CLAIMS

What is claimed is:

1. A targeted complement-activating molecule comprising:

(a) a target-binding domain; and

(b) a complement-activating serine protease effector domain.

2. The molecule of claim 1, wherein the complement-activating serine protease effector domain comprises MASP-1 or a fragment thereof, MASP-2 or a fragment thereof, MASP-3 or a fragment thereof, C1r or a fragment thereof, C1s or a fragment thereof, factor D or a fragment thereof, C2a or a fragment thereof, or factor Bb or a fragment thereof.

3. The molecule of claim 1 or claim 2, wherein the target-binding domain binds to an antigen present on a cell.

4. The molecule of claim 3, wherein the target-binding domain binds to CD20, CD38, or CD52.

5. The molecule of claim 1 or claim 2, wherein the target-binding domain binds to an antigen present on a microbial pathogen.

6. The molecule of claim 5, wherein the target-binding domain binds to an antigen present on a bacterial pathogen, a viral pathogen, a fungal pathogen, or a parasitic pathogen.

7. The molecule of claim 6, wherein the pathogen is Neisseria meningitidis, Staphylococcus aureus, Borrelia burgdorferi, Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae, Serratia marcenscens, Haemophilus influenzae, Mycobacterium tuberculosis, Treponema pallidum, Neisseria gonorrhea, Clostridium dificile, a Salmonella species, a Helicobacter species, a Shigella species, a Campylobacter species, a Listeria species, an Epstein-Barr virus, a Human Immunodeficiency Virus 1 (HIV-1), a Herpesvirus, an Influenza virus, a West Nile virus, a Cytomegalovirus, a Coronavirus, Schistosoma mansoni, Plasmodium falciparum, or Trypanosoma cruzei.

8. The molecule any of claims 1-7, wherein the target-binding domain comprises an antibody or an antigen-binding fragment thereof.

9. The molecule of claim 8, wherein the target-binding domain comprises an antibody heavy chain or fragment thereof and an antibody light chain or fragment thereof.

10. The molecule of claim 9, wherein the molecule comprises:

a) a fusion protein comprising:

i) the N-terminus of the complement-activating serine protease effector domain fused to the C-terminus of the antibody heavy chain or fragment thereof; or

ii) the C-terminus of the complement-activating serine protease effector domain fused to the N-terminus of the antibody heavy chain or fragment thereof; and

an antibody light chain or fragment thereof; or

b) a fusion protein comprising:

i) the N-terminus of the complement-activating serine protease effector domain fused to the C-terminus of the antibody light chain or fragment thereof; or

ii) the C-terminus of the complement-activating serine protease effector domain fused to the N-terminus of the antibody light chain or fragment thereof; and

an antibody heavy chain or fragment thereof.

11. The molecule of claim 8, wherein the molecule comprises a fusion protein comprising:

a) the N-terminus of the complement-activating serine protease effector domain fused to the C-terminus of a single-chain antibody or fragment thereof or single-domain antibody or fragment thereof; or

b) the C-terminus of the complement-activating serine protease effector domain fused to the N-terminus of a single-chain antibody or fragment thereof or single-domain antibody or fragment thereof.

12. The molecule of any one of claims 1-11, wherein the target-binding domain and the serine protease effector domain are connected by a linker.

13. The molecule of any one of claims 8-12, wherein the target-binding domain comprises rituximab, alemtuzumab, daratumumab, anti-fHbP antibody clone 19, anti-PspA antibody RX1MI005, anti-Fnbp antibody clone G, anti-Candida antibody 1A2, anti-PfRH5 antibody R5.004, anti-PfRH5 antibody R5.016, anti-GP120 antibody PGT121, bebtelovimab, anti-SARS-CoV-2 M protein antibody RB572, anti-SARS-CoV-2 M protein antibody RB574, anti-Aspergillus antibody hJF5, or an antigen-binding fragment of any of the foregoing.

14. The molecule of any one of claims 8-12, wherein the serine protease effector domain comprises factor D, C1r, C1s, MASP-2, MASP-3, MASP-1, C2a, or Bb, or a fragment of any of the foregoing.

15. The molecule of any one of claims 8-12, wherein the target-binding domain comprises a heavy chain as set forth in any one of SEQ ID NOs:1, 3, 20, 54-56, 93, 95, 97, 98, 103, 105, 113-115, 120, 124, 128, 132, 136, 140, 144, and 148.

16. The molecule of any one of claims 9-12, wherein the target-binding domain comprises a light chain as set forth in any one of SEQ ID NO:2, 94, 96, 102, 104, 106, 121, 125, 129, 133, 137, 141, 145, and 149.

17. The molecule of any one of claims 8-12, wherein:

a) the target-binding domain comprises a heavy chain as set forth in any one of SEQ ID NOs:1, 3, 20, and 54-56 and a light chain as set forth in SEQ ID NO:2;

b) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:93 or 97 and a light chain as set forth in SEQ ID NO:94;

c) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:95 or 98 and a light chain as set forth in SEQ ID NO:96;

d) the target-binding domain comprises a heavy chain as set forth in any one of SEQ ID NOs:103, 114, 116, 117, 118, and 119 and a light chain as set forth in SEQ ID NO:104;

e) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO: 122 or 123 and a light chain as set forth in SEQ ID NO:121;

f) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:126 or 127 and a light chain as set forth in SEQ ID NO:125;

g) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:130 or 131 and a light chain as set forth in SEQ ID NO:129;

h) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:138 or 139 and a light chain as set forth in SEQ ID NO:137;

i) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:142 or 143 and a light chain as set forth in SEQ ID NO:141;

j) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:146 or 147 and a light chain as set forth in SEQ ID NO:145;

k) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:150 or 151 and a light chain as set forth in SEQ ID NO:149; or

l) the target-binding domain comprises a heavy chain as set forth in SEQ ID NO:134 or 135 and a light chain as set forth in SEQ ID NO:133.

18. The molecule of any one of claims 1-17, wherein the serine protease effector domain comprises an amino acid sequence set forth in any one of SEQ ID NOs:57-92.

19. The molecule of claim 10, wherein the fusion protein comprises an amino acid sequence set forth in any one of SEQ ID NOs:4-9, 12-19, 21, 23, 25-53, 97, 98, 108, 111, 116, 117, 119, 122, 123, 126, 127, 130, 131, 134, 135, 138, 139, 142, 143, 146, 147, 150, and 151.

20. The molecule of claim 19, wherein the fusion protein comprises an amino acid sequence set forth in any one of SEQ ID NOs: 4-6, 9, 12, 13, 16, 18, 19, 21, 23, 25-28, and 31-53 and a light chain as set forth in SEQ ID NO:2.

21. The molecule of claim 19, wherein the fusion protein comprises an amino acid sequence set forth in any one of SEQ ID NO: 7, 8, 14, 15, 17, 29, and 30 and a heavy chain as set forth in any one of SEQ ID NOs:1, 3, 20, and 54-56.

22. The molecule of claim 10, wherein the fusion protein comprises an amino acid sequence set forth in any one of SEQ ID NO: 97, 98, 108, 111, 116, 117, 119, 122, 123, 126, 127, 130, 131, 134, 135, 138, 139, 142, 143, 146, 147, 150, and 151.

23. The molecule of claim 22, comprising:

a) a fusion protein as set forth in SEQ ID NO:97 and a light chain as set forth in SEQ ID NO:94;

b) a fusion protein as set forth in SEQ ID NO:98 and a light chain as set forth in SEQ ID NO:96;

c) a fusion protein as set forth in any one of SEQ ID NOs:108, 111, 116, 117, and 119, and a light chain as set forth in SEQ ID NO:104;

d) a fusion protein as set forth in SEQ ID NO:122 or 123 and a light chain as set forth in SEQ ID NO:121

e) a fusion protein as set forth in SEQ ID NO:126 or 127 and a light chain as set forth in SEQ ID NO:125

f) a fusion protein as set forth in SEQ ID NO:130 or 131 and a light chain as set forth in SEQ ID NO:129;

g) a fusion protein as set forth in SEQ ID NO:138 or 139 and a light chain as set forth in SEQ ID NO:137;

h) a fusion protein as set forth in SEQ ID NO:142 or 143 and a light chain as set forth in SEQ ID NO:141;

i) a fusion protein as set forth in SEQ ID NO:146 or 147 and a light chain as set forth in SEQ ID NO:145;

j) a fusion protein as set forth in SEQ ID NO:150 or 151 and a light chain as set forth in SEQ ID NO:149; or

k) a fusion protein as set forth in SEQ ID NO:134 or 135 and a light chain as set forth in SEQ ID NO:133.

24. The molecule of any one of claims 1-23, wherein the molecule binds to a target with an affinity between 1 pM and 1 μM.

25. The molecule of any one of claims 1-24, wherein the molecule has a serine protease activity that is at least 70% of the serine protease activity of the serine protease domain alone.

26. The molecule of any one of claims 1-25, wherein the molecule binds to a target on a cell surface and activates a complement pathway when administered to a mammalian subject.

27. A polynucleotide encoding the molecule of any one of claims 1-26.

28. A polynucleotide encoding the fusion protein of any one of claims 10, 11, and 19-26.

29. A cloning vector or expression cassette comprising the polynucleotide of claim 27 or 28.

30. A cloning vector or expression cassette comprising a first polynucleotide encoding the fusion protein of any one of claims 10, 11, and 19-26 and a second polynucleotide; wherein the second polynucleotide encodes an antibody heavy chain or fragment thereof if the fusion protein comprises an antibody light chain or fragment thereof, and the second polynucleotide encodes an antibody light chain or fragment thereof if the fusion protein comprises an antibody heavy chain or fragment thereof.

31. A first cloning vector or expression cassette comprising a first polynucleotide encoding the fusion protein of any one of claims 10, 11, and 19-26 and a second cloning vector or expression cassette comprising a second polynucleotide; wherein the second polynucleotide encodes an antibody heavy chain or fragment thereof if the fusion protein comprises an antibody light chain or fragment thereof, and the second polynucleotide encodes an antibody light chain or fragment thereof if the fusion protein comprises an antibody heavy chain or fragment thereof.

32. A host cell expressing the molecule of any one of claims 1-26, or comprising the cloning vector(s) or expression cassette(s) of any one of claims 29-31.

33. A method of producing a molecule comprising:

(a) a target-binding domain; and

(b) a complement-activating serine protease effector domain; the method comprising culturing the host cell of claim 32 under conditions allowing for expression of the molecule and isolating the molecule.

34. A composition comprising the molecule of any one of claims 1-26 and one or more excipients.

35. Use of the molecule of any one of claims 1-26 or the composition of claim 34 in the manufacture of a medicament for activating at least one complement pathway in a mammalian subject.

36. Use of the molecule of any one of claims 1-26 or the composition of claim 34 in the manufacture of a medicament for inducing complement dependent cell death (CDC), complement-dependent cell-mediated cytotoxicity (CDCC), or complement-dependent cellular phagocytosis (CDCP) in a target cell.

37. Use of the molecule of any one of claims 1-26 or the composition of claim 34 in the manufacture of a medicament for treating cancer, autoimmune disease, or a microbial infection.

38. The use of claim 37, wherein the infection is a bacterial infection, a viral infection, a fungal infection, or a parasitic infection.

39. A method of inducing complement-dependent cell-mediated cytotoxicity (CDCC) or complement-dependent cellular phagocytosis (CDCP) toward a target cell, comprising contacting the target cell with the molecule of any one of claims 1-26 or the composition of claim 34, wherein said contacting results in complement deposition on the target cell, thereby leading to complement-mediated cell death.