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 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 an unmet 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 objects herein, it is an object to provide such therapeutics to target the activation of the complement cascade and to provide therapeutics and methods of treatment of diseases.

## SUMMARY

In one aspect, there is provided the use of a modified MT-SP1 protease, or a catalytically active portion thereof, for formulation of a medicament for treatment of an inflammatory disease or disorder, wherein:

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

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

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

the target substrate is C2 or C3;

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

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

In one aspect, there is provided a pharmaceutical composition comprising a modified MT-SP1 protease, or a catalytically active portion thereof, for use in inhibiting complement activation to thereby treat an inflammatory condition or disorder, wherein:

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

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

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

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

the target substrate is C2 or C3; and

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

In one aspect, there is provided a modified MT-SP1 protease or a catalytically active portion thereof, wherein:

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

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

the target substrate is C2 or C3;

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

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

In one aspect, there is provided a pharmaceutical composition, comprising a modified MT-SP1 protease, or a catalytically active portion thereof, as defined above.

In one aspect, there is provided a nucleic acid molecule, comprising a sequence of nucleotides that encodes any one of the modified MT-SP1 proteases, or a catalytically active portion thereof, as defined above.

In one aspect, there is provided a vector, comprising the nucleic acid molecule as defined above.

In one aspect, there is provided a cell, comprising the vector as defined above.

Provided herein are therapeutics and methods that target the activation of the complement cascade and methods of treatment of diseases, including acute and chronic inflammatory diseases. The therapeutics are non-complement proteases that target complement pathway substrates. Included among the non-complement proteases are unmodified proteases that cleave their native substrate as well as a complement substrate and also proteases modified to have increased selectivity or substrate specificity for a target substrate. The modified proteases can exhibit reduced or altered activity with respect to their native substrates.

Among the methods provided herein are methods of modulating complement activation by contacting a non-complement protease with any one or more, such as 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30 or more target substrates of a complement pathway, whereby a target substrate protein is cleaved such that complement activation in a pathway comprising the target substrate is altered. Uses of proteases for treatment and/or for formulation of medicaments also are provided. Target substrates for these methods and for any of the methods and uses provide herein are complement proteins, including: C1q, C2, C3, iC3, C4, iC4, C5, C6, C7, C8, C9, MBL, Factor B, Factor D, Factor P, MASP-1, MASP-2, C1r, C1s, C4b, C4a,