg
		35				40						45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Val	Asp	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115				120						125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Leu	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asn	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr

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4939SEQ.PC2

240

<213> Artificial Sequence

Q38H/I41S/D60bT/S90T/F97D/ins97aV/T98P/F99L/C122S/
S127N/I136F/Q192G/D217Q

225

<210> 404

4939SEQ.PC2

<211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F93S/ins97aV/F97D/T98P/F99L/C122S/
 I136L/Q192G/D217A

<400> 404

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Ser	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Leu	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Ala	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 405
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

I41S/D60bH/ins97aV/F97D/T98P/F99L/C122S/I136V/Q192
G/D217N

<400> 405

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp His Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115      120      125
Gly Lys Ala Val Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195      200      205
Gly Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 406

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainL33M/Q38H/I41A/D60bA/ins97aV/F97D/T98P/F99L/C122S/
Q192G/D217N

<400> 406

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val

4939SEQ.PC2

```

      1             5             10             15
Ser Met His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ala Arg
      35             40             45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50             55             60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65             70             75             80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85             90             95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100            105            110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115            120            125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130            135            140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145            150            155            160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165            170            175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180            185            190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195            200            205
Gly Val Val Ser Trp Gly Asn Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210            215            220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225            230            235            240
Gly Val

```

<210> 407

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bY/D96Y/ins97aV/F97D/T98P/F99L/L106M/C122S/I136M/Q192G/Q209L/D217T

<400> 407

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
      1             5             10             15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
      35             40             45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```

4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Tyr Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Met Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Met Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Leu Ala
      195      200      205
Gly Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 408

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 408

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ile Tyr Asn Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser

```

4939SEQ.PC2

```

      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 409

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 409

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Asp Ala Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln

```

4939SEQ.PC2

```

145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

```

<210> 410

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41T/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G
/F99L/C122S/G151N/Q175L/Q192D

<400> 410

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Thr Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
          35          40          45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ile Tyr Asn Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala

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4939SEQ.PC2

195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 411
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41A/D60bV/F60eR/Y60gW/D96Y/ins97aI/F97E/T98N
 /F99M/C122S/G151N/Q175L/Q192V

<400> 411
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Tyr Glu Ile Asn Met Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 412
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41A/D60bV/F60eR/Y60gW/D96S/ins97aR/F97A/T98S
 /F99L/C122S/G151N/Q175L/Q192T

<400> 412
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ser Ala Arg Ser Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 413
 <211> 242
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G
 /F99L/C122S/G151N/Q175L/Q192E

<400> 413

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
          35          40          45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Trp Asn Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
          145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
          225          230          235          240
Gly Val

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<210> 414

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38H/I41S/D60bT/F60eS/Y60gW/F97D/F99L/C122S/G151H/

Q175L/Q192D

<400> 414

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 415

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

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

<400> 415

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile

4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Tyr Glu Val Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 416

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 416

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ala Arg
      35      40      45
Gly Phe Arg Gly Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

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4939SEQ.PC2

```

65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Thr Thr Gln Tyr Gly Gly
      130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
      180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230          235          240
Gly Val

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<210> 417

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 417

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly His Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

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4939SEQ.PC2

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      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Arg Thr Gln Tyr Gly Gly
  130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

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<210> 418
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bS/F60eQ/Y60gF/ins97aV/F97D/T98P/F99L
 /C122S/H143R/G151N/Q175L/Q192T

```

<400> 418
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ser Arg
      35      40      45
Gly Gln Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Arg Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met

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4939SEQ.PC2

				165					170					175					
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Thr	Gly	Asp	Ser				
			180						185					190					
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala				
		195					200						205						
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly				
	210				215						220								
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr				
225				230						235					240				
Gly	Val																		

<210> 419

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bF/F60eT/ins97aV/F97D/T98P/F99L/C122S
/H143Q/G151N/Q175L/Q192G

<400> 419

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val				
1				5				10						15					
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile				
		20					25					30							
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Phe	Arg				
	35					40						45							
Gly	Thr	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu				
	50				55						60								
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu				
65				70						75					80				
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp				
			85						90					95					
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser				
		100					105					110							
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala				
	115					120						125							
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	Gln	Thr	Gln	Tyr	Gly	Gly				
	130					135					140								
Thr	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln				
145				150						155					160				
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met				
			165						170					175					
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser				
		180						185					190						
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala				
	195					200						205							
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly				

4939SEQ.PC2

210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 420
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bF/F60eQ/Y60gF/ins97aV/F97D/T98P/F99L
 /C122S/H143A/G151N/Q175L/Q192A

<400> 420
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Phe Arg
 35 40 45
 Gly Gln Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Ala Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 421
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eT/ins97aV/F97D/T98P/F99L/C122S
 /H143Q/G151Q/Q175L/Q192G

<400> 421
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Thr Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Gln Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 422
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D60bQ/F60eQ/F97D/ins97aV/T98P/F99L/C122S
/H143Q/G151Q/Q175L/Q192G

<400> 422

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Gln	Arg
		35					40					45			
Gly	Gln	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75					80	
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	Gln	Thr	Gln	Tyr	Gly	Gly
	130					135				140					
Thr	Gln	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155				160	
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235				240	
Gly	Val														

<210> 423

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D60bS/F60eQ/ins97aV/F97D/T98P/F99L/C122S
/H143A/G151N/Q175L/Q192G

4939SEQ.PC2

<400> 423

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Ser Arg
          35           40           45
Gly Gln Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
          85           90           95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Ala Thr Gln Tyr Gly Gly
 130           135           140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

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<210> 424

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41A/D60bV/F60eR/Y60gW/D96Q/F97E/ins97aD/T98S
/F99L/C122S/G151N/Q175L/Q192R

<400> 424

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
          20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg

```

4939SEQ.PC2

```

      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Gln Glu Asp Ser Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Arg Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 425

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97D/ins97aE/T98S
/F99L/C122S/G151H/Q175L/Q192A

<400> 425

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Phe Asp Glu Ser Leu Asp

```

4939SEQ.PC2

```

      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 426

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F60eS/Y60gW/D96L/ins97aG/F97D/T98N
/F99L/C122S/G151H/Q175L/Q192E

<400> 426

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Leu Asp Gly Asn Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly

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4939SEQ.PC2

130						135						140					
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln		
145						150						155					
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met		
					165						170						
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser		
					180						185						
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala		
					195						200						
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly		
					210						215						
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr		
225						230						235					
Gly	Val																

<210> 427

$\langle 211 \rangle$ 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 427

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
Gly	Ser	Arg	Trp	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Lys	Gly	Val	Pro	Leu	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys	Ala	Ile	Trp	Val	Thr 130	Gly	Trp	Gly	His	Thr 140	Gln	Tyr	Gly	Gly
Thr 145	His	Ala	Leu	Ile	Leu	Gln 150	Lys	Gly	Glu	Ile	Arg 155	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp 170	Ser	Cys	Asp	Gly	Asp	Ser

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180 185 190															
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
195 200 205															
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
210 215 220															
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225 230 235 240															
Gly	Val														

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<210> 428
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/ins97aN/F97Y/T98G
/F99L/C122S/G151H/Q175L/Q192D

<400> 428															
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ala	Cys	Gly	Ala 30	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Val	Arg
Gly 50	Arg	Arg	Trp	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Ile	Tyr	Asn	Gly	Leu 95	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu 105	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp 120	Ala	Ser	His	Val 125	Phe	Pro	Ala
Gly 130	Lys	Ala	Ile	Trp	Val	Thr 135	Gly	Trp	Gly	His	Thr 140	Gln	Tyr	Gly	Gly
Thr 145	His	Ala	Leu	Ile	Leu 150	Gln	Lys	Gly	Glu	Ile 155	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu 170	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val 185	Asp	Ser	Cys	Asp 190	Gly	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile 205	Phe	Gln	Ala
Gly 210	Val	Val	Ser	Trp	Gly	Asp 215	Gly	Cys	Ala	Gln	Arg	Asn 220	Lys	Pro	Gly
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr

2018290281

4939SEQ.PC2

225	230	235	240
Gly Val			

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<210> 429
<211> 241
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41A/D60bV/F60eR/Y60gW/D96I/F97N/T98G/F99L/C1
22S/G151H/Q175L/Q192D

[illegible]

$\langle 210 \rangle$ 430

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eS/Y60gW/F97D/F99L/C122S/G151N/
 Q175L/Q192D

<400> 430

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Ser	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
				165					170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210				215						220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 431
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/ins97aV/F97E/T98G
/F99L/C122S/G151N/Q175L/Q192D

<400> 431

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Tyr Glu Val Gly Leu Asp
 85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

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<210> 432

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainQ38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G
/F99L/C122S/G151H/Q175L/Q192E

<400> 432

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val

4939SEQ.PC2

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      1             5             10             15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35             40             45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50             55             60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65             70             75             80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Trp Asn Gly Leu Asp
      85             90             95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100            105            110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115            120            125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130            135            140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145            150            155            160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165            170            175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180            185            190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195            200            205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210            215            220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225            230            235            240
Gly Val

```

<210> 433

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G
/F99L/C122S/G151N/Q175L/Q192D

<400> 433

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
      1             5             10             15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35             40             45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```

4939SEQ.PC2

```

      50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Trp Asn Gly Leu Asp
      85              90              95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100             105             110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115             120             125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130             135             140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145             150             155             160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165             170             175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180             185             190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195             200             205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210             215             220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225             230             235             240
Gly Val

```

<210> 434

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bV/F60eR/Y60gW/D96P/ins97aN/F97W/T98G
/F99L/C122S/G151H/Q175L/Q192D

<400> 434

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1              5              10              15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20              25              30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35              40              45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Trp Asn Gly Leu Asp
      85              90              95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser

```

4939SEQ.PC2

```

      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 435

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bV/F60eR/Y60gW/F97D/F99L/C122S/G151H/

Q175L/Q192D

<400> 435

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

```

4939SEQ.PC2

145	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys	160
				165						170						175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly		
			180					185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		
		195					200					205					
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val		
	210				215						220						
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly		
225					230					235					240		
Val																	

<210> 436

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F60eS/Y60gW/D96I/F97N/T98G/F99L/C1

22S/G151N/Q175L/Q192D

<400> 436

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
1				5				10						15			
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile		
			20				25					30					
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg		
		35				40						45					
Gly	Ser	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55						60						
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu		
65				70					75						80		
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Ile	Asn	Gly	Leu	Asp	Tyr		
			85					90					95				
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met		
		100					105					110					
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly		
	115					120					125						
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr		
	130				135						140						
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr		
145				150				155						160			
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys		
			165					170						175			
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly		
		180					185					190					
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		

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		195					200				205				
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 437

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41A/D60bV/F60eR/Y60gW/F97D/F99L/C122S/G151N/Q175L/Q192D

<400> 437

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
		20				25						30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Val	Arg
		35				40						45			
Gly	Arg	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Thr	Leu	Asp	Tyr
			85					90						95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
		100					105						110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
	115					120						125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130				135					140					
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145				150					155						160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
			165					170					175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly
		180					185					190			
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
	195					200					205				
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 438
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122
 S/G151H/Q175L/Q192E

<400> 438
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 439
 <211> 242
 <212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122
S/G151H/Q175L/Q192E

<400> 439

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ile	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Ser	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Val	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215						220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 440

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/F60eS/Y60gW/ins97aV/F97D/T98P/F99L/C122S

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/G151H/Q175L/Q192E

<400> 440

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 441

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/T98P/F99L/C122
S/G151H/Q175L/Q192E

<400> 441

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile

```


4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 442

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

Q38H/I41S/D60bT/F60eS/Y60gW/F97D/T98P/F99L/C122S/G

151H/Q175L/Q192E

<400> 442

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

```

4939SEQ.PC2

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65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Pro Leu Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100        105        110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115        120        125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130        135        140
His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145        150        155
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165        170        175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser Gly
      180        185        190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195        200        205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210        215        220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225        230        235        240
Val

```

<210> 443

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/F99L/C122

S/G151H/Q175L/Q192E

<400> 443

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Thr Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

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4939SEQ.PC2

```

      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 444

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/C122

S/G151H/Q175L/Q192E

<400> 444

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met

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[illegible]

$\langle 210 \rangle$ 445

<211> 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 445

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ser	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Thr	Arg
Gly	Ser 50	Arg	Trp	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Asp	Val	Pro	Leu	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr 135	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
Thr 145	Gly	Ala	Leu	Ile	Leu 150	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly

4939SEQ.PC2

210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 446
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aV/T98P/F99L
 /C122S/G151H/Q192E

<400> 446
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 447
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eS/Y60gW/ins97aV/F97D/T98P/F99L
 /C122S/G151H/Q175L

<400> 447
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 448
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D60bT/F60eS/Y60gW/F97D/ins97aA/T98P/F99L
/C122S/G151H/Q175L/Q192E

<400> 448

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Ser	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Asp	Ala	Pro	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Glu	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 449

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
Q38H/I41S/D60bT/Y60gW/ins97aV/F97D/T98P/F99L/C122S
/G151H/Q175L/Q192E

4939SEQ.PC2

<400> 449

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
          35          40          45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Val Pro Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130          135          140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

```

<210> 450

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bT/F60eG/Y60gW/D96V/F97N/T98G/F99L/C1
22S/G151N/Q175L/Q192D

<400> 450

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg

```


4939SEQ.PC2

```

      35      40      45
Gly Gly Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
  50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Val Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 451

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38K/I41G/F60eG/Y60gW/D96P/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D

<400> 451

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Lys Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Gly Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Asn Gly Leu Asp Tyr

```

4939SEQ.PC2

Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170				175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly
		180						185				190			
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
	195						200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 452

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38Y/I41E/D60bS/F60eV/Y60gF/D96W/F97N/T98G/F99L/C1

22S/G151N/Q175L/Q192D

<400> 452

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Tyr	Gly	His	Glu	Cys	Gly	Ala	Ser	Leu	Ile
		20					25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Ser	Arg
		35					40					45			
Gly	Val	Arg	Phe	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Trp	Asn	Gly	Leu	Asp	Tyr
			85						90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
		100						105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr

4939SEQ.PC2

```

      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 453

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainQ38H/I41S/D60bT/F60eG/D96Y/F97N/T98G/F99L/C122S/G1
51N/Q175L/Q192D

<400> 453

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Gly Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Tyr Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly

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4939SEQ.PC2

180 185 190															
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
195 200 205															
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
210 215 220															
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225 230 235 240															
Val															

<210> 454
<211> 241
<212> PRT
<213> Artificial Sequence

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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      Q38V/I41G/F60eG/Y60gW/D96P/F97N/T98G/F99L/C122S/G1
      51N/Q175L/Q192D
```

<400> 454															
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Val	Gly	His 25	Gly	Cys	Gly	Ala 30	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Gly 50	Arg	Trp	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Pro	Asn	Gly	Leu	Asp 95	Tyr
Asp	Ile	Ala	Leu 100	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser	Met
Val	Arg	Pro	Ile 115	Ser	Leu	Pro	Asp 120	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
Lys	Ala	Ile	Trp 130	Val	Thr	Gly 135	Trp	Gly	His	Thr	Gln 140	Tyr	Gly	Gly	Thr
Asn 145	Ala	Leu	Ile	Leu	Gln 150	Lys	Gly	Glu	Ile	Arg 155	Val	Ile	Asn	Gln	Thr
Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu	Ile 170	Thr	Pro	Arg	Met	Met	Cys
Val	Gly	Phe	Leu 180	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Asp	Gly	Asp	Ser	Gly
Gly	Pro	Leu	Ser 195	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
Val	Val	Ser	Trp 210	Gly	Asp	Gly 215	Cys	Ala	Gln	Arg	Asn 220	Lys	Pro	Gly	Val
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly

225 Val 230 235 240

<210> 455
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38Y/I41A/D60bT/F60eG/Y60gW/D96V/F97N/T98G/F99L/C1
 22S/G151H/Q175L/Q192D

<400> 455
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Tyr Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Gly Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Val Asn Gly Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 456

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eG/D96P/F97N/T98G/F99L/C122S/G1
 51Q/Q175L/Q192D

<400> 456

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35          40          45
Gly Gly Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Asn Gly Leu Asp Tyr
 85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100         105         110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115         120         125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130         135         140
Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145         150         155         160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165         170         175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180         185         190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195         200         205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210         215         220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225         230         235         240
Val

```

<210> 457
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

Q38K/I41G/D60bT/F60eG/Y60gW/D96P/F97N/T98G/F99L/C1
22S/G151N/Q175L/Q192D

<400> 457

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Lys Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Gly Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 458

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainQ38K/I41G/D60bT/F60eG/Y60gW/D96L/F97N/T98G/F99L/C1
22S/G151N/Q175L/Q192D

<400> 458

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val

```

4939SEQ.PC2

1	5	10	15
Ser Leu His	Ala Leu Gly Lys Gly His Gly Cys Gly	Ala Ser Leu Ile	
20	25	30	
Ser Pro Asn	Trp Leu Val Ser Ala Ala His Cys Tyr	Ile Asp Thr Arg	
35	40	45	
Gly Gly Arg	Trp Ser Asp Pro Thr Gln Trp Thr	Ala Phe Leu Gly Leu	
50	55	60	
His Asp Gln	Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg	Leu	
65	70	75	80
Lys Arg Ile	Ile Ser His Pro Phe Phe Asn Leu Asn Gly	Leu Asp Tyr	
85	90	95	
Asp Ile Ala	Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr	Ser Ser Met	
100	105	110	
Val Arg Pro	Ile Ser Leu Pro Asp Ala Ser His Val Phe	Pro Ala Gly	
115	120	125	
Lys Ala Ile	Trp Val Thr Gly Trp Gly His Thr Gln Tyr	Gly Gly Thr	
130	135	140	
Asn Ala Leu	Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr		
145	150	155	160
Thr Cys Glu	Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys		
165	170	175	
Val Gly Phe	Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly		
180	185	190	
Gly Pro Leu	Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly		
195	200	205	
Val Val Ser	Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val		
210	215	220	
Tyr Thr Arg	Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly		
225	230	235	240
Val			

<210> 459

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38E/I41S/D60bV/F60eK/Y60gW/D96P/F97N/T98G/F99L/C1

22S/G151N/Q175L/Q192D

<400> 459

Val Val Gly	Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val		
1	5	10	15
Ser Leu His	Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile		
20	25	30	
Ser Pro Asn	Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg		
35	40	45	
Gly Lys Arg	Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu		

4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Pro Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 460

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38E/I41S/D60bW/F60eG/D96M/F97N/T98G/F99L/C122S/G1

51N/Q175L/Q192D

<400> 460

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Trp Arg
      35      40      45
Gly Gly Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met

```

4939SEQ.PC2

```

      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 461

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38M/I41S/F60eH/Y60gW/D96Y/F97N/T98G/F99L/C122S/G1
51N/Q175L/Q192D

<400> 461

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Met Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly His Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Tyr Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

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145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
				165					170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210				215						220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 462

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 462

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
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Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Val	Arg
		35				40						45			
Gly	Arg	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75					80	
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Phe	Asp	Glu	Gly	Met	Asp
			85					90					95		
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
		100				105						110			
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115				120						125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130				135					140					
Thr	Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145				150					155					160	
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
			165					170						175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Arg	Gly	Asp	Ser
		180					185					190			
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala

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195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 463
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97E/ins97aT/T98G
 /F99M/C122S/G151N/Q175L/Q192G

<400> 463
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Phe Glu Thr Gly Met Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 464
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 <212> PRT
 <213> Artificial Sequence

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 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
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 /F99M/C122S/G151N/Q175L/Q192G

<400> 464
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Phe Glu Ser Gly Met Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 465
 <211> 242
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38H/I41A/D60bV/F60eR/Y60gW/D96W/F97D/ins97aD/T98G
 /F99L/C122S/G151N/Q175L/Q192G

<400> 465

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
          35          40          45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Trp Asp Asp Gly Leu Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
          145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
          225          230          235          240
Gly Val

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<210> 466

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97Y/ins97aE/T98G

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/F99M/C122S/G151N/Q175L/Q192R

<400> 466

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Phe Tyr Glu Gly Met Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Arg Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 467

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 467

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile

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4939SEQ.PC2

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      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Trp Asp Thr Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 468

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38H/I41S/D60bT/F60eK/Y60gF/D96M/F97N/T98G/F99L/C1

22S/G151N/Q175L/Q192D

<400> 468

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Lys Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

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4939SEQ.PC2

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65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

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<210> 469

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

Q38H/I41A/D60bV/F60eR/Y60gW/D96F/F97S/ins97aH/T98G

/F99L/C122S/G151N/Q175L/Q192G

<400> 469

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Phe Ser His Gly Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

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4939SEQ.PC2

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      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

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<210> 470

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 470

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Phe Tyr Asn Gly Met Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met

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4939SEQ.PC2

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<210> 471

$\langle 211 \rangle$ 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 471

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ser	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Thr	Arg
Gly	Ser 50	Arg	Trp	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Phe	Ser	Asp	Gly	Leu	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr 135	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
Thr 145	His	Ala	Leu	Ile	Leu 150	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly

4939SEQ.PC2

210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 472
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38H/I41S/D60bT/F60eS/Y60gW/D96F/F97Y/ins97aD/T98G
 /F99L/C122S/G151H/Q175L/Q192D

<400> 472
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Phe Tyr Asp Gly Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 473
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
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 /F99L/C122S/G151H/Q175L/Q192D

<400> 473
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 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Tyr Asn Glu Ser Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 474
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 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

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<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38H/I41S/D60bT/F60eS/Y60gW/D96Y/F97R/ins97aD/T98G/F99L/C122S/G151H/Q175L/Q192D

<400> 474

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Ser	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Tyr	Arg	Asp	Gly	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	His	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 475

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
 Q38H/I41A/D60bT/F60eK/Y60gF/F97T/ins97aE/T98G/F99L/C122S/H143R/G151N/Q175L/Q192V

4939SEQ.PC2

<400> 475

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
          20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
          35           40           45
Gly Lys Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Glu Gly Leu Asp
          85           90           95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Arg Thr Gln Tyr Gly Gly
 130           135           140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145           150           155           160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225           230           235           240
Gly Val

```

<210> 476

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38Y/I41S/D60bV/F60eR/Y60gF/D96M/F97N/T98G/F99L/C1
22S/G151N/Q175L/Q192D

<400> 476

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
          20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg

```

4939SEQ.PC2

```

      35      40      45
Gly Arg Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225      230      235      240
Val

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<210> 477

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38E/I41S/D60bV/F60eK/Y60gW/D96M/F97N/T98G/F99L/C1
22S/G151N/Q175L/Q192D

<400> 477

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Glu Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Val Arg
      35      40      45
Gly Lys Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr

```


4939SEQ.PC2

```

      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 478

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C1

22S/G151N/Q175L/Q192D

<400> 478

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr

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4939SEQ.PC2

130					135					140					
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
165					170					175					
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly
180					185					190					
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
195					200					205					
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
210					215					220					
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					
240					245					250					
Val															

<210> 479

<211> 241

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 479

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
Gly	Thr 50	Arg	Trp	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Met	Asn	Gly	Leu	Asp	Tyr
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys 100	Pro	Ala	Glu	Tyr	Ser	Ser	Met
Val	Arg	Pro 115	Ile	Ser	Leu	Pro	Asp 120	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
Asn 145	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly

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4939SEQ.PC2

180							185					190							
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly				
195							200					205							
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val				
210							215					220							
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly				
225					230					235					240				
Val																			

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<210> 480
<211> 241
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
Q38H/I41S/D60bT/F60eK/D96V/F97N/T98G/F99L/C122S/G151N/Q175L/Q192D

<400> 480															
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ser	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Thr	Arg
Gly	Lys 50	Arg	Tyr	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Val	Asn	Gly	Leu	Asp 95	Tyr
Asp	Ile	Ala	Leu 100	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser	Met
Val	Arg	Pro	Ile 115	Ser	Leu	Pro	Asp	Ala 120	Ser	His	Val	Phe	Pro	Ala	Gly
Lys	Ala	Ile	Trp 130	Val	Thr	Gly	Trp 135	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
Asn 145	Ala	Leu	Ile	Leu	Gln 150	Lys	Gly	Glu	Ile	Arg 155	Val	Ile	Asn	Gln	Thr
Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu	Ile 170	Thr	Pro	Arg	Met	Met	Cys
Val	Gly	Phe	Leu 180	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Asp	Gly	Asp	Ser	Gly
Gly	Pro	Leu	Ser 195	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
Val	Val	Ser	Trp 210	Gly	Asp	Gly	Cys 215	Ala	Gln	Arg	Asn 220	Lys	Pro	Gly	Val
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly

4939SEQ.PC2

225 Val 230 235 240

<210> 481
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G
 151N/Q175L/Q192D

<400> 481
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 482

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38Y/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G
 151N/Q175L/Q192D

<400> 482

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Tyr Gly His Ile Cys Gly Ala Ser Leu Ile
 20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35          40          45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
 85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

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<210> 483
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

Q38Y/I41S/F60eR/Y60gW/D96M/F97N/T98G/F99L/C122S/G1
51N/Q175L/Q192D

<400> 483

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
 85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225      230      235      240
Val

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<210> 484

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domainQ38Y/I41S/D60bT/Y60gW/D96M/F97N/T98G/F99L/C122S/G1
51N/Q175L/Q192D

<400> 484

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val

4939SEQ.PC2

```

      1             5             10             15
Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35             40             45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50             55             60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65             70             75             80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
      85             90             95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100            105            110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115            120            125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130            135            140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145            150            155            160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165            170            175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180            185            190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195            200            205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210            215            220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225            230            235            240
Val

```

<210> 485

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38Y/I41S/D60bT/F60eR/D96M/F97N/T98G/F99L/C122S/G1
51N/Q175L/Q192D

<400> 485

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
      1             5             10             15
Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
      20             25             30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35             40             45
Gly Arg Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```

4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 486

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38Y/I41S/D60bT/F60eR/Y60gW/F97N/T98G/F99L/C122S/G
151N/Q175L/Q192D

<400> 486

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asn Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met

```


4939SEQ.PC2

```

      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 487

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/T98G/F99L/C122S/G

151N/Q175L/Q192D

<400> 487

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Phe Gly Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

```

4939SEQ.PC2

145	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys	160
				165						170						175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly		
			180					185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		
		195					200					205					
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val		
	210				215						220						
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly		
225					230					235					240		
Val																	

<210> 488

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/F99L/C122S/G

151N/Q175L/Q192D

<400> 488

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
1				5				10						15			
Ser	Leu	His	Ala	Leu	Gly	Tyr	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile		
			20				25					30					
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg		
		35				40						45					
Gly	Arg	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55						60						
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu		
65				70					75						80		
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Met	Asn	Thr	Leu	Asp	Tyr		
			85					90						95			
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met		
		100					105					110					
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly		
	115					120						125					
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr		
	130					135					140						
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr		
145				150					155						160		
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys		
			165						170					175			
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly		
			180					185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		

4939SEQ.PC2

195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 489

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

 Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/C122S/G
 151N/Q175L/Q192D

<400> 489

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Phe Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 490
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C1
 22S/G151N/Q192D

<400> 490
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Tyr Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Arg Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Asn Gly Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 491
 <211> 241
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C1
22S/G151N/Q175L

<400> 491

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Tyr	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Thr	Arg
		35					40					45			
Gly	Arg	Arg	Trp	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Met	Asn	Gly	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met	
			100				105					110			
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Leu	Ile	Thr	Pro	Arg	Met	Met	Cys
				165					170					175	
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 492

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38Y/I41S/D60bT/F60eR/Y60gW/D96M/F97N/T98G/F99L/C1

4939SEQ.PC2

22S/Q175L/Q192D

<400> 492

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 493

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

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

<400> 493

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile

4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Lys Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

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<210> 494

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 494

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Gln Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

```

4939SEQ.PC2

```

65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100        105        110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115        120        125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130        135        140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150        155        160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165        170        175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180        185        190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195        200        205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210        215        220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225          230        235        240
Gly Val

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<210> 495

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

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

<400> 495

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
      35      40      45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100        105        110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

```


4939SEQ.PC2

```

      115              120              125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130              135              140
Ser His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145              150              155              160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
              165              170              175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
              180              185              190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Leu Ala
   195              200              205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
   210              215              220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225              230              235              240
Gly Val

```

<210> 496

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

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

<400> 496

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1              5              10              15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
              20              25              30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
   35              40              45
Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Ala Pro Leu Asp
              85              90              95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
              100              105              110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
              115              120              125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130              135              140
Thr His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145              150              155              160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met

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4939SEQ.PC2

[illegible]

<210> 497

$\langle 211 \rangle$ 241

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
I41G/F97A/F99L/C122S/G151H/O175L/O192G/D217L

<400> 497

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Gln	Gly	His 25	Gly	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala	Phe 60	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu 80
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Ala	Thr	Leu	Asp 95	Tyr
Asp	Ile	Ala	Leu 100	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser 110	Ser	Met
Val	Arg	Pro 115	Ile	Ser	Leu	Pro	Asp 120	Ala	Ser	His	Val	Phe 125	Pro	Ala	Gly
Lys	Ala 130	Ile	Trp	Val	Thr	Gly 135	Trp	Gly	His	Thr	Gln 140	Tyr	Gly	Gly	Thr
His 145	Ala	Leu	Ile	Leu	Gln 150	Lys	Gly	Glu	Ile	Arg 155	Val	Ile	Asn	Gln	Thr 160
Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Leu	Ile 170	Thr	Pro	Arg	Met 175	Met	Cys
Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val 185	Asp	Ser	Cys	Gly	Gly	Asp 190	Ser	Gly
Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile	Phe 205	Gln	Ala	Gly
Val	Val 210	Ser	Trp	Gly	Leu	Gly 215	Cys	Ala	Gln	Arg	Asn 220	Lys	Pro	Gly	Val

4939SEQ.PC2

Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 498
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41G/F97S/F99L/C122S/G151N/Q175I/Q192T/D217T

<400> 498
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 499

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41R/F97A/F99L/C122S/G151N/Q175R/Q192G/D217Q

<400> 499
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ala Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Gln Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 500
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

4939SEQ.PC2

I41S/F97E/F99L/C122S/G151N/Q175G/Q192R/D217A

<400> 500

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Glu Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gly Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Arg Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 501

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41G/F97S/F99L/C122S/G151T/Q175R/Q192A/D217Y

<400> 501

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30

```

4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
   85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
  100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
  115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
  130          135          140
Thr Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
  165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
  180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
  195          200          205
Val Val Ser Trp Gly Tyr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
  210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225          230          235          240
Val

```

<210> 502

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

```

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      I41G/F97L/F99L/C122S/G151N/Q175A/Q192V/D217R

```

<400> 502

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
  20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
  35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
  50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Thr Leu Asp Tyr

```

4939SEQ.PC2

```

      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Ala Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Arg Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 503

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41G/F97T/F99M/C122S/G151D/Q175T/Q192T/D217V

<400> 503

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Thr Met Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140

```

4939SEQ.PC2

```

Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 504

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

```

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      I41G/F97L/F99L/C122S/G151T/Q175M/Q192D/D217M

```

<400> 504

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Thr Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly

```


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4939SEQ.PC2

195 200 205
 Val Val Ser Trp Gly Met Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 505

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97S/F99L/C122S/G151N/Q175I/Q192T/D217T

<400> 505

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 506
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41G/F99L/C122S/G151N/Q175I/Q192T/D217T

<400> 506
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 507
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain I41G/F97S/C122S/G151N/Q175I/Q192T/D217T

<400> 507

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 508

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F97S/F99L/C122S/Q175I/Q192T/D217T

<400> 508

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg

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4939SEQ.PC2

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      35              40              45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
      85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100              105              110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115              120              125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130              135              140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145              150              155              160
Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met Cys
      165              170              175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180              185              190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195              200              205
Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210              215              220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225              230              235              240
Val

```

<210> 509

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F97S/F99L/C122S/G151N/Q192T/D217T

<400> 509

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1              5              10              15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20              25              30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35              40              45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
      85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met

```

4939SEQ.PC2

```

      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

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<210> 510

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F97S/F99L/C122S/G151N/Q175I/D217T

<400> 510

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met Cys

```

4939SEQ.PC2

				165				170					175				
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly		
			180					185					190				
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		
		195					200					205					
Val	Val	Ser	Trp	Gly	Thr	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val		
	210					215					220						
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly		
225					230					235					240		
Val																	

<210> 511

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F97S/F99L/C122S/G151N/Q175I/Q192T

<400> 511

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val		
1				5				10						15			
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Gly	Cys	Gly	Ala	Ser	Leu	Ile		
		20					25					30					
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg		
		35				40						45					
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu		
	50				55					60							
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu		
65				70					75						80		
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Ser	Thr	Leu	Asp	Tyr		
			85					90					95				
Asp	Ile	Ala	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met			
		100				105						110					
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly		
	115					120						125					
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr		
	130				135						140						
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr		
145				150					155					160			
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Ile	Ile	Thr	Pro	Arg	Met	Met	Cys		
			165					170					175				
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Thr	Gly	Asp	Ser	Gly		
		180					185					190					
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly		
	195					200						205					
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val		
	210					215					220						
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly		

225 Val 230 235 240

<210> 512
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97R/ins97aT/T98V/C122S/Q175M/Q192T/D217S

<400> 512
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Val Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Ser Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 513
 <211> 242
 <212> PRT

4939SEQ.PC2

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
F97V/ins97aH/T98R/F99L/C122S/Q175R/Q192G/D217S

<400> 513

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ile	Cys	Gly	Ala	Ser	Leu	Ile
			20					25					30		
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55						60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Val	His	Arg	Leu	Asp
				85					90					95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130					135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155					160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Arg	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Ser	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 514

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain F97Q/F99L/C122S/Q175N/Q192V/D217G

<400> 514

4939SEQ.PC2

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gln Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Asn Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Gly Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 515

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

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<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      F97L/ins97aM/T98N/F99L/C122S/Q175T/Q192T/D217S

```

<400> 515

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```

4939SEQ.PC2

50	55	60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu		
65	70	75
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Met Asn Leu Asp		80
	85	90
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser		95
	100	105
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala		110
	115	120
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly		125
	130	135
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln		140
145	150	155
Thr Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met		160
	165	170
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser		175
	180	185
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala		190
	195	200
Gly Val Val Ser Trp Gly Ser Gly Cys Ala Gln Arg Asn Lys Pro Gly		205
	210	215
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr		220
225	230	235
Gly Val		240

<210> 516

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

F97S/ins97aN/T98G/F99M/C122S/Q175T/Q192T/D217S

<400> 516

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val		
1	5	10
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile		15
	20	25
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg		30
	35	40
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu		45
	50	55
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu		60
65	70	75
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Asn Gly Met Asp		80
	85	90
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser		95
	100	105
		110

4939SEQ.PC2

```

Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
    115                      120                      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
    130                      135                      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145                      150                      155                      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met
    165                      170                      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
    180                      185                      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
    195                      200                      205
Gly Val Val Ser Trp Gly Ser Gly Cys Ala Gln Arg Asn Lys Pro Gly
    210                      215                      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225                      230                      235                      240
Gly Val

```

<210> 517

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain

I41T/F97H/F99L/C122S/G151N/Q175H/Q192V/D217L

<400> 517

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                      5                      10                      15
Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile
    20                      25                      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
    35                      40                      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                      55                      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                      70                      75                      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp His Thr Leu Asp Tyr
    85                      90                      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
    100                      105                      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
    115                      120                      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                      135                      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                      150                      155                      160
Thr Cys Glu Asn Leu Leu Pro Gln His Ile Thr Pro Arg Met Met Cys

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2018290281

4939SEQ.PC2

[illegible]

<210> 518

<211> 241

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain
I41R/F97T/F99L/C122S/G151N/O175T/O192T/D217I

<400> 518

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Gln	Gly	His 25	Arg	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala	Phe 60	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Thr	Thr	Leu	Asp 95	Tyr
Asp	Ile	Ala	Leu 100	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser	Met
Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp 120	Ala	Ser	His	Val	Phe 125	Pro	Ala	Gly
Lys	Ala 130	Ile	Trp	Val	Thr	Gly 135	Trp	Gly	His	Thr	Gln	Tyr 140	Gly	Gly	Thr
Asn 145	Ala	Leu	Ile	Leu	Gln 150	Lys	Gly	Glu	Ile	Arg 155	Val	Ile	Asn	Gln	Thr 160
Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Thr	Ile 170	Thr	Pro	Arg	Met	Met	Cys
Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Thr	Gly	Asp 190	Ser	Gly
Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala 200	Asp	Gly	Arg	Ile	Phe 205	Gln	Ala	Gly
Val	Val 210	Ser	Trp	Gly	Ile	Gly 215	Cys	Ala	Gln	Arg	Asn 220	Lys	Pro	Gly	Val

4939SEQ.PC2

Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 519
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41E/F97V/F99L/C122S/G151N/Q175L/Q192S/D217H

<400> 519
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Val Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly His Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 520

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41D/F97R/F99L/C122S/G151Q/Q175R/Q192V/D217L

<400> 520
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 521
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain

4939SEQ.PC2

I41E/F97R/F99L/C122S/G151Q/Q175G/Q192T/D217V

<400> 521

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gly Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 522

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41D/F97T/F99L/C122S/G151N/Q175S/Q192T/D217A

<400> 522

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30

```

4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
          145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
          225          230          235          240
Val

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<210> 523

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

I41E/F97A/F99M/C122S/G151N/Q175R/Q192S/D217E

<400> 523

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
   1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
          65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ala Thr Met Asp Tyr

```


4939SEQ.PC2

Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Arg	Ile	Thr	Pro	Arg	Met	Met	Cys
			165					170					175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ser	Gly	Asp	Ser	Gly
		180						185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
	195						200					205			
Val	Val	Ser	Trp	Gly	Glu	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 524

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F99L/C122S/Q175I/Q192T/D217T

<400> 524

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Gly	Cys	Gly	Ala	Ser	Leu	Ile
		20					25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
	35					40					45				
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Phe	Thr	Leu	Asp	Tyr
		85						90					95		
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
		100						105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
	115						120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr

4939SEQ.PC2

```

145              150              155              160
Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met Cys
              165              170              175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
              180              185              190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
              195              200              205
Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
              210              215              220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225              230              235              240
Val

```

<210> 525

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F99L/C122S/G151N/Q192T/D217T

<400> 525

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1              5              10              15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
              20              25              30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
              35              40              45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
              85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
              100              105              110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
              115              120              125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130              135              140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145              150              155              160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
              165              170              175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
              180              185              190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
              195              200              205
Val Val Ser Trp Gly Thr Gly Cys Ala Gln Arg Asn Lys Pro Gly Val

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4939SEQ.PC2

210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 526
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41G/F99L/C122S/G151N/Q175I/Q192T

<400> 526
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Ile Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 527

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97V/F99L/C122S/G151N/Q175L/Q192S/D217H

<400> 527
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Val Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly His Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 528
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41E/F99L/C122S/G151N/Q175L/Q192S/D217H

4939SEQ.PC2

<400> 528

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly His Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225          230          235          240
Val

```

<210> 529

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41E/F97V/F99L/C122S/Q175L/Q192S/D217H

<400> 529

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

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4939SEQ.PC2

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      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Val Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly His Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 530

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41E/F97V/F99L/C122S/G151N/Q192S/D217H

<400> 530

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Val Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly

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4939SEQ.PC2

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      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly His Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225      230      235      240
Val

```

<210> 531
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41E/F97V/F99L/C122S/G151N/Q175L/D217H

```

<400> 531
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Val Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly

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180 185 190															
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
195 200 205															
Val	Val	Ser	Trp	Gly	His	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
210 215 220															
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225 230 235 240															
Val															

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<210> 532
<211> 241
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain I41E/F97V/F99L/C122S/G151N/O175L/O192S

[illegible]

<210> 533
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97R/F99L/C122S/G151Q/Q175R/Q192V/D217L

<400> 533
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 534
 <211> 241
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F99L/C122S/G151Q/Q175R/Q192V/D217L

<400> 534

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

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<210> 535

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97R/F99L/C122S/Q175R/Q192V/D217L

<400> 535

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile

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4939SEQ.PC2

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      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

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<210> 536

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97R/F99L/C122S/G151Q/Q192V/D217L

<400> 536

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr

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4939SEQ.PC2

Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gln	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170				175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Val	Gly	Asp	Ser	Gly
		180						185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
	195						200					205			
Val	Val	Ser	Trp	Gly	Leu	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 537

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97R/F99L/C122S/G151Q/Q175R/D217L

<400> 537

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Asp	Cys	Gly	Ala	Ser	Leu	Ile
		20					25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
	35					40					45				
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Arg	Thr	Leu	Asp	Tyr
		85						90					95		
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
		100					105						110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
	115						120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gln	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr

4939SEQ.PC2

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145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 538

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97R/F99L/C122S/G151Q/Q175R/Q192V

<400> 538

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val

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4939SEQ.PC2

210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 539
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41E/F97R/F99L/C122S/G151Q/Q175G/Q192T

<400> 539
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gly Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 540

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41D/F99L/C122S/G151N/Q175S/Q192T/D217A

<400> 540
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 541
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41D/F97T/F99L/C122S/Q175S/Q192T/D217A

4939SEQ.PC2

<400> 541

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Thr Leu Asp Tyr
      85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225          230          235          240
Val

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<210> 542

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97T/F99L/C122S/G151N/Q192T/D217A

<400> 542

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```


4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 543

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97T/F99L/C122S/G151N/Q175S/D217A

<400> 543

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly

```

4939SEQ.PC2

```

      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225      230      235      240
Val

```

<210> 544
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41D/F97T/F99L/C122S/G151N/Q175S/Q192T

```

<400> 544
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly

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2018290281

185

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<210> 545
<211> 241
<212> PRT
<213> Artificial Sequence
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 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain F97T/F99L/C122S/G151N/O175S/O192T/D217A

<400> 545

Page 447

<210> 546
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/F97Q/F99L/C122S/Q175W/Q192V/D217R

<400> 546
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gln Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Trp Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Arg Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 547
 <211> 241
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F97L/F99L/C122S/G151N/Q192V/D217L

<400> 547

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 548

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F97A/F99L/C122S/G151N/Q175M/Q192S

<400> 548

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile

```

4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ala Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 549

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F97V/F99L/C122S/G151N/Q192T/D217V

<400> 549

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Val Thr Leu Asp Tyr

```

4939SEQ.PC2

```

      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

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<210> 550

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97R/F99L/C122S/Q175L/Q192T/D217I

<400> 550

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

```

4939SEQ.PC2

```

145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 551

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41E/F97S/F99L/C122S/Q175L/Q192V/D217A

<400> 551

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly Val

```


4939SEQ.PC2

210	215	220
Tyr Thr Arg Leu Pro	Leu Phe Arg Asp Trp	Ile Lys Glu Asn Thr Gly
225	230	235
Val		240

<210> 552

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain F97L/F99L/C122S/Q175K/Q192V/D217M

<400> 552

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val	1	5	10	15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile	20	25	30	
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg	35	40	45	
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu	50	55	60	
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu	65	70	75	80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Thr Leu Asp Tyr	85	90	95	
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met	100	105	110	
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly	115	120	125	
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr	130	135	140	
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr	145	150	155	160
Thr Cys Glu Asn Leu Pro Gln Lys Ile Thr Pro Arg Met Met Cys	165	170	175	
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly	180	185	190	
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly	195	200	205	
Val Val Ser Trp Gly Met Gly Cys Ala Gln Arg Asn Lys Pro Gly Val	210	215	220	
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly	225	230	235	240
Val				

<210> 553

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97E/F99L/C122S/G151A/Q192V

<400> 553
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Glu Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Ala Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 554
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F97E/F99L/C122S/Q175H/Q192V/D217P

4939SEQ.PC2

<400> 554

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Glu Thr Leu Asp Tyr
      85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln His Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Pro Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225          230          235          240
Val

```

<210> 555

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain F97R/ins97aI/T98P/C122S/Q175M/Q192V/D217I

<400> 555

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```

4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Ile Pro Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Ile Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 556

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F99L/C122S/G151N/Q192T/D217A

<400> 556

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly

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4939SEQ.PC2

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      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Ala Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225      230      235      240
Val

```

<210> 557

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F99L/C122S/G151N/Q175S/Q192T

<400> 557

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly

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185

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<210> 558
<211> 241
<212> PRT
<213> Artificial Sequence
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 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F97T/F99L/C122S/G151N/O192T

<400> 558

Page 458

<210> 559
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41D/F99L/C122S/G151N/Q192T

<400> 559
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 560
 <211> 241
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F99L/C122S/Q175S/Q192T

<400> 560

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 561

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F99L/C122S/Q192T

<400> 561

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile

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4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 562

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38R/I41G/Y60gG/F99M/C122S/G151N/Q192R

<400> 562

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly Arg Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Gly Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Met Asp Tyr

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4939SEQ.PC2

```

      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Arg Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 563

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38K/I41G/Y60gG/F99L/C122S/G151N/Q192H

<400> 563

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Lys Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Gly Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

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4939SEQ.PC2

```

145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 564

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38L/I41R/Y60gF/F99L/C122S/G151N/Q192A

<400> 564

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1          5          10          15
Ser Leu His Ala Leu Gly Leu Gly His Arg Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val

```

4939SEQ.PC2

210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 565
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Q38K/I41D/Y60gG/F99L/C122S/G151N

<400> 565
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Lys Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Gly Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 566

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Q38R/I41R/Y60gF/F99L/C122S/G151N/Q192G

<400> 566
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Arg Gly His Arg Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Phe Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 567
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Q38S/I41S/Y60gW/F99L/C122S/G151D/Q192T

4939SEQ.PC2

<400> 567

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Ser Gly His Ser Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145          150          155          160
Thr Cys Glu Asn Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225          230          235          240
Val

```

<210> 568

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38K/I41G/Y60gW/F99L/C122S/G151N/Q192A

<400> 568

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Lys Gly His Gly Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

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4939SEQ.PC2

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      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 569

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41S/Y60gW/C122S/G151H/Q192A

<400> 569

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly

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4939SEQ.PC2

```

      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225      230      235      240
Val

```

<210> 570

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38K/I41S/Y60gW/F99L/C122S/G151N/Q192G

<400> 570

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Lys Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly

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185

<210> 571
<211> 241
<212> PRT
<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain O38F/I41S/Y60gA/C122S/G151N/Q192R

<400> 571

Page 469

<210> 572
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Q38R/I41S/Y60gW/F99L/C122S/G151N/Q192E

<400> 572
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Arg Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Glu Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 573
 <211> 241
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38K/I41R/Y60gG/F99L/C122S/G151N/Q192G

<400> 573

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Lys Gly His Arg Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35      40      45
Gly Phe Arg Gly Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
 180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225      230      235      240
Val

```

<210> 574

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38R/I41R/F99L/C122S/G151N/Q192G

<400> 574

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Arg Gly His Arg Cys Gly Ala Ser Leu Ile

```

4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 575

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38R/I41R/Y60gL/F99L/C122S/G151N/Q192G

<400> 575

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly Arg Gly His Arg Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Leu Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr

```

4939SEQ.PC2

```

      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 576

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41E/C122S/G151N/Q175L/Q192A

<400> 576

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

```

4939SEQ.PC2

```

145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 577

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F99M/C122S/G151N/Q175L/Q192G

<400> 577

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Met Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val

```

4939SEQ.PC2

210	215	220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly		
225	230	235
Val		240

<210> 578

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41E/F99L/C122S/G151N/Q175L/Q192A

<400> 578

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val	
1 5 10 15	
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile	
20 25 30	
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg	
35 40 45	
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu	
50 55 60	
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu	
65 70 75 80	
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr	
85 90 95	
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met	
100 105 110	
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly	
115 120 125	
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr	
130 135 140	
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr	
145 150 155 160	
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys	
165 170 175	
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly	
180 185 190	
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly	
195 200 205	
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val	
210 215 220	
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly	
225 230 235 240	
Val	

<210> 579

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/F99L/C122S/G151H/Q175L/Q192V

<400> 579
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 580
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41G/F99L/C122S/G151N/Q192A

4939SEQ.PC2

<400> 580

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85           90           95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145          150          155          160
Thr Cys Glu Asn Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225          230          235          240
Val

```

<210> 581

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F99M/C122S/G151N/Q175G/Q192R

<400> 581

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```

4939SEQ.PC2

```

      50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65              70              75              80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Met Asp Tyr
      85              90              95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100             105             110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115             120             125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130             135             140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145             150             155             160
Thr Cys Glu Asn Leu Leu Pro Gln Gly Ile Thr Pro Arg Met Met Cys
      165             170             175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Arg Gly Asp Ser Gly
      180             185             190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195             200             205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210             215             220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225             230             235             240
Val

```

<210> 582

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41E/F99L/C122S/G151N/Q175R/Q192H

<400> 582

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100     105     110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly

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4939SEQ.PC2

```

      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser Gly
   180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
   195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
   210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225      230      235      240
Val

```

<210> 583

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F99M/C122S/G151N/Q175E/Q192R

<400> 583

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Met Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
   100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
   115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Glu Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Arg Gly Asp Ser Gly

```

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180 185 190															
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
195 200 205															
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
210 215 220															
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225 230 235 240															
Val															

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<210> 584
<211> 241
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain I41E/F99L/C122S/G151N/O192V

[illegible]

<210> 585
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41E/F99L/C122S/G151N/Q192S

<400> 585
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 586
 <211> 241
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F99L/C122S/G151N/Q175P/Q192V

<400> 586

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Pro Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 587

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41E/F99L/C122S/G151N/Q175G/Q192T

<400> 587

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile

```

4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gly Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

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<210> 588

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/C122S/G151N/Q175R/Q192R

<400> 588

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr

```

4939SEQ.PC2

Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Arg	Ile	Thr	Pro	Arg	Met	Met	Cys
			165					170					175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Arg	Gly	Asp	Ser	Gly
		180						185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
	195						200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 589

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F99M/C122S/G151N/Q175P/Q192S

<400> 589

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
		20					25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
	35					40					45				
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Phe	Thr	Met	Asp	Tyr
		85						90					95		
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
		100						105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
	115						120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Asn	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr

4939SEQ.PC2

```

145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Pro Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 590

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/C122S/G151N/Q175D/Q192R

<400> 590

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Asp Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Arg Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val

```

4939SEQ.PC2

210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 591
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41E/F99L/C122S/G151N/Q175R/Q192T

<400> 591
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 592

4939SEQ.PC2

<211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41G/F99L/C122S/G151N/Q175R/Q192A

<400> 592
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 593
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain F99L/C122S/G151N/Q192T

4939SEQ.PC2

<400> 593

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225          230          235          240
Val

```

<210> 594

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F99L/C122S/G151N

<400> 594

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

```

4939SEQ.PC2

```

      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 595

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F99L/C122S/Q175P/Q192V

<400> 595

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly

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4939SEQ.PC2

```

      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Pro Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
   180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
   195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
  210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
  225      230      235      240
Val

```

<210> 596

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F99L/C122S/G151N/Q175P

<400> 596

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
   100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
   115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
   130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Pro Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly

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185

180 185 190															
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
195 200 205															
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
210 215 220															
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225 230 235 240															
Val															

<211> 241

<213> Art

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain I41E/F99L/C122S/Q175G/Q192T

<400> 597

[illegible]

<210> 598
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41E/F99L/C122S/G151N/Q175G

<400> 598
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Glu Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gly Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 599
 <211> 241
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/Y59F/F99L/C122S/G151N/Q192T/V213A

<400> 599

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195      200      205
Val Ala Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225      230      235      240
Val

```

<210> 600

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41D/G43A/F99L/C122S/G151N/Q192T/P232S/K239R

<400> 600

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15

```

4939SEQ.PC2

```

Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Ala Ala Ser Leu Ile
   20                               25                               30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35                               40                               45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                               55                               60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65                               70                               75                               80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
   85                               90                               95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
  100                               105                               110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
  115                               120                               125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
  130                               135                               140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
  145                               150                               155                               160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
  165                               170                               175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
  180                               185                               190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
  195                               200                               205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
  210                               215                               220
Tyr Thr Arg Leu Ser Leu Phe Arg Asp Trp Ile Arg Glu Asn Thr Gly
  225                               230                               235                               240
Val

```

<210> 601

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/G43A/D96E/F99L/C122S/G151N/Q192T

<400> 601

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                               5                               10                               15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Ala Ala Ser Leu Ile
   20                               25                               30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35                               40                               45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                               55                               60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65                               70                               75                               80

```

4939SEQ.PC2

Lys Arg Ile Ile Ser His Pro Phe Phe Asn Glu Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 602

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41D/D96E/F99L/C122S/G151N/Q192T

<400> 602

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Glu Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140

4939SEQ.PC2

```

Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 603

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/D96E/C122S/G151N/Q192T

<400> 603

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
          20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Glu Phe Thr Phe Asp Tyr
          85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100     105     110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115     120     125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130     135     140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
          180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195      200      205

```

4939SEQ.PC2

Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 604
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41D/D96E/F99L/C122S/G151N/Q192T/D217E

<400> 604
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Glu Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Glu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

4939SEQ.PC2

<210> 605
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41D/F99L/M117T/C122S/G151N/Q192T/A204D/D217E

<400> 605
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Thr
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Asp Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Glu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 606
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain I41D/F99L/C122S/G151N/Q192T/D217E

<400> 606

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Glu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 607

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

```

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      I41D/F99L/C122S/I136M/G151N/Q192T/D217L/K224R

```

<400> 607

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30

```

4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
           85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
           100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
           115          120          125
Lys Ala Met Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
           130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
   145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
           165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
           180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
           195          200          205
Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Arg Pro Gly Val
   210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
   225          230          235          240
Val

```

<210> 608

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/F60eI/D96E/F99L/C122S/G151N/Q192T

<400> 608

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
   1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
           20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35          40          45
Gly Ile Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Glu Phe Thr Leu Asp Tyr
           85          90          95

```


4939SEQ.PC2

```

Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 609

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41D/C122S/G151N/Q192T/D217E

<400> 609

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160

```

4939SEQ.PC2

```

Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Glu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 610

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain D96E/C122S/G151N/Q192T

<400> 610

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Glu Phe Thr Phe Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210      215      220

```

4939SEQ.PC2

Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 611
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Y59F/C122S/G151N/Q192T

<400> 611
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 612
 <211> 241

4939SEQ.PC2

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

Q38H/I41S/D60bT/F60eS/Y60gW/D96K/F97G/F99L/C122S/G

151H/Q175L/Q192D

<400> 612

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Thr Arg
 35 40 45
 Gly Ser Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 His Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 613

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain I41S/ins97aV/C122S/Q192D

4939SEQ.PC2

<400> 613

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225          230          235          240
Gly Val

```

<210> 614

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97L/F99L/C122S/Q192S

<400> 614

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45

```

4939SEQ.PC2

```

Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100        105        110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115        120        125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130        135        140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150        155        160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165        170        175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
          180        185        190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195        200        205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210        215        220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230        235          240
Val

```

<210> 615

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41T/F97R/ins97aV/T98L/C122S/Q192S

<400> 615

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Val Leu Phe Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100        105        110

```

4939SEQ.PC2

```

Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
    115                      120                      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
    130                      135                      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145                      150                      155                      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
    165                      170                      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
    180                      185                      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
    195                      200                      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
    210                      215                      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225                      230                      235                      240
Gly Val

```

<210> 616

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97V/T98N/F99L/C122S/Q192S

<400> 616

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                      5                      10                      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
    20                      25                      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
    35                      40                      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                      55                      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                      70                      75                      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Val Asn Leu Asp Tyr
    85                      90                      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
    100                      105                      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
    115                      120                      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                      135                      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                      150                      155                      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
    165                      170                      175

```

4939SEQ.PC2

Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 617

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/F97G/ins97aA/T98L/C122S/Q192A

<400> 617

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gly Ala Leu Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240

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4939SEQ.PC2

Gly Val

<210> 618
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97D/F99L/C122S/Q192V

<400> 618
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Asp Thr Leu Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 619
<211> 241
<212> PRT
<213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41E/F97L/F99L/C122S/Q192A

<400> 619

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Glu	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Leu	Thr	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170				175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 620

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97A/ins97aV/T98L/C122S/Q192A

<400> 620

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	

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```

Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ala Val Leu Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 621

<211> 240

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97del/T98S/F99L/C122S/Q192S

<400> 621

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80

```

4939SEQ.PC2

```

Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Leu Asp Tyr Asp
      85                      90                      95
Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met Val
      100                      105                      110
Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly Lys
      115                      120                      125
Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr Gly
      130                      135                      140
Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr Thr
      145                      150                      155                      160
Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys Val
      165                      170                      175
Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly Gly
      180                      185                      190
Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly Val
      195                      200                      205
Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val Tyr
      210                      215                      220
Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly Val
      225                      230                      235                      240

```

<210> 622

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41A/Y60gW/D96F/F97G/F99M/C122S/Q175W/Q192A

<400> 622

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                      5                      10                      15
Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
      20                      25                      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35                      40                      45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50                      55                      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65                      70                      75                      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Phe Gly Thr Met Asp Tyr
      85                      90                      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100                      105                      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115                      120                      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130                      135                      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145                      150                      155                      160

```

4939SEQ.PC2

```

Thr Cys Glu Asn Leu Leu Pro Gln Trp Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

```

<210> 623

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/Y60gW/F99L/C122S/Q175R/Q192S

<400> 623

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220

```

4939SEQ.PC2

Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 624
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41A/Y60gW/ins97aE/F99L/C122S/Q175M/Q192T

<400> 624
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Glu Thr Leu Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 625
 <211> 242

4939SEQ.PC2

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41T/ins97aA/F99Y/C122S/Q175L/Q192A

<400> 625

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Ala Thr Tyr Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100     105     110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115     120     125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130     135     140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145     150     155     160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met
      165     170     175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
      180     185     190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195     200     205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210     215     220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225     230     235     240
Gly Val

```

<210> 626

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41A/ins97aY/F99L/C122S/Q175R/Q192H

<400> 626

4939SEQ.PC2

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Tyr Thr Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 627

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/ins97aT/F99L/C122S/Q175R/Q192H

<400> 627

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60

```


4939SEQ.PC2

```

His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Thr Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 628

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/Y60gW/ins97aN/F99L/C122S/Q175R/Q192T

<400> 628

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Asn Thr Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125

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4939SEQ.PC2

```

Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130                      135                      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145                      150                      155                      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met
                      165                      170                      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
          180                      185                      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195                      200                      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210                      215                      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225                      230                      235                      240
Gly Val

```

<210> 629

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41S/D96S/ins97aK/C122S/G151N/Q192A

<400> 629

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1                      5                      10                      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
          20                      25                      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35                      40                      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50                      55                      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                      70                      75                      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ser Phe Lys Thr Phe Asp
          85                      90                      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100                      105                      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115                      120                      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130                      135                      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145                      150                      155                      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
          165                      170                      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
          180                      185                      190

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Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 630

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Q38H/I41A/D96A/ins97aA/C122S/G151D/Q192T

<400> 630

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ala Phe Ala Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 631
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Q38H/I41S/D96Q/ins97aT/C122S/G151N/Q192A

<400> 631
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Gln Phe Thr Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 632
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

4939SEQ.PC2

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41T/D96M/ins97aA/C122S/G151D

<400> 632

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Thr Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Phe Ala Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 633

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38Y/I41A/D96I/ins97aQ/C122S

<400> 633

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Tyr Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30

```

4939SEQ.PC2

```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ile Phe Gln Thr Phe Asp
           85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Lys Pro Ala Glu Tyr Ser Ser
           100        105        110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
           115        120        125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
           130        135        140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
           145        150        155        160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
           165        170        175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
           180        185        190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
           195        200        205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
           210        215        220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
           225        230        235        240
Gly Val

```

<210> 634

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41S/D96K/ins97aT/C122S/G151K/Q192A

<400> 634

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
           20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
           35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
           50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
           65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Phe Thr Thr Phe Asp
           85          90          95

```

4939SEQ.PC2

```

Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Lys Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 635

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38W/I41S/D96R/ins97aA/C122S/G151N/Q192A

<400> 635

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Trp Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Arg Phe Ala Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160

```

4939SEQ.PC2

Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215						220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225				230						235					240
Gly	Val														

<210> 636

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41A/D96R/ins97aQ/C122S

<400> 636

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5					10					15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ala	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35				40						45			
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75						80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Arg	Phe	Gln	Thr	Phe	Asp
			85					90						95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
			100			105						110			
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115			120							125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
	130				135					140					
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145				150					155						160
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
			165					170						175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser
			180					185					190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210				215						220				

4939SEQ.PC2

Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 637
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Q38F/I41V/D96Q/ins97aT/C122S/G151D

<400> 637
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Phe Gly His Val Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Gln Phe Thr Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Asp Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 638
 <211> 242

4939SEQ.PC2

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain

L33M/Q38F/I41S/D96A/ins97aW/C122S/G151N/Q192S

<400> 638

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Met His Ala Leu Gly Phe Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Ala Phe Trp Thr Phe Asp
          85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
          145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
          210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
          225          230          235          240
Gly Val

```

<210> 639

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain Q38H/I41S/D96V/ins97aA/C122S/G151N/Q192A

4939SEQ.PC2

<400> 639

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Val Phe Ala Thr Phe Asp
      85          90          95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130          135          140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
      180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195          200          205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

```

<210> 640

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41T/D96K/ins97aL/C122S/G151N/Q192A

<400> 640

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly His Gly His Thr Cys Gly Ala Ser Leu Ile
      20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

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4939SEQ.PC2

[illegible]

<210> 641

<211> 242

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41S/D96Q/ins97aA/C122S/Q192T

<400> 641

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	His	Gly	His 25	Ser	Cys	Gly	Ala 30	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro 55	Thr	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu 80
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Gln	Phe	Ala	Thr	Phe	Asp 95
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu 105	Lys	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala

4939SEQ.PC2

```

      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Thr Gly Asp Ser
   180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
   195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
   210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 642

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38W/I41V/D96R/ins97aA/C122S/G151N

<400> 642

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Trp Gly His Val Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Arg Phe Ala Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
   100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
   115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser

```

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180 185 190															
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
195 200 205															
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
210 215 220															
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225 230 235 240															
Gly	Val														

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<210> 643
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain 038Y/I41T/D96M/ins97aS/C122S/G151N

<400> 643

Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Tyr	Gly	His 25	Thr	Cys	Gly	Ala	Ser 30	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Tyr	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala	Phe 60	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg	Ser	Ala 70	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Met	Phe	Ser	Thr	Phe	Asp
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala 120	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
Thr 145	Asn	Ala	Leu	Ile 150	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Gln	Gly	Asp	Ser
Gly	Gly	Pro 195	Leu	Ser	Ser	Val	Glu	Ala	Asp 200	Gly	Arg	Ile	Phe	Gln	Ala
Gly	Val 210	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
Val 225	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
Gly	Val				230					235					240

<210> 644
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain Q38H/I41S/D96K/ins97aS/C122S/G151P/Q192S

<400> 644
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Phe Ser Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Pro Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 645
 <211> 242
 <212> PRT
 <213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41S/D96G/ins97aG/C122S/G151N/Q192A

<400> 645

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Gly Phe Gly Thr Phe Asp
 85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
 180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 646

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41S/D96K/ins97aD/C122S/G151N/Q192S

<400> 646

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly His Gly His Ser Cys Gly Ala Ser Leu Ile

```


4939SEQ.PC2

```

      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Phe Asp Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 647

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/D96E/ins97aG/C122S/G151Q/Q192A

<400> 647

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Glu Phe Gly Thr Phe Asp

```

4939SEQ.PC2

```

      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gln Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 648

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/Y59F/ins97aV/C122S/G187D/Q192V/D217V

<400> 648

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln

```

4939SEQ.PC2

145	Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
					165					170					175	
	Cys	Val	Gly	Phe	Leu	Ser	Gly	Asp	Val	Asp	Ser	Cys	Val	Gly	Asp	Ser
				180					185					190		
	Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala
			195					200					205			
	Gly	Val	Val	Ser	Trp	Gly	Val	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
		210				215						220				
	Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225						230					235					240
	Gly	Val														

<210> 649

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain A35V/I41S/Y59F/C122S/Q192D/D217V

<400> 649

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Val	Leu	Gly	Gln	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Phe	Ile	Asp	Asp	Arg
		35				40					45				
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50				55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65				70					75					80	
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Phe	Thr	Phe	Asp	Tyr
			85					90					95		
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
		100				105					110				
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115				120					125				
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130				135					140					
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145				150					155					160	
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	Cys
			165					170					175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Asp	Gly	Asp	Ser	Gly
		180					185					190			
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195				200					205				
Val	Val	Ser	Trp	Gly	Val	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val

4939SEQ.PC2

210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 650
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/F93L/ins97aV/C122S/Q192V/D217V

<400> 650
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Leu Phe Asn Asp Phe Val Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 651

4939SEQ.PC2

<211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/S90P/ins97aV/C122S/Y146E/Q192N/D217V

<400> 651
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Pro His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Glu Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asn Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 652
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/S90T/ins97aV/C122S/Q192N/D217V

4939SEQ.PC2

<400> 652

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65           70           75           80
Lys Arg Ile Ile Thr His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
      85           90           95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asn Gly Asp Ser
      180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195          200          205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210          215          220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225          230          235          240
Gly Val

```

<210> 653

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/S90T/ins97aV/C122S/Q192V/D217V

<400> 653

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu

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4939SEQ.PC2

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      50              55              60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65              70              75              80
Lys Arg Ile Ile Thr His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
      85              90              95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100             105             110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115             120             125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130             135             140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145             150             155             160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165             170             175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180             185             190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195             200             205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210             215             220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225             230             235             240
Gly Val

```

<210> 654

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/Y59F/ins97aV/C122S/Q192G

<400> 654

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100     105     110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala

```

4939SEQ.PC2

```

      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
  130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225      230      235      240
Gly Val

```

<210> 655
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41S/Y59F/F97S/ins97aV/S116Y/C122S/Q192G/D217V

```

<400> 655
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Val Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Tyr
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175

```


4939SEQ.PC2

Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 656

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/ins97aV/C122S/Q192G/Q209L

<400> 656

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Leu Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240

Gly Val

<210> 657

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41S/ins97aV/A112V/C122S/Q192A/Q209L

<400> 657

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	His	Gly	His	Ser	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35				40					45				
Gly	Phe	Arg	Tyr	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
50					55					60					
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70				75					80	
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asn	Asp	Phe	Val	Thr	Phe	Asp
			85					90						95	
Tyr	Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Val	Glu	Tyr	Ser	Ser
			100					105					110		
Met	Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala
		115					120					125			
Gly	Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly
130						135					140				
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln
145					150					155				160	
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met
				165					170					175	
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser
		180					185						190		
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Leu	Ala
		195					200					205			
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly
	210					215					220				
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr
225					230					235					240
Gly	Val														

<210> 658

<211> 242

<212> PRT

<213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/ins97aV/C122S/Q192V/D217V

<400> 658

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly
210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 659

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/Y59F/ins97aV/C122S/Q192A

<400> 659

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15

```

4939SEQ.PC2

```

Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
   20                25                30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
   35                40                45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                55                60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65                70                75                80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
   85                90                95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
  100                105                110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
  115                120                125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
  130                135                140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145                150                155                160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
  165                170                175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
  180                185                190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
  195                200                205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
  210                215                220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
  225                230                235                240
Gly Val

```

<210> 660

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41A/F97G/ins97aM/T98L/C122S

<400> 660

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1                5                10                15
Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
   20                25                30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35                40                45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50                55                60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65                70                75                80

```

4939SEQ.PC2

Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gly Met Leu Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 661

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41G/F97E/F99L/C122S/Q192A

<400> 661

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Glu Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140

4939SEQ.PC2

```

Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 662

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97V/ins97aV/T98P/C122S

<400> 662

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
          20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Val Val Pro Phe Asp
          85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
          100     105     110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
          115     120     125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
          130     135     140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
          165          170          175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
          180          185          190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
          195          200          205

```

4939SEQ.PC2

Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 663
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/T98S/F99L/C122S/Q192A

<400> 663
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Ser Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

4939SEQ.PC2

<210> 664
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97Q/F99L/C122S/Q192S

<400> 664
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gln Thr Leu Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 665
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41G/F97L/F99L/C122S/Q192S

4939SEQ.PC2

<400> 665

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
          50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

```

<210> 666

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97G/ins97aA/T98P/C122S/Q192A

<400> 666

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45

```

4939SEQ.PC2

Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gly Ala Pro Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 667

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41A/F97G/ins97aV/T98E/C122S

<400> 667

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Gly Val Glu Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110

4939SEQ.PC2

```

Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
   115               120               125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
   130               135               140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145               150               155               160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
               165               170               175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
   180               185               190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
   195               200               205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
   210               215               220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
  225               230               235               240
Gly Val

```

<210> 668

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41A/F97S/ins97aA/C122S

<400> 668

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1           5           10           15
Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
   20           25           30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35           40           45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50           55           60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
  65           70           75           80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Ala Thr Phe Asp
   85           90           95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
  100          105          110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
  115          120          125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
  130          135          140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
  145          150          155          160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
  165          170          175

```

4939SEQ.PC2

Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 669

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41A/F97W/T98S/F99L/C122S/Q192A

<400> 669

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Trp Ser Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240

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2018290281

4939SEQ.PC2

Val

<210> 670
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41L/N95D/D96T/F97W/F99L/C122S/Q192A

<400> 670
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Leu Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asp Thr Trp Thr Leu Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 671
<211> 241
<212> PRT
<213> Artificial Sequence

4939SEQ.PC2

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41T/Y60gL/N95D/D96F/F97S/F99L/C122S/Q175S/Q192A

<400> 671

Val	Val	Gly	Gly	Thr	Asp	Ala	Asp	Glu	Gly	Glu	Trp	Pro	Trp	Gln	Val
1				5				10						15	
Ser	Leu	His	Ala	Leu	Gly	Gln	Gly	His	Thr	Cys	Gly	Ala	Ser	Leu	Ile
			20				25					30			
Ser	Pro	Asn	Trp	Leu	Val	Ser	Ala	Ala	His	Cys	Tyr	Ile	Asp	Asp	Arg
		35					40					45			
Gly	Phe	Arg	Leu	Ser	Asp	Pro	Thr	Gln	Trp	Thr	Ala	Phe	Leu	Gly	Leu
	50					55					60				
His	Asp	Gln	Ser	Gln	Arg	Ser	Ala	Pro	Gly	Val	Gln	Glu	Arg	Arg	Leu
65					70					75					80
Lys	Arg	Ile	Ile	Ser	His	Pro	Phe	Phe	Asp	Phe	Ser	Thr	Leu	Asp	Tyr
				85					90					95	
Asp	Ile	Ala	Leu	Leu	Glu	Leu	Glu	Lys	Pro	Ala	Glu	Tyr	Ser	Ser	Met
			100					105					110		
Val	Arg	Pro	Ile	Ser	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly
		115					120					125			
Lys	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr
	130					135					140				
Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr
145					150					155					160
Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Ser	Ile	Thr	Pro	Arg	Met	Met	Cys
			165						170				175		
Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Ala	Gly	Asp	Ser	Gly
			180					185					190		
Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly
		195					200					205			
Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val
	210					215					220				
Tyr	Thr	Arg	Leu	Pro	Leu	Phe	Arg	Asp	Trp	Ile	Lys	Glu	Asn	Thr	Gly
225					230					235					240
Val															

<210> 672

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain
I41A/Y60gW/N95D/D96F/F97G/F99L/C122S/Q175H/Q192A

<400> 672

4939SEQ.PC2

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asp Phe Gly Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145      150      155      160
Thr Cys Glu Asn Leu Pro Gln His Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225      230      235      240
Val

```

<210> 673

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41A/Y60gW/F99L/C122S/Q175T/Q192A

<400> 673

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ala Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Trp Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60

```

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```

His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Thr Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225      230      235      240
Val

```

<210> 674

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38M/I41T/D96M/ins97aH/C122S/G151E

<400> 674

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Met Gly His Thr Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Met Phe His Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125

```


4939SEQ.PC2

```

Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130                      135                      140
Thr Glu Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145                      150                      155                      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
                      165                      170                      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
      180                      185                      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195                      200                      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210                      215                      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225                      230                      235                      240
Gly Val

```

<210> 675

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain Q38H/I41T/D96R/ins97aG/C122S/G151S

<400> 675

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1                      5                      10                      15
Ser Leu His Ala Leu Gly His Gly His Thr Cys Gly Ala Ser Leu Ile
      20                      25                      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35                      40                      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50                      55                      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                      70                      75                      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Arg Phe Gly Thr Phe Asp
      85                      90                      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100                      105                      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115                      120                      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130                      135                      140
Thr Ser Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145                      150                      155                      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165                      170                      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser
      180                      185                      190

```

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Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 676

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/D60bY/ins97aV/T98N/C122S/Q192H

<400> 676

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Asn Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 677
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/Y59F/D60bY/ins97aV/C122S/Q192G

<400> 677
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Tyr Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 678
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>

4939SEQ.PC2

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/D60bY/ins97aV/A112V/C122S/Q192G/Q209L

<400> 678

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Tyr Arg
 35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
 85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Val Glu Tyr Ser Ser
 100     105     110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115     120     125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130     135     140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145     150     155     160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165     170     175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180     185     190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Leu Ala
 195     200     205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210     215     220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225     230     235     240
Gly Val

```

<210> 679

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

A35T/I41S/Y59F/ins97aV/C122S/Y146F/V183A/Q192G/R23
5H

<400> 679

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10      15

```

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```

Ser Leu His Thr Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Phe Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
      145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Ala Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe His Asp Trp Ile Lys Glu Asn Thr
      225      230      235      240
Gly Val

```

<210> 680

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q175H/Q192D

<400> 680

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

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```

65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
      130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln His Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Asp Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
      210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 681

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/ins97aV/C122S/N164D/Q192G/R235H

<400> 681

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly

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130					135					140									
Thr	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asp	Gln				
145					150					155					160				
Thr	Thr	Cys	Glu	Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met				
165					170					175									
Cys	Val	Gly	Phe	Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gly	Gly	Asp	Ser				
180					185					190									
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala				
195					200					205									
Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly				
210					215					220									
Val	Tyr	Thr	Arg	Leu	Pro	Leu	Phe	His	Asp	Trp	Ile	Lys	Glu	Asn	Thr				
225					230					235					240				
Gly	Val																		

```
<210> 682
<211> 242
<212> PRT
<213> Artificial Sequence
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<220>
<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease domain I41S/Y59F/ins97aV/C122S/Q192G/N223D

<400> 682															
Val 1	Val	Gly	Gly	Thr 5	Asp	Ala	Asp	Glu	Gly 10	Glu	Trp	Pro	Trp	Gln 15	Val
Ser	Leu	His	Ala 20	Leu	Gly	Gln	Gly	His 25	Ser	Cys	Gly	Ala 30	Ser	Leu	Ile
Ser	Pro	Asn 35	Trp	Leu	Val	Ser	Ala 40	Ala	His	Cys	Phe	Ile 45	Asp	Asp	Arg
Gly	Phe 50	Arg	Tyr	Ser	Asp	Pro	Thr 55	Gln	Trp	Thr	Ala 60	Phe	Leu	Gly	Leu
His 65	Asp	Gln	Ser	Gln	Arg 70	Ser	Ala	Pro	Gly	Val 75	Gln	Glu	Arg	Arg	Leu 80
Lys	Arg	Ile	Ile	Ser 85	His	Pro	Phe	Phe	Asn 90	Asp	Phe	Val	Thr	Phe	Asp 95
Tyr	Asp	Ile	Ala 100	Leu	Leu	Glu	Leu	Glu	Lys 105	Pro	Ala	Glu	Tyr	Ser	Ser
Met	Val	Arg 115	Pro	Ile	Ser	Leu	Pro	Asp	Ala 120	Ser	His	Val	Phe	Pro	Ala
Gly	Lys 130	Ala	Ile	Trp	Val	Thr	Gly	Trp	Gly	His 140	Thr	Gln	Tyr	Gly	Gly
Thr 145	Gly	Ala	Leu	Ile	Leu	Gln	Lys	Gly	Glu	Ile 155	Arg	Val	Ile	Asn	Gln 160
Thr	Thr	Cys	Glu	Asn 165	Leu	Leu	Pro	Gln	Gln	Ile 170	Thr	Pro	Arg	Met	Met
Cys	Val	Gly	Phe 180	Leu	Ser	Gly	Gly	Val	Asp 185	Ser	Cys	Gly	Gly	Asp	Ser
Gly	Gly	Pro	Leu	Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala

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195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asp Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 683
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/ins97aV/C122S/N164D/Q192G/R235L

<400> 683
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Val Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asp Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Leu Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

4939SEQ.PC2

<210> 684
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41S/Y59F/F97Y/ins97aV/C122S/Q192G

<400> 684
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Phe Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Tyr Val Thr Phe Asp
 85 90 95
 Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
 100 105 110
 Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
 115 120 125
 Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
 130 135 140
 Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
 145 150 155 160
 Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
 165 170 175
 Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser
 180 185 190
 Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
 195 200 205
 Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
 210 215 220
 Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
 225 230 235 240
 Gly Val

<210> 685
 <211> 242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

4939SEQ.PC2

domain

I41S/D96K/F97G/ins97aV/T98P/F99L/C122S/Q192V

<400> 685

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Lys Gly Val Pro Leu Asp
      85      90      95
Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser
      100      105      110
Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala
      115      120      125
Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly
130      135      140
Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln
145      150      155      160
Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met
      165      170      175
Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser
      180      185      190
Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala
      195      200      205
Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly
210      215      220
Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr
225      230      235      240
Gly Val

```

<210> 686

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease

domain I41S/F99L/C122S/G151N/Q175M/Q192G/D217V

<400> 686

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1      5      10
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30

```

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```

Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
   35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
   50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
           85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
           100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
           115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
           130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
   145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Met Ile Thr Pro Arg Met Met Cys
           165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
           180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
           195          200          205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
   210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
   225          230          235          240
Val

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<210> 687

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain I41S/F97L/F99L/C122S/G151N/Q192G/D217V

<400> 687

```

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
   1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
           20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
           35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
           50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
   65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Thr Leu Asp Tyr
           85          90          95

```

4939SEQ.PC2

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Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
      145      150      155      160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
      165      170      175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gly Gly Asp Ser Gly
      180      185      190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
      195      200      205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
      210      215      220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
      225      230      235      240
Val

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<210> 688

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
domain

I41S/F97S/F99L/C122S/G151N/Q175L/Q192A/D217L

<400> 688

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
  1      5      10      15
Ser Leu His Ala Leu Gly Gln Gly His Ser Cys Gly Ala Ser Leu Ile
      20      25      30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
      35      40      45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
      50      55      60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
      65      70      75      80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Ser Thr Leu Asp Tyr
      85      90      95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
      100      105      110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
      115      120      125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
      130      135      140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr

```

4939SEQ.PC2

```

145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ala Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205
Val Val Ser Trp Gly Leu Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
          210          215          220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225          230          235          240
Val

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<210> 689

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

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<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
      domain
      I41G/F97R/F99L/C122S/G151N/Q175L/Q192S/D217V

```

<400> 689

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Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1          5          10          15
Ser Leu His Ala Leu Gly Gln Gly His Gly Cys Gly Ala Ser Leu Ile
          20          25          30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
          35          40          45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50          55          60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65          70          75          80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Arg Thr Leu Asp Tyr
          85          90          95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
          100          105          110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
          115          120          125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
          130          135          140
Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145          150          155          160
Thr Cys Glu Asn Leu Leu Pro Gln Leu Ile Thr Pro Arg Met Met Cys
          165          170          175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
          180          185          190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
          195          200          205

```

4939SEQ.PC2

Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 690

<211> 241

<212> PRT

<213> Artificial Sequence

<220>

<223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain
 I41T/F97L/F99L/C122S/G151N/Q175S/Q192S/D217W

<400> 690

Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Leu Thr Leu Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Asn Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Ser Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Ser Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Trp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 691
 <211> 241
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MEMBRANE TYPE SERINE PROTEASE 1 (MT-SP1) protease
 domain I41D/F97T/F99M/C122S/Q192V/D217M

<400> 691
 Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1 5 10 15
 Ser Leu His Ala Leu Gly Gln Gly His Asp Cys Gly Ala Ser Leu Ile
 20 25 30
 Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
 35 40 45
 Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
 50 55 60
 His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
 65 70 75 80
 Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Thr Thr Met Asp Tyr
 85 90 95
 Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
 100 105 110
 Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
 115 120 125
 Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
 130 135 140
 Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
 145 150 155 160
 Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
 165 170 175
 Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Val Gly Asp Ser Gly
 180 185 190
 Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
 195 200 205
 Val Val Ser Trp Gly Met Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
 210 215 220
 Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
 225 230 235 240
 Val

<210> 692
 <211> 444
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> ATIII Bait (ATIII modified by insertion of
 QHARASHLG in the RSL loop)

<400> 692

His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro
1				5					10					15	
Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu
			20					25					30		
Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val
		35				40						45			
Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
	50					55					60				
His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
65					70					75				80	
Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
				85				90						95	
Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
			100					105					110		
Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
		115				120						125			
Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
	130					135					140				
Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
145					150					155					160
Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
				165				170						175	
Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
			180					185					190		
Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
		195				200						205			
Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
	210					215					220				
Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
225					230					235					240
Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
				245					250					255	
Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
			260					265					270		
Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
		275				280						285			
Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
	290					295					300				
Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
305					310					315					320
Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
				325					330					335	
Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro
			340					345					350		
Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe
		355					360					365			
His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala
	370					375					380				
Ser	Thr	Ala	Val	Val	Gln	His	Ala	Arg	Ala	Ser	His	Leu	Gly	Arg	Val
385					390					395					400

4939SEQ.PC2

Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro
				405					410					415	
Leu	Asn	Thr	Ile	Ile	Phe	Met	Gly	Arg	Val	Ala	Asn	Pro	Cys	Val	Lys
			420					425					430		
Gly	Gly	Gly	Ser	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys				
		435					440								