CLAIMS

1. An engineered protease comprising a modified chymase protease domain, a modified membrane type serine protease 1 (MTSP-1) protease domain, a modified urokinase-type plasminogen activator (uPA) protease domain, or a modified Kallikrein-related peptidase 5 (KLK5) protease domain, wherein the engineered protease is capable of cleaving Factor B.

2. The engineered protease of claim 1, wherein

a) cleavage of Factor B by the engineered protease generates one or more functionally inactive fragments, optionally

wherein the one or more functionally inactive fragments are capable of reducing complement activation; and/or b) cleavage of Factor B results in the generation of a Factor B fragment that is reduced in function.

3. The engineered protease of any claim 1 or 2, wherein:

a) the Factor B is a non-human primate Factor B; optionally

wherein the non-human primate is cynomolgus monkey: or

b) the Factor B is human Factor B, optionally

wherein the Factor B comprises the amino acid sequence as set forth in SEQ ID NO: 1.

4. The engineered protease of any one of claims 1-3, wherein cleavage of Factor B occurs at a site not targeted by Factor D, optionally wherein:

a) cleavage at the site not targeted by Factor D generates at least two fragments that are not Ba and Bb;

b) the Factor B cleavage site comprises a sequence selected from: WEHR/KGT (SEQ ID NO: 10), KNQKR/QKQ (SEQ ID NO: 11), DVFY/QMI (SEQ ID NO: 12), EGVD/AE (SEQ ID NO: 13), DHKL/KSG (SEQ ID NO: 14), TPW/SLA (SEQ ID NO: 15), KVSEAD (SEQ ID NO: 20), IRPSKG (SEQ ID NO: 4), GGEKRD (SEQ ID NO: 5), GKKEAG (SEQ ID NO: 3), and DHKL/KSG (SEQ ID NO: 21); or

c) the Factor B cleavage site comprises a sequence selected from WEHR/KGT (SEQ ID NO: 10) and KNQKR/QKQ (SEQ ID NO: 11), and wherein the engineered protease comprises a modified MTSP-1 protease domain or a modified uPA protease domain.

5. The engineered protease of any one of claims 1-4, wherein cleavage of Factor B results in a reduction of the generation of Factor B cleavage products Ba and Bb as compared to cleavage by Factor D.

6. The engineered protease of any one of claims 1-3, wherein cleavage of Factor B occurs at a site that is targeted by Factor D; optionally

wherein the Factor B cleavage site targeted by Factor D comprises QQKR/KIV (SEQ ID NO: 9).

7. The engineered protease of any one of claims 1-6, wherein the engineered protease comprises a modified MTSP-1 protease domain; optionally:

a) comprising one or more modifications with respect to a MTSP-1 protease domain comprising an amino acid sequence as set forth in SEQ ID NO: 7;

b) wherein the one or more modifications is at one or more positions corresponding to one or more positions selected from D622, I640, L678, A686, F703, D705, F706, T707, F708, K719, C731, D734, Y755, Q783, V791, Q802, A814, D828, and K835 in a MTSP-1 protease domain comprising the sequence of amino acids set forth in SEQ ID NO: 18;

c) wherein the one or more modifications are selected from those presented in Table 5A; or

d) wherein the one or more modifications are selected from those exemplary mutation strings presented in Table 5B.

8. The engineered protease of any one of claims 1-6, wherein the engineered protease does not comprise a modified MTSP-1 protease domain; optionally

wherein the modification is one or more of a substitution, an addition, and deletion of one or more amino acid residues.

9. The engineered protease of any one of claims 1-6, wherein the engineered protease comprises a modified uPA protease domain: optionally:

a) comprising one or more modifications with respect to a uPA protease domain comprising an amino acid sequence as set forth in SEQ ID NO: 8, optionally wherein the modification is one or more of a substitution, an addition, and deletion of one or more amino acid residues;

b) wherein the one or more modifications is at one or more positions corresponding to one or more positions selected from S37, D60, L97, G161, R179, H180, V185, Y187, I207, A247, D248, A251, H252, C279, Y308, V316, A343, Q353, R378, K385 in a uPA protease domain comprising the sequence of amino acids set forth SEQ ID NO: 8;

c) wherein the one or more modifications are selected from those presented in Table 3A; or

d) wherein the one or more modifications are selected from those exemplary mutation strings presented in Table 3B.

10. The engineered protease of any one of claims 1-6, wherein the engineered protease does not comprise a modified uPA protease domain.

11. The engineered protease of any one of claims 1-8, wherein the engineered protease comprises a modified chymase protease domain

a) wherein the engineered protease comprises a modified chymase protease domain, and the cleavage site comprises a sequence selected from DVFY/QMI (SEQ ID NO: 12), EGVD/AE (SEQ ID NO: 13), DHKL/KSG (SEQ ID NO: 14), and TPW/SLA (SEQ ID NO: 15);

b) comprising one or more modifications with respect to a chymase protease domain comprising an amino acid sequence as set forth in SEQ ID NO: 6, optionally wherein the modification is one or more of a substitution, an addition, and deletion of one or more amino acid residues;

c) wherein the one or more modifications is one or more positions corresponding to one or more positions selected from S36 C7, V21, P26, G31, R37, K74, K80, I90, L101, L103, F110, V125, F157, D159, S176, A177, F178, K179, L186, V196, G199, A203, A207, F209 in a chymase protease domain comprising the sequence of amino acids set forth in SEQ ID NO: 6;

d) wherein the one or more modifications are selected from those presented in Table 7A; or

e) wherein the one or more modifications are selected from those exemplary mutation strings presented in Table 7B.

12. The engineered protease of any one of claims 1-8, wherein the engineered protease does not comprise a modified chymase protease domain.

13. The engineered protease of any one of claims 1-8, wherein the engineered protease comprises a modified KLK5 protease domain, optionally comprising one or more amino acid modifications of SEQ ID NO: 23.

14. The engineered protease of any one of claims 1-8, wherein the engineered protease does not comprise a modified KLK5 protease domain.

15. The engineered protease of any one of claims 1-14, wherein the engineered protease has a k_{cat}/K_m of about 100, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1,000, about 1,000, about 1,100, about 1,200, about 1,300, about 1,400, about 1,500, about 1,600, about 1.700, about 1,800, or about 1,900 M^{-1} s^{-1} for Factor B cleavage.

16. The engineered protease of any one of claims 1-15, wherein the engineered protease has a k_{cat}/K_m of about 10^3 to about 10^9 M^{-1} s^{-1} for Factor B cleavage; optionally wherein:

a) the engineered protease has an EC_{50} for Factor B of less than about 20 nM:

b) the engineered protease has an EC_{50} for Factor B of about 20, about 25, or about 60 nM; or

c) wherein the engineered protease has an EC_{50} for cleaving Factor B of about 1,000 to about 4,500 nM.

17. The engineered protease of any one of claims 1-16, wherein the engineered protease has an EC_{50} for Factor B of less than about 1 nM.

18. The engineered protease of any one of claims 1-17, wherein the engineered protease has a plasma half-life in human plasma

a) of over about 72 hours;

b) of over about 120 hours; and/or

c) of about 7 days, optionally

wherein the catalytic activity is about 10% to about 50%, or about 90% to about 100%.

19. The engineered protease of claim 7, wherein the engineered protease:

a) has an increased half-life compared to protease comprising a MTSP-1 protease domain that is not modified; or

b) has an increased bioavailability compared to an protease comprising a MTSP-1 protease domain that is not modified.

20. The engineered protease of claim 9, wherein the engineered protease:

a) has an increased half-life compared to a protease comprising a uPA protease domain that is not modified; or

b) has an increased bioavailability compared to a protease comprising a uPA protease domain that is not modified.

21. The engineered protease of claim 11, wherein the engineered protease:

a) has an increased half-life compared to protease comprising a chymase protease domain that is not modified; or

b) has an increased bioavailability compared to protease comprising a chymase protease domain that is not modified.

22. The engineered protease of any one of claims 1-21, wherein the engineered protease is non-immunogenic.

23. The engineered protease of any one of claims 1-22, wherein the engineered protease is in a zymogen form.

24. The engineered protease of any one of claims 1-23, wherein the engineered protease is in an active form.

25. The engineered protease of any one of claims 1-24, wherein the engineered protease is fused to a component that extends the half-life of the engineered protease; optionally wherein:

a) the component is a Fc domain; or

b) the component is a human serum albumin.

26. The engineered protease of any one of claims 1-6, comprising a modified chymase protease domain having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 95% sequence identity to SEQ ID NO: 6; optionally

wherein the modified chymase protease domain of SEQ ID NO: 6 comprises one of the mutation strings of Table 7B.

27. The engineered protease of any one of claims 1-6, comprising a modified membrane type serine protease 1 (MTSP-1) protease domain having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 95% sequence identity to SEQ ID NO: 7; optionally

wherein the modified MTSP-1 protease domain of SEQ ID NO: 7 comprises one of the mutation strings of Table 5B.

28. The engineered protease of any one of claims 1-6, comprising a modified urokinase-type plasminogen activator (uPA) protease domain having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 95% sequence identity to SEQ ID NO: 22; optionally

wherein the modified uPA protease domain of SEQ ID NO: 22 comprises one of the mutation strings of Table 3B.

29. The engineered protease of any one of claims 1-6, comprising a modified Kallikrein-related peptidase 5 (KLK5) protease domain having at least 50%, at least 55%, at least 60%, at

least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 95% sequence identity to SEQ ID NO: 23.

30. A method of inactivating Factor B, comprising contacting the Factor B with any of the engineered proteases of claims 1-29.

31. A method of treating a disease or condition in a subject in need thereof, comprising administering to the subject any one of the engineered proteases of claims 1-29, optionally

wherein the disease or condition is associated with dysregulated complement.

32. The method of claim 31, wherein the disease or condition

a) is an inflammatory disease or condition;

b) is a congenital complement deficiency;

c) is selected from lupus nephritis, C3 glomerulopathy (C3G), primary IgA nephropathy, kidney transplant ischemia and reperfusion (I/R) injury, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), sepsis, acute respiratory distress syndrome (ARDS), SARS-associated coronavirus (SARS-CoV), atypical hemolytic uremic syndrome (aHUS), membranous nephropathy (MN) and paroxysmal nocturnal hemoglobinuria (PNH); and/or

d) is a control protein deficiency, a secondary complement disorder, or an immunity-related disease or condition.

33. The method of any one of claims 31-32, wherein the treatment:

a) is a replacement therapy;

b) blocks complement activation;

c) modulates autoimmunity; and/or

d) is for endothelial or kidney cell injury.

34. The method of any one of claims 31-33, wherein:

a) the engineered protease is administered to the subject subcutaneously, optionally

b) wherein the engineered protease is activated in situ at the site of a dysregulated complement component; and/or

b) the engineered protease is provided in a liquid stable formulation.

35. A pharmaceutical composition comprising any of the engineered proteases of claims 1-29, and optionally a pharmaceutically acceptable carrier; optionally wherein:

a) the engineered protease is provided in a liquid stable formulation; and/or

b) the composition is formulated for subcutaneous administration.