CLAIMS

WHAT IS CLAIMED IS:

1. A fusion protein construct comprising:

(1) an antibody or an antigen-binding fragment thereof that specifically binds to complement protein 3d (c3d), wherein the antibody or antigen-binding fragment thereof comprises

a) a heavy chain comprising three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 29, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 260, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 31, and

b) a light chain comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 32, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 33, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 34;

and

(2) a complement modulator peptide, wherein the complement modulator polypeptide comprises factor H, or a biologically active fragment thereof.

2. A fusion protein construct comprising:

(1) an antibody or an antigen-binding fragment thereof that specifically binds to complement protein 3d (c3d), wherein the antibody or antigen-binding fragment thereof comprises

a) a heavy chain comprising three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 29, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 260, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 31, and

b) a light chain comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 32, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 33, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 34;

and

(2) a complement modulator peptide, wherein the complement modulator polypeptide comprises CR1, or a biologically active fragment thereof.

3. The fusion protein construct of claim 3, wherein the light chain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:258.

4. The fusion protein construct of claim 3, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 279.

5. The fusion protein construct of any one of claims 1 to 4, wherein the heavy chain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 254.

6. The fusion protein construct of claim 5, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 284.

7. The fusion protein construct of claim 6, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 282.

8. The fusion protein construct of claim 6, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 285.

9. The fusion protein construct of any one of claims 1 to 8, wherein:

(a) the light chain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 258; and,

(b) the heavy chain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 254.

10. The fusion protein construct of claim 9, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 279.

11. The fusion protein construct of claim 10, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 284.

12. The fusion protein construct of claim 11, wherein the fusion protein construct further comprises a linker linking the antibody or antigen binding fragment thereof to the complement modulator polypeptide.

13. The fusion protein construct of claim 12, wherein the linker comprises the amino acid sequence of any of SEQ ID NO: 138, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 182, SEQ ID NO: 183, and SEQ ID NO: 241.

14. The fusion protein construct of claim 12, wherein the linker is bound to the C-terminus of the heavy chain and comprises the amino acid sequence of SEQ ID NO: 138.

15. The fusion protein construct of any one of claims 1 or 3 to 14, wherein the complement modulator polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 72 and SEQ ID NO: 108.

16. The fusion protein construct of any one of claims 2 to 14, wherein the complement modulator polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 91, and SEQ ID NO: 92.

17. The fusion protein construct of claim 15, wherein the complement modulator polypeptide comprises an amino acid sequence of SEQ ID NO: 72.

18. The fusion protein construct of claim 16, wherein the complement modulator polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 41 and SEQ ID NO: 42.

19. The fusion protein construct of any one of claims 1 to 18, wherein the antibody or antigen binding fragment thereof comprises:

(a) a first heavy chain and a second heavy chain, wherein each of the first and the second heavy chain comprises three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 29, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 260, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 31, and

(b) a first light chain and a second light chain, wherein each of the first and the second light chain comprises three light chain complementarity determining regions (CDRL1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 32, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 33, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 34.

20. The fusion protein construct of claim 19, wherein each of the first and the second heavy chain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 254, and wherein each of the first and the second light chain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 258.

21. The fusion protein construct of claim 20, wherein the first and the second heavy chain each comprises the amino acid sequence of SEQ ID NO: 284, and wherein the first and the second light chain each comprises the amino acid sequence of SEQ ID NO: 279.

22. The fusion protein construct of claim 21, wherein the first and the second heavy chain each comprises the amino acid sequence of SEQ ID NO: 282.

23. The fusion protein construct of claim 21, wherein the first and the second heavy chain each comprises the amino acid sequence of SEQ ID NO: 285.

24. The fusion protein construct of claim 21, wherein the fusion protein further comprises a linker linking the antibody or antigen binding fragment thereof to one of the complement modulator polypeptides.

25. The fusion protein construct of claim 24, wherein the linker comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 138, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 182, SEQ ID NO: 183, and SEQ ID NO: 241.

26. The fusion protein construct of claim 24, comprising:

(c) a first linker bound to the C-terminus of the first heavy chain and comprising the amino acid sequence of SEQ ID NO: 138; and

(d) a second linker bound to the C-terminus of the second heavy chain and comprising the amino acid sequence of SEQ ID NO: 138.

27. The fusion protein construct of claim 26, wherein the complement modulator polypeptide that comprises Factor H or a biologically active fragment thereof comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 72 and SEQ ID NO: 108.

28. The fusion protein construct of claim 26, wherein the complement modulator polypeptide that comprises CR1 or a biologically active fragment thereof comprises an amino acid sequence

selected from the group consisting of: SEQ ID NO: 41, SEQ ID NO:42, SEQ ID NO:91, and SEQ ID NO: 92.

29. The fusion protein construct of any one of claims 1 to 28, wherein the fusion protein construct is selected from the group consisting of:

(1) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 282, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41; and, two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 279;

(2) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 285, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41; and, two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 279;

(3) a heavy chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 284, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41; and, a light chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 279, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41;

(4) a heavy chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 284, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41; and, a light chain comprising the amino acid sequence of SEQ ID NO: 279;

(5) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 282, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and, two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 279;

(6) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 285, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and, two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 279;

(7) a heavy chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 284, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and, a light chain-containing polypeptide comprising,

from N- to C-terminal, the amino acid sequence of SEQ ID NO: 279, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and,

(8) a heavy chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 284, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and, a light chain comprising the amino acid sequence of SEQ ID NO: 279.

30. An antibody or antigen-binding fragment thereof comprising: a heavy chain comprising: three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3) comprising the following set of amino acid sequences: SEQ ID NOs: 29, 260, and 31, and a light chain comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3) comprising the following set of amino acid sequences: SEQ ID NOs: 32, 33, and 34.

31. The antibody or antigen-binding fragment thereof of claim 30, wherein:

(a) the heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 254; and

(b) the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 258.

32. The antibody or antigen-binding fragment thereof of claim 31, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 279.

33. The antibody or antigen-binding fragment thereof of claim 32, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 284.

34. The antibody or antigen-binding fragment thereof of claim 33, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 282.

35. The antibody or antigen-binding fragment thereof of claim 33, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 285.

36. A pharmaceutical composition comprising the fusion protein of any one of claims 1 to 29 or the antibody or antigen-binding fragment thereof of any one of claims 30 to 35.

37. Use of a fusion protein construct in the manufacture of a medicament for treating a complement mediated disease characterized by an increased deposition of C3d, wherein the fusion protein construct comprises:

(1) an antibody or an antigen-binding fragment thereof that specifically binds to a complement protein 3d (c3d), wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain comprising three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 29, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 260, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 31, and

(b) a light chain comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 32, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 33, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 34; and

(2) a complement modulator polypeptide comprising a complement protein selected from the group consisting of: CR1, DAF, MCP, Crry, MAp44, MAp19, CD59, factor H, and a biologically active fragment thereof.

38. The use of claim 37, wherein the complement mediated disease is a complement mediated kidney disease.

39. The use of claim 38, wherein the complement mediated kidney disease is selected from the group consisting of: focal segmental glomerulosclerosis, glomerulonephritis, complement 3 glomerulopathy (C3G), membranoproliferative glomerulonephritis, C3 glomerulonephritis, type II membranoproliferative glomerulonephritis (MPGN II), membranous nephropathy (MN), IgA nephropathy (IgAN), lupus nephritis (LN), hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), and diabetic retinopathy.

40. The use of claim 37, wherein the light chain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 258, or wherein the light chain comprises the amino acid sequence of SEQ ID NO: 279.

41. The use of claim 37, wherein the heavy chain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 254, or wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 282, 284, or 285.

42. The use of claim 37, wherein:

(a) the light chain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 258; and,

(b) the heavy chain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 254.

43. The use of claim 42, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 279, and wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 284.

44. The use of claim 43, wherein the fusion protein construct further comprises a linker linking the antibody or antigen binding fragment thereof to the complement modulator polypeptide, wherein the linker is bound to the C-terminus of the heavy chain and comprises the amino acid sequence of and one of SEQ ID NO: 138, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 182, SEQ ID NO: 183, and SEQ ID NO: 241.

45. The use of claim 37, wherein the complement modulator polypeptide comprises:

(a) an amino acid sequence selected from the group consisting of: SEQ ID NO: 72 and SEQ ID NO: 108, or,

(b) an amino acid sequence selected from the group consisting of: SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 91, and SEQ ID NO: 92.

46. The use of claim 45, wherein the complement modulator polypeptide comprises:

(a) an amino acid sequence of SEQ ID NO: 72, or,

(b) an amino acid sequence selected from the group consisting of: SEQ ID NO: 41 and SEQ ID NO: 42.

47. The use of claim 37, wherein the antibody or antigen binding fragment thereof comprises:

(a) a first heavy chain and a second heavy chain, wherein each of the first and the second heavy chain comprises three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 29, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 260, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 31, and

(b) a first light chain and a second light chain, wherein each of the first and the second light chain comprises three light chain complementarity determining regions (CDRL1, CDR-L2,

CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 32, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 33, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 34.

48. The use of claim 47, wherein the first and the second heavy chain each comprises the amino acid sequence of SEQ ID NO: 282.

49. The use of claim 48, comprising:

(c) a first linker bound to the C-terminus of the first heavy chain and comprising the amino acid sequence of SEQ ID NO: 138; and

(d) a second linker bound to the C-terminus of the second heavy chain and comprising the amino acid sequence of SEQ ID NO: 138.

50. The use of claim 49, wherein the complement modulator polypeptide comprises:

(a) an amino acid sequence selected from the group consisting of: SEQ ID NO: 72 and SEQ ID NO: 108, or,

(b) an amino acid sequence selected from the group consisting of: SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 91, and SEQ ID NO: 92.

51. The use of claim 37, wherein the fusion protein construct is selected from the group consisting of:

(1) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 282, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41; and, two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 279;

(2) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 285, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41; and, two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 279;

(3) a heavy chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 284, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41; and, a light chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 279, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41;

(4) a heavy chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 284, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72 or 41; and, a light chain-comprising the amino acid sequence of SEQ ID NO: 279;

(5) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 282, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and, two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 279;

(6) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 285, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and, two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 279;

(7) a heavy chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 284, the amino acid sequence of SEQ ID NO:138, and the amino acid sequence of SEQ ID NO: 108 or 42; and, a light chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 279, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and,

(8) a heavy chain-containing polypeptide comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 284, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 108 or 42; and, a light chain comprising the amino acid sequence of SEQ ID NO: 279.

52. The use of claim 37, wherein the fusion protein construct comprises:

(i) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 282, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 72; and,

(ii) two light chain-containing polypeptides, each comprising the amino acid sequence of SEQ ID NO: 279.

53. The use of claim 37, wherein the fusion protein construct comprises:

(i) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 282, the amino acid sequence of SEQ ID NO: 138, and the amino acid sequence of SEQ ID NO: 41; and,

(ii) two light chain-containing polypeptides, each comprising the amino acid sequence of SEQ ID NO: 279.

54. The use of claim 51, wherein the complement mediated disease is a complement mediated kidney disease.

55. The use of claim 54, wherein the complement mediated kidney disease is selected from the group consisting of: focal segmental glomerulosclerosis, glomerulonephritis, complement 3 glomerulopathy (C3G), membranoproliferative glomerulonephritis, C3 glomerulonephritis, type II membranoproliferative glomerulonephritis (MPGN II), membranous nephropathy (MN), IgA nephropathy (IgAN), lupus nephritis (LN), hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), and diabetic retinopathy.

56. The use of claim 54, wherein the complement mediated kidney disease is IgA nephropathy (IgAN), complement 3 glomerulopathy (C3G), or lupus nephritis (LN).