Claims

1. A soluble composition capable of targeted delivery of a complement modulator to sites of complement system activation comprising a construct, wherein the construct comprises:

(a) a complement receptor 2 (CR2) portion comprising ~~a CR2 protein of SEQ ID NO:1 or a biologically active fragment thereof, wherein the CR2 portion contains~~ at least the first two N-terminal short consensus repeat (SCR) domains of CR2 ~~SCR domains of the CR2 protein~~; and

(b) a complement modulator portion;

wherein the CR2 portion contains at least one amino acid substitution ~~that decreases binding affinity of the CR2 portion for EBV gp350 and Interferon-alpha (IFNα)~~ selected from the group consisting of N11, Y64, S42, and K50 of SEQ ID NO: 2, and wherein the construct exhibits decreased binding affinity for EBV gp350 and/or Interferon-alpha (IFNα) but comparable binding affinity for at least one of complement component 3 (C3) proteolytic fragments compared to a construct in which the CR2 portion does not contain the at least one amino acid substitution.

2. The soluble composition of claim 1, wherein the at least one amino acid ~~substitution~~ to be substituted is N11 or Y64 of SEQ ID NO: 2 and the construct exhibits decreased binding affinity for EBV gp350 ~~that decreases binding affinity of the CR2 portion for EBV gp350 is selected from the group consisting of: N11, R36, K41, Y64 and K67 and the at least one amino acid substitution that decreases binding affinity of the CR2 portion for IFNα is selected from the group consisting of S42 and K50~~.

3. The soluble composition of claim 1, wherein the at least one amino acid to be substituted is S42 or K40 of SEQ ID NO: 2 and the construct exhibits decreased binding affinity for IFNα.

4.~~3.~~ The soluble composition of claim 1, wherein the construct is a fusion protein with or without a linker.

5. The soluble composition of claim 1, wherein the CR2 portion comprises at least the first three N-terminal SCR domains of the human CR2 protein (amino acids 23 through 212 of SEQ ID NO: 1), at least the first four N-terminal SCR domains of the human CR2 protein (amino acids 23 through 271 of SEQ ID NO: 1), or the full-length human CR2 (SEQ ID NO: 1).

6.4. The soluble composition of claim 1, wherein the complement modulator portion comprises a complement inhibitor or biologically-active fragment thereof.

7.5. The soluble composition of claim 63, wherein the complement inhibitor or biologically active fragment thereof is selected from the group consisting of: human factor H (SEQ ID NO:5) or biologically-active fragment thereof, mouse factor H (SEQ ID NO: 8) or biologically-active fragment thereof, an anti-complement component 5 (C5) antibody or antigen-binding fragment thereof, an anti-factor B antibody or antigen-binding fragment thereof, an anti-factor D antibody or antigen-binding fragment thereof, an anti-properdin antibody or antigen-binding fragment thereof, human membrane complement protein (MCP) (SEQ ID NO:10) or biologically-active fragment thereof, human decay accelerating factor (DAF) (SEQ ID NO:11) or biologically-active fragment thereof, mouse DAF (SEQ ID NO:12) or biologically-active fragment thereof, mouse complement receptor 1-related gene/protein y (Crry) (SEQ ID NO:4) or biologically-active fragment thereof, human CD59 (SEQ ID NO:3) or biologically-active fragment thereof, mouse CD59 isoform A (SEQ ID NO:6) or biologically-active fragment thereof, mouse CD59 isoform B (SEQ ID NO:7) or biologically-active fragment thereof, and human complement receptor 1 (CR1) (SEQ ID NO:9) or biologically-active fragment thereof~~, human factor H (SEQ ID NO:5), and mouse factor H (SEQ ID NO:8)~~.

8.6. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises human membrane complement protein (MCP) (SEQ ID NO:10) or a biologically-active fragment thereof.

9~~7~~. The soluble composition of claim 8~~claim 5~~, wherein the biologically active fragment of human MCP (SEQ ID NO:10) is selected from the group consisting of SCR1-4 (amino acids 35-285 of SEQ ID NO:10), SCR1-4 plus the serine/threonine-rich domain (amino acids 35-326 of SEQ ID NO:10), and the extracellular domain of MCP (amino acids 35-343 of SEQ ID NO:10).

10~~8~~. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises human DAF (SEQ ID NO:11) or a biologically-active fragment thereof.

11~~9~~. The soluble composition of claim 10~~claim 7~~, wherein the biologically active fragment of human DAF (SEQ ID NO:11) is selected from the group consisting of SCR1-4 (amino acids 25-285 of SEQ ID NO:11) and SCR1-4 plus the O-glycosylated serine/threonine-rich domain (amino acids 25-353 of SEQ ID NO:11).

12~~10~~. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises mouse DAF (SEQ ID NO:12) or a biologically-active fragment thereof.

13~~11~~. The soluble composition of claim 12~~claim 9~~, wherein the biologically active fragment of mouse DAF (SEQ ID NO:12) is selected from the group consisting of SCR1-4 (amino acids 35-286 of SEQ ID NO:12) and SCR1-4 plus the O-glycosylated serine/threonine-rich domain (amino acids 35-362 of SEQ ID NO:12).

14~~12~~. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises Crry (SEQ ID NO:4) or a biologically-active fragment thereof.

15~~13~~. The soluble composition of claim 14~~claim 11~~, wherein the biologically-active fragment of Crry (SEQ ID NO:4) is selected from the group consisting of SCR1-5 (amino acids 41-400 of SEQ ID NO:4) and the extracellular domain mouse Crry protein (amino acids 41-405 of SEQ ID NO:4).

16~~14~~. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises human CD59 (SEQ ID NO:3) or a biologically-active fragment thereof.

1715. The soluble composition of claim 16~~claim 13~~, wherein the biologically-active fragment of human CD59 (SEQ ID NO:3) comprises the extracellular domain of human CD59 lacking its GPI anchor (amino acids 26-101 of SEQ ID NO:3).

1816. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises mouse CD59 isoform A (SEQ ID NO:6) or a biologically-active fragment thereof.

1917. The soluble composition of claim 18~~claim 15~~, wherein the biologically-active fragment of mouse CD59 isoform A (SEQ ID NO:6) comprises the extracellular domain of mouse CD59, isoform A lacking its GPI anchor (amino acids 24-95 of SEQ ID NO:6).

2018. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises mouse CD59 isoform B (SEQ ID NO:7) or a biologically-active fragment thereof.

2119. The soluble composition of claim 20~~claim 17~~, wherein the biologically-active fragment of mouse CD59 isoform B (SEQ ID NO:7) comprises the extracellular domain of mouse CD59, isoform B lacking its GPI anchor (amino acids 24-103 of SEQ ID NO:7).

2220. The soluble composition of claim 6~~claim 3~~, wherein the complement inhibitor or biologically-active fragment thereof comprises human CR1 (SEQ ID NO:9) or a biologically-active fragment thereof.

2321. The soluble composition of claim 22~~claim 19~~, wherein the biologically-active fragment of human CR1 (SEQ ID NO:9) is selected from the group consisting of SCR1-3 (amino acids of 42-234 of SEQ ID NO:9), SCR1-4 (amino acids 42-295 of SEQ ID NO:9), SCR1-10 (amino acids 42-684 of SEQ ID NO:9), SCR8-10 (amino acids of 491-684 of SEQ ID NO:9), SCR 8-11 (amino acids 491-745 of SEQ ID NO:9), SCR15-17 (amino acids of 941-1134 of SEQ ID NO:9), SCR15-18 (amino acids 941-1195 of SEQ ID NO:9), and SCR22-28 (amino acids 1394-1842 of SEQ ID NO:9).

2422. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises human factor H (SEQ ID NO:5) or biologically-active fragment thereof.

2523. The soluble composition of claim 24~~claim 21~~, wherein the biologically-active fragment of human factor H (SEQ ID NO:5) is selected from the group consisting of SCR1-4 (amino acids 21-262 of SEQ ID NO:5), SCR1-5 (amino acids 21-320 of SEQ ID NO:5), SCR1-8

(amino acids 21-507 of SEQ ID NO:5), and SCR1-18 (amino acids 21-1104 of SEQ ID NO:5).

2624. The soluble composition of claim 6~~claim 4~~, wherein the complement inhibitor or biologically-active fragment thereof comprises mouse factor H (SEQ ID NO:8) or biologically-active fragment thereof.

2725. The soluble composition of claim 26~~claim 23~~, wherein the biologically-active fragment of mouse factor H (SEQ ID NO:8) is selected from the group consisting of SCR1-4 (amino acids 19-264 of SEQ ID NO:8), SCR1-5 (amino acids 19-322 of SEQ ID NO:8), SCR1-8 (amino acids 19-507 of SEQ ID NO:8), and SCR1-18 (amino acids 19-1109 of SEQ ID NO:8).

2826. The soluble composition of claim 1, wherein the complement modulator portion comprises a complement activator or biologically-active fragment thereof.

2927. The soluble composition of claim 2825, wherein the complement activator or biologically-active fragment thereof is selected from the group consisting of human IgG_1, human IgG_1 Fc domain, human IgM, human IgM Fc domain, mouse IgG_3, mouse IgG_3 Fc domain, mouse IgM, mouse IgM Fc domain, and cobra venom factor (CVF).

~~28. The soluble composition of claim 1, wherein the construct exhibits decreased binding affinity for EBV-gp350 or IFNα compared to a construct in which the CR2 or biologically active fragment thereof does not contain any amino acid substitution.~~

~~29. The soluble composition of claim 27, wherein the construct exhibits decreased binding affinity for EBV-gp350 compared to a construct in which the CR2 or biologically active fragment thereof does not contain any amino acid substitution.~~

~~30. The soluble composition of claim 28, wherein the CR2 or biologically active fragment thereof contains at least one amino acid substitution of an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67.~~

~~31. The soluble composition of claim 27, wherein the construct exhibits decreased binding affinity for IFNα compared to a construct in which the CR2 or biologically active fragment thereof does not contain any amino acid substitution.~~

~~32. The soluble composition of claim 30, wherein the CR2 or fragment thereof contains at least one amino acid substitution to an amino acid residue selected from the group consisting of: S42 and K50.~~

30. The soluble composition of any one of claims 1 to 29, wherein the at least one of C3 proteolytic fragments is selected from the group consisting of: C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to CR2.

31. The soluble composition of any one of claims 1 to 30, wherein the at least one amino acid substitution in the CR2 portion of the construct is a substitution to the amino acid alanine.

32. The soluble composition of any one of claims 1 to 31 formulated for intravenous, intraperitoneal, or intraocular injection or oral administration.

33. The soluble composition of any one of claims 1 to 32 for treating a complement-associated disease or condition.

34~~33~~. A method for making a construct that selectively binds to one or more C3 proteolytic fragments but does not selectively bind to EBV gp350 or IFNα, wherein the method comprises:

(a) mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct at a position selected from the group consisting of: N11~~, R36, K41,~~ and Y64 ~~and K67~~ of SEQ ID NO:2; and

(b) mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct at a position selected from the group consisting of: S42 and K50 of SEQ ID NO:2,

wherein the construct comprises:

(i) a complement receptor 2 (CR2) portion comprising ~~a CR2 protein of SEQ ID NO:1 or a biologically active fragment thereof, wherein the CR2 portion contains~~ at least the first two N-terminal SCR domains of the CR2 protein; and

(ii) a complement modulator portion.

3534. The method of claim 34 ~~claim 33~~, wherein the one or more mutations in the complement receptor 2 (CR2) portion of the construct are mutations to the amino acid alanine.

3635. The method of claim 34 ~~claim 33~~, wherein the method further comprises mutating one or more amino acids in the complement receptor 2 (CR2) portion of the construct at a position selected from the group consisting of: R13, Y16, A22, R28, S32, R36, K41, K48, K57, K67, Y68, R83, G84, and R89 of SEQ ID NO:2.

3736. A method of reducing the binding affinity of ~~the CR2 portion of the~~ a construct ~~of claim 1~~ for EBV-gp350 but not for at least one of C3 proteolytic fragments, wherein the construct comprises:

(a) a complement receptor 2 (CR2) portion comprising at least the first two N-terminal short consensus repeat (SCR) domains of CR2; and

(b) a complement modulator portion,

said method comprising mutating at least one amino acid residue of the CR2 portion selected from the group consisting of N11~~, R36, K41,~~ and Y64 ~~and K67~~ of SEQ ID NO:2.

3837. A method of reducing the binding affinity of ~~the CR2 portion of the~~ a construct ~~of claim 1~~ for IFNα but not for at least one of C3 proteolytic fragments, wherein the construct comprises:

(a) a complement receptor 2 (CR2) portion comprising at least the first two N-terminal short consensus repeat (SCR) domains of CR2; and

(b) a complement modulator portion,

said method comprising mutating at least one amino acid residue of the CR2 portion selected from the group consisting of S42 and K50 of SEQ ID NO:2.

39. Use of the soluble composition of any one of claims 1 to 32 for the preparation of a medicament for treating a subject having a complement-associated disease or condition.