IMPROVED COMPLEMENT RECEPTOR 2 (CR2) TARGETING GROUPS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit to U.S. Provisional Patent Application No. 61/345,035, filed May 14, 2010, the disclosure of which is hereby incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] This application pertains to improved compositions for targeted delivery of therapeutics, including complement inhibitors, to sites of inflammation.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0003] This invention was made in part during work supported by Grant No. RO1-CA53617 from the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

[0004] Human complement receptor 2 (CR2/CD21) is a 145 kiloDalton ("kDa") transmembrane protein comprised of 15 or 16 short consensus repeat (SCR) extracellular domains, a 28 amino acid single pass transmembrane domain and a short 34 amino acid intracellular domain (1-5). Each of the extracellular SCRs comprises approximately 60-70 amino acid residues and is connected by linker regions of three to eight amino acid residues. All SCRs contain a number of conserved amino acid residues including four cysteine residues, which form a pattern of disulfide bridges connecting Cys1-Cys3 and Cys2-Cys4. CR2 is primarily present on B cells, where it is found in complex with other membrane proteins that promote normal humoral and cellular immune responses (6-9). Using the most distally located (*i.e.*, amino-terminal) SCR domains, SCR1-2, CR2 binds four classes of ligands – complement component 3 (C3) proteolytic fragments iC3b, C3dg and C3d (10, 11);

the Epstein-Barr virus (EBV) glycoprotein gp350/220 (gp350) (12-14); the low affinity IgE receptor CD23 (15, 16); and the cytokine interferon alpha (IFNα) (17-19).

[0005] The primary role of CR2 is to function as a B cell co-receptor for antigen-mediated B cell activation through enhanced signal transduction (20, 21). This function is carried out through co-ligation via C3d and surface IgM, when C3d is covalently attached to an antigen (22-28). CR2 is also the obligate cellular receptor for EBV through its envelope surface glycoprotein gp350 (12, 20, 29-31). Actual cellular EBV infection is achieved after the ligation of CR2 to gp350 tethers the virus close enough to the cell surface (14, 32, 33), allowing viral gp42 to bind human leukocyte antigen class II molecules (34, 35) and subsequently triggering host cell fusion via three additional viral glycoproteins gB, gH and gL (36-38). IFNα has been shown to be a ligand of CR2, though the physiologic importance of this interaction remains unclear (17-19). It has been suggested, however, that IFNα and CR2 may be involved in the development of the autoimmune disease systemic lupus erythematosus (39-41).

[0006] Mutagenesis studies along with structural studies of the CR2-gp350 interaction have suggested residues on CR2 that are required for the interaction (20, 42, 43). ELISA and flow cytometry was used to test candidate CR2 mutants for the binding of gp350 and CR2 (20, 42, 43). In recent studies specific residues on CR2 which were found to have a deleterious effect on gp350-binding when mutated included R13, S15, R28, R36, K41, K57, K67, R83 and R89 (42, 43). In separate work residues P8-S15 within the first conserved inter-cysteine region of SCR1 and the linker region between SCR1 and SCR2 were also highlighted as being essential for gp350-binding to occur (20). These data, in conjunction with separate mutagenesis analyses targeting the gp350 molecule were used to drive an *in silico* model of the CR2-gp350 interaction utilizing the soft docking program HADDOCK (43-45). This analysis suggested that the primary interaction on CR2 was between SCR1 and the linker region joining SCR1 to SCR2, and for gp350, the linker region between domain 1 and domain 2 (43).

[0007] CR2 has been suggested as a receptor for IFNα by the finding that IFNα mimics both gp350 and C3d binding, and the observation that all three ligands bind a similar region on CR2 (18, 19). The mimicry was shown to be functional as well (18). After both the C3d and IFNα structures were solved, the putative CR2 binding sequence was found to have similar

structural motifs. IFNα has been described as being able to bind to multiple forms of CR2 from full length to SCR1-2, although to varying degrees (17). Though CR2 has been shown to be a receptor for IFNα, the IFNα binding site within CR2 SCR1-2 is unknown.

[0008] Further analysis of CR2 interactions with known ligands to identify specific amino acid residues involved in binding to these ligands would enable the design of modified CR2 molecules with defined binding specificity for each known CR2 ligand (*e.g.*, C3 proteolytic fragments iC3b, C3dg and C3d; EBV glycoprotein gp350; CD23; and IFNα..

BRIEF SUMMARY

[0009] Provided herein are compositions and methods directed to soluble proteins which can selectively deliver modulators of complement activity. Targeted delivery of these modulators is accomplished by selectively mutating particular amino acids in a targeting protein portion of the composition corresponding to at least the first two N-terminal SCR domains of CR2. Depending on the particular combination of mutations introduced into the targeting portion, a complement activity modulator can be selectively delivered to particular ligands of CR2 at sites where complement system activation or suppression is desired.

[0010] Accordingly, in one aspect, provided herein are soluble compositions 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67. In certain embodiments, the construct is a fusion protein.

[0011] In certain embodiments, the complement modulator portion comprises a complement inhibitor or biologically-active fragment thereof. In certain embodiments, the complement inhibitor or biologically active fragment thereof is selected from the group consisting of human membrane complement protein (MCP)(SEQ ID NO:10), human decay accelerating factor (DAF)(SEQ ID NO:11), mouse DAF (SEQ ID NO:12), mouse complement receptor 1-related gene/protein y (Crry) (SEQ ID NO:4), human CD59 (SEQ ID NO:3), mouse CD59 isoform A (SEQ ID NO:6), mouse CD59 isoform B (SEQ ID NO:7), human complement

receptor 1 (CR1) (SEQ ID NO:9), human factor H (SEQ ID NO:5), and mouse factor H (SEQ ID NO:8).

[0012] In certain embodiments, the complement inhibitor comprises human membrane complement protein (MCP) (SEQ ID NO:10) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises human DAF (SEQ ID NO:11) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises mouse DAF (SEQ ID NO:12) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises Crry (SEQ ID NO:4) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises human CD59 (SEQ ID NO:3) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises mouse CD59 isoform A (SEQ ID NO:6) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises mouse CD59 isoform B (SEQ ID NO:7) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises human CR1 (SEQ ID NO:9) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises human factor H (SEQ ID NO:5) or a biologically-active fragment thereof. In certain embodiments, 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). In certain embodiments, the complement inhibitor comprises mouse factor H (SEQ ID NO:8) or a biologically-active fragment thereof. In certain embodiments, 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).

[0013] In certain embodiments, the complement modulator portion comprises a complement activator or biologically-active fragment thereof. In certain embodiments, 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).

[0014] In certain embodiments, 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. In certain embodiments, 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. In certain embodiments, 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. In certain embodiments, 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. In certain embodiments, 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.

[0015] In another aspect, provided herein are methods of reducing the binding affinity of a construct comprising: (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 SCR domains of the CR2 portion; and (b) a complement modulator portion, for EBV-gp350, comprising mutating at least one amino acid residue selected from the group consisting of N11, R36, K41, Y64 and K67.

[0016] In another aspect, provided herein are methods of reducing the binding affinity of a contruct comprising: (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 SCR domains of the CR2 portion; and (b) a complement modulator portion, for IFNα, comprising mutating at least one amino acid residue selected from the group consisting of S42 and K50.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **Figure 1. NMR titration analysis reveals that SCR1 and SCR2 of CR2 are both involved in ligating gp350.** Two superimposed ^{1}H-^{15}N Transverse Relaxation Optimized Spectroscopy-Heteronuclear Single Quantum Coherence (TROSY-HSQC) spectra of ^{15}N-labled CR2 SCR1-2 (0.6 mM in 1/3X PBS) collected during titration with increasing amounts of gp350. Black, no gp350 and grey, saturating amounts of gp350. Inset, detailed view of chemical shift change. The numbering scheme used here for CR2 is based on the amino acid sequence for the mature protein.

[0018] **Figure 2. NMR titration analysis reveals that SCR1 and SCR2 of CR2 are both involved in ligating IFNα.** Five superimposed ^{1}H-^{15}N TROSY-HSQC spectra of ^{15}N-labled

CR2 SCR1-2 (0.6 mM in 1/3X PBS) collected during titration with increasing amounts of IFNα.

[0019] **Figure 3. NMR derived CR2-ligand binding residue comparison.** Histogram illustrates chemical shift changes induced in the backbone amides of CR2 SCR1-2 upon binding C3d, IFNα or gp350.

[0020] **Figures 4A, 4B and 4C. Surface representation of CR2 SCR1-2 x-ray crystal structure in its ligand-bound state (C3d not shown) with NMR-determined ligand binding residues.** Figure 4A. NMR-determined gp350 binding residues. Gray residues represent residues unaffected by gp350 titration. The black residues on SCR1, the linker region and SCR2 represent residues involved in gp350 binding to CR2 SCR1-2. Figure 4B. NMR determined IFNα binding residues. Gray residues represent residues unaffected by IFNα titration. The black residues on SCR1, the linker region and SCR2 represent residues involved in IFNα binding to CR2 SCR1-2. Figure 4C. NMR determined ligand unique and shared binding residues. The black residues represent residues that are uniquely involved in CR2 binding to IFNα and gp350. The dark grey residues represent residues that are uniquely involved in CR2 binding to C3d. The light grey residues represent residues that are involved in all three CR2 ligand binding events.

[0021] **Figure 5. HADDOCK CR2-gp350 docking model with NMR derived CR2-gp350 ligand binding residues highlighted**. Model from Young, *et al* (43). Black ribbons represent gp350 and light grey represents glycosyl-groups that decorate the surface of gp350. Dark grey ribbons represent CR2 SCR1-2. Inset, magnified view of theoretical side-chain interactions between NMR derived binding residues and gp350 mapped on the docking model of Young, *et al.*

[0022] **Table 1. CR2 binding constants from NMR titrations and ITC.** Shown are weak and upper limit to tight binding constants for CR2-ligand interactions determined using NMR titrations monitoring chemical shift changes. Also shown are CR2-ligand binding constants determined using ITC. UL, upper limit. ITC, isothermal titration calorimetry.

[0023] **Table 2. Comparison of CR2 ligand binding residues.** Shown are residues involved in each CR2-ligand binding interaction. Residues with an asterisk are unique to the respective binding interaction.

BRIEF DESCRIPTION OF THE SEQUENCES

[0024] SEQ ID NO:1 is the complete amino acid sequence of human complement receptor 2 (CR2).

[0025] SEQ ID NO:2 is the complete amino acid sequence of short consensus repeat (SCR) domains 1 and 2 of human CR2.

[0026] SEQ ID NO:3 is the complete amino acid sequence of human CD59 protein.

[0027] SEQ ID NO:4 is the complete amino acid sequence of mouse complement receptor 1-related gene/protein y (Crry).

[0028] SEQ ID NO:5 is the complete amino acid sequence of human factor H.

[0029] SEQ ID NO:6 is the complete amino acid sequence of mouse CD59A protein.

[0030] SEQ ID NO:7 is the complete amino acid sequence of mouse CD59B protein.

[0031] SEQ ID NO:8 is the complete amino acid sequence of mouse factor H.

[0032] SEQ ID NO:9 is the complete amino acid sequence of human complement receptor 1 (CR1).

[0033] SEQ ID NO:10 is the complete amino acid sequence of human membrane cofactor protein (MCP).

[0034] SEQ ID NO:11 is the complete amino acid sequence of human decay accelerating factor (DAF/CD55).

[0035] SEQ ID NO:12 is the complete amino acid sequence of mouse decay accelerating factor (DAF/CD55).

[0036] SEQ ID NO:13 is the complete amino acid sequence of cobra venom factor (CVF) from the monocled cobra (*Naja kaouthia*).

[0037] SEQ ID NO:14 is the complete amino acid sequence of the human IgG_1 heavy chain, C domain.

[0038] SEQ ID NO:15 is the complete amino acid sequence of the human IgG_1 light chain, C domain.

[0039] SEQ ID NO:16 is the complete amino acid sequence of the Fc domain of human IgG_1.

[0040] SEQ ID NO:17 is the complete amino acid sequence of human IgM heavy chain, C domain.

[0041] SEQ ID NO:18 is the complete amino acid sequence of human IgM light chain, C domain.

[0042] SEQ ID NO:19 is the complete amino acid sequence of the Fc domain of human IgM.

[0043] SEQ ID NO:20 is the complete amino acid sequence of mouse IgG_3 heavy chain, C domain.

[0044] SEQ ID NO:21 is the complete amino acid sequence of mouse IgG_3 light chain, C domain.

[0045] SEQ ID NO:22 is the complete amino acid sequence of mouse IgG_3 Fc domain.

[0046] SEQ ID NO:23 is the complete amino acid sequence of mouse IgM heavy chain, C domain.

[0047] SEQ ID NO:24 is the complete amino acid sequence of mouse IgM light chain, C domain.

[0048] SEQ ID NO:25 is the complete amino acid sequence of mouse IgM Fc domain.

[0049] SEQ ID NO:26 is a linking sequence between the first two N-terminal SCRs of human CR2.

[0050] SEQ ID NO:27 is a linking sequences between the first two N-terminal SCRs of human CR2.

[0051] SEQ ID NO:28 is a linking sequence between the fourth and the fifth N-terminal short consensus repeat domains of human CR2.

DETAILED DESCRIPTION

[0052] Complement is an important component of immunity, but inappropriate and excessive activation of the complement system is involved in numerous pathological and inflammatory conditions. Complement activation products that mediate tissue injury are generated at various points in the complement pathway. Complement activation on cell surfaces results in the cleavage of serum complement component 3 (C3) and the covalent attachment of C3 fragments that serve as opsonins for immune effector cells to the cell surfaces. The resulting C3 fragments include C3a, a soluble peptide that is a potent anaphylatoxin, and C3b, a component of the alternative complement pathway C3 convertase. Later in the pathway, serum complement component 5 (C5) is cleaved to release soluble C5a, another potent anaphylatoxin and chemoattractant with a wide range of bioactive properties. Cleavage of C5 also initiates formation of the membrane attack complex (MAC), a cytolytic protein complex that assembles in cell membranes, ultimately resulting in lysis of opsonized cells.

[0053] Complement component 3 (C3) is a zymogen. Intact C3 circulates at high concentrations (1-2 mg/ml). M. Janzi et al., *Mol. Cell. Proteomics* (2005) 4(12):1942-1947. During complement activation, whole C3 is cleaved to form C3b, a component of the alternative complement pathway C3 convertase, which becomes covalently bound to target surfaces. Endogenous complement regulatory proteins inactivate tissue-bound C3b to form iC3b and eventually the 35 kilodalton ("kD") C3d fragment. The C3d fragment remains fixed to tissues and serves as a durable marker of complement-mediated inflammation. I. Leivo et al., *J. Cell. Biol.* (1986) 103:1091-1100.

[0054] Targeted delivery of complement inhibitors to sites of complement activation and disease can improve their efficacy. Since complement plays an important role in host defense and the shaping of immunity, as well as in immune homeostatic mechanisms such as immune complex catabolism and apoptotic cell clearance, targeted delivery of complement inhibitors reduces potentially serious side effects resulting from systemic complement inhibition, particularly long-term complement inhibition.

General Techniques

[0055] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, cell biology, biochemistry, and

nucleic acid chemistry which are well known to those skilled in the art. Such techniques are explained fully in the literature, such as, *Molecular Cloning: A Laboratory Manual*, second edition (Sambrook et al., 1989) and *Molecular Cloning: A Laboratory Manual*, third edition (Sambrook and Russell, 2001), (jointly referred to herein as "Sambrook"); *Current Protocols in Molecular Biology* (F.M. Ausubel et al., eds., 1987, including supplements through 2001); *PCR: The Polymerase Chain Reaction* (Mullis et al., eds., 1994); *Current Protocols in Nucleic Acid Chemistry* John Wiley & Sons, Inc., New York, 2000), *Handbook of Experimental Immunology*, 4th edition (D. M. Weir & C. C. Blackwell, eds., Blackwell Science Inc., 1987); and *Gene Transfer Vectors for Mammalian Cells* (J. M. Miller & M. P. Calos, eds., 1987).

Complement Receptor 2

[0056] Human complement receptor 2, also referred to as CD21 (CR2/CD21)(SEQ ID NO:1 and SEQ ID NO:2), is a ~145 kD transmembrane protein of the C3 binding protein family comprising 15 or 16 short consensus repeat (SCR) domains, structural units characteristic of such proteins. CR2 is expressed on mature B cells and follicular dendritic cells, and plays an important role in humoral immunity. J. Hannan et al., *Biochem. Soc. Trans.* (2002) 30:983-989; K.A. Young et al., *J. Biol. Chem.* (2007) 282(50):36614-36625. CR2 protein does not bind intact C3 protein, but binds its breakdown products, including the C3b, iC3b, and C3d cleavage fragments, via a binding site located within the first two amino-terminal short consensus repeats ("SCRs 1-2") of the CR2 protein. Consequently, the SCR1-2 domain of CR2 discriminates between cleaved (*i.e.*, activated) forms of C3 and intact circulating C3. As a targeting group, SCRs 1-2 of CR2 are therefore able to discriminate between circulating C3 and the C3 fragments generated during complement activation. While the affinity of CR2 for C3d is only 620-658 nM (J. Hannan et al., *Biochem. Soc. Trans.* (2002) 30:983-989; J.M. Guthridge et al., *Biochem.* (2001) 40:5931-5941), the avidity of CR2 for clustered C3d makes it an effective method of targeting molecules to sites of complement activation.

[0057] Cleavage of C3 results initially in the generation and deposition of C3b on the activating cell surface. The C3b fragment is involved in the generation of enzymatic complexes that amplify the complement cascade. On a cell surface, C3b is rapidly converted to inactive iC3b, particularly when deposited on a host surface containing regulators of complement activation (*i.e.*, most host tissue). Even in the absence of membrane-bound

complement regulators, substantial levels of iC3b are formed because of the action of serum factor H and serum factor I. iC3b is subsequently digested to the membrane-bound fragments C3dg and then C3d by factor I and other proteases and cofactors, but this process is relatively slow. Thus, the C3 ligands for CR2 are relatively long lived once they are generated and are present in high concentrations at sites of complement activation.

Definitions

[0058] General reference to "the composition" or "compositions" includes and is applicable to compositions of the invention.

[0059] As used herein, the singular form of the articles "a," "an," and "the" includes plural references unless indicated otherwise. For example, the phrase "a biologically active CR2 fragment" includes one or more biologically active CR2 fragments.

[0060] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. For example, description referring to "about X" includes description of "X."

[0061] It is understood that aspects and embodiments of the invention described herein include consisting and/or consisting essentially of aspects and embodiments.

[0062] As used herein, the term "individual" refers to a vertebrate, preferably a mammal, more preferably a human. Mammals include, but are not limited to, research animals, domestic animals, farm animals, sport animals, pets, primates, mice and rats. In certain embodiments, the individual is human. In certain embodiments, the individual is an individual other than a human. In certain embodiments, the individual is an animal model for the study of a disease in which the alternative complement pathway is implicated.

[0063] It is intended that every maximum numerical limitation given throughout this specification includes every lower numerical limitation, as if such lower numerical limitations were expressly written herein. Every minimum numerical limitation given throughout this specification will include every higher numerical limitation, as if such higher numerical limitations were expressly written herein. Every numerical range given throughout this specification will include every narrower numerical range that falls within such broader numerical range, as if such narrower numerical ranges were all expressly written herein.

Amino Acid Substitutions

[0064] Twenty amino acids are commonly found in proteins. Those amino acids can be grouped into nine classes or groups based on the chemical properties of their side chains. Substitution of one amino acid residue for another within the same class or group is referred to herein as a "conservative" substitution. Conservative amino acid substitutions can frequently be made in a protein without significantly altering the conformation or function of the protein. Substitution of one amino acid residue for another from a different class or group is referred to herein as a "non-conservative" substitution. In contrast, non-conservative amino acid substitutions tend to disrupt conformation and function of a protein.

Table 3: Example of amino acid classification

Small/Aliphatic residues:	Gly, Ala, Val, Leu, Ile
Cyclic Imino Acid:	Pro
Hydroxyl-containing Residues:	Ser, Thr
Acidic Residues:	Asp, Glu
Amide Residues:	Asn, Gln
Basic Residues:	Lys, Arg
Imidazole Residue:	His
Aromatic Residues:	Phe, Tyr, Trp
Sulfur-containing Residues:	Met, Cys

[0065] In certain embodiments, the conservative amino acid substitution comprises substituting any of glycine (G), alanine (A), isoleucine (I), valine (V), and leucine (L) for any other of these aliphatic amino acids; serine (S) for threonine (T) and vice versa; aspartic acid (D) for glutamic acid (E) and vice versa; glutamine (Q) for asparagine (N) and vice versa; lysine (K) for arginine (R) and vice versa; phenylalanine (F), tyrosine (Y) and tryptophan (W) for any other of these aromatic amino acids; and methionine (M) for cysteine (C) and

vice versa. Other substitutions can also be considered conservative, depending on the environment of the particular amino acid and its role in the three-dimensional structure of the protein. For example, glycine (G) and alanine (A) can frequently be interchangeable, as can alanine (A) and valine (V). Methionine (M), which is relatively hydrophobic, can frequently be interchanged with leucine and isoleucine, and sometimes with valine. Lysine (K) and arginine (R) are frequently interchangeable in locations in which the significant feature of the amino acid residue is its charge and the differing pKs of these two amino acid residues are not significant. Still other changes can be considered "conservative" in particular environments (*see, e.g.*, BIOCHEMISTRY at pp. 13-15, 2nd ed. Lubert Stryer ed. (Stanford University); Henikoff et al., *Proc. Nat'l Acad. Sci. USA* (1992) 89:10915-10919; Lei et al., *J. Biol. Chem.* (1995) 270(20):11882-11886).

[0066] In certain embodiments, the non-conservative amino acid substitution comprises substituting any of glycine (G), alanine (A), isoleucine (I), valine (V), and leucine (L) for any of serine (S), threonine (T), aspartic acid (D), glutamic acid (E), glutamine (Q), asparagine (N), lysine (K), arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), methionine (M), cysteine (C), histidine (H), and proline (P). In certain embodiments, the non-conservative amino acid substitution comprises substituting any of serine (S) and threonine (T) for any of glycine (G), alanine (A), isoleucine (I), valine (V), leucine (L), aspartic acid (D), glutamic acid (E), glutamine (Q), asparagine (N), lysine (K), arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), methionine (M), cysteine (C), histidine (H) and proline (P). In certain embodiments, the non-conservative amino acid substitution comprises substituting any of aspartic acid (D)and glutamic acid (E) for any of glycine (G), alanine (A), isoleucine (I), valine (V), leucine (L), serine (S), threonine (T), glutamine (Q), asparagine (N), lysine (K), arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), methionine (M), cysteine (C), histidine (H), and proline (P). In certain embodiments, the non-conservative amino acid substitution comprises substituting any of glutamine (Q) and asparagine (N) for any of glycine (G), alanine (A), isoleucine (I), valine (V), leucine (L), serine (S), threonine (T), aspartic acid (D), glutamic acid (E), lysine (K), arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), methionine (M), cysteine (C), histidine (H), and proline (P). In certain embodiments, the non-conservative amino acid substitution comprises substituting any of lysine (K) and arginine (R) for any of glycine (G), alanine (A), isoleucine (I), valine (V), leucine (L), serine (S), threonine (T), aspartic acid (D), glutamic acid (E), glutamine (Q), asparagine (N), phenylalanine (F), tyrosine (Y), tryptophan (W), methionine (M), cysteine

(C), histidine (H), and proline (P). In certain embodiments, the non-conservative amino acid substitution comprises substituting any of phenylalanine (F), tyrosine (Y), and tryptophan (W) for any of glycine (G), alanine (A), isoleucine (I), valine (V), leucine (L), serine (S), threonine (T), aspartic acid (D), glutamic acid (E), glutamine (Q), asparagine (N), lysine (K), arginine (R), methionine (M), cysteine (C), histidine (H), and proline (P). In certain embodiments, the non-conservative amino acid substitution comprises substituting any of methionine (M) and cysteine (C) for any of glycine (G), alanine (A), isoleucine (I), valine (V), leucine (L), serine (S), threonine (T), aspartic acid (D), glutamic acid (E), glutamine (Q), asparagine (N), lysine (K), arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), histidine (H), and proline (P). In certain embodiments, the non-conservative amino acid substitution comprises substituting histidine (H) for any of glycine (G), alanine (A), isoleucine (I), valine (V), leucine (L), serine (S), threonine (T), aspartic acid (D), glutamic acid (E), glutamine (Q), asparagine (N), lysine (K), arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), methionine (M), cysteine (C), and proline (P). In certain embodiments, the non-conservative amino acid substitution comprises substituting proline (P) for any of glycine (G), alanine (A), isoleucine (I), valine (V), leucine (L), serine (S), threonine (T), aspartic acid (D), glutamic acid (E), glutamine (Q), asparagine (N), lysine (K), arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), methionine (M), cysteine (C), and histidine (H).

Modulators of Complement Activity

[0067] As used herein, the term "complement modulator" refers to a compound, composition, or protein that modulates (*e.g.*, inhibits or activates) complement activity or a biologically active fragment thereof. A complement modulator can be a complement inhibitor or a complement activator.

[0068] As used herein, the term "complement inhibitor" refers to any compound, composition, or protein that reduces or eliminates complement activity or a biologically active fragment thereof. The reduction in complement activity may be incremental (*e.g.*, a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction in activity) or complete. A complement inhibitor may be a soluble or membrane-bound protein such as, for example, membrane cofactor protein (MCP), decay accelerating factor (DAF/CD55), CD59, mouse complement receptor 1-related gene/protein y (Crry), human complement receptor 1 (CR1)

and factor H, or an antibody specific for a component of a complement pathway such as, for example, eculizumab (an anti-C5 antibody marketed under the trade name Soliris®), pexelizumab (a single-chain antibody (scFv) comprising the antigen-binding fragment of eculizumab), an anti-factor B antibody (such as the monoclonal antibody 1379 produced by ATCC Deposit No. PTA-6230), an anti-properdin antibody, an anti-factor D antibody, and the like. Alternatively, a complement inhibitor may be a small molecule or a linear or cyclic peptide such as, for example, compstatin, N-acetylaspartylglutamic acid (NAAGA), and the like.

[0069] As used herein the term "complement activator" refers to any compound, composition, or protein that increases or activates complement activity or a biologically active fragment thereof. The increase in complement activity may be incremental (*e.g.*, a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase in activity). A complement activator may be a soluble or membrane-bound protein such as, for example, human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), and mouse IgM Fc, as well as cobra venom factor (CVF) and biologically-active fragments thereof, such as the Fc domain of Ig proteins, such as human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, and mouse IgM Fc domain. Complement activators may also include, for example, hybrid CVF molecules comprising a CVF portion and a complement component 3 (C3) portion, such as those described in Fritzinger et al., "Functional characterization of human C3/cobra venom factor hybrid proteins for therapeutic complement depletion," *Develop. Comp. Immunol.* 33(1):105-116 (2009). Those hybrids comprise proteins in which the 113 or 315 C-terminal residues of C3 were replaced with corresponding CVF sequences.

Complement Inhibitor Proteins

[0070] Provided herein are soluble compositions 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 SCR domains of the CR2 protein; and (b) a complement inhibitor portion; wherein the CR2 portion contains at least one amino acid substitution. In certain embodiments, the construct is a fusion protein. A number of endogenous soluble and membrane-bound proteins that inhibit complement have been identified. These complement inhibitor proteins include, but are not limited to, membrane cofactor protein (MCP), decay

accelerating factor (DAF/CD55), CD59, mouse complement receptor 1-related gene/protein y (Crry), human complement receptor 1 (CR1) and factor H. In certain embodiments, the complement modulator portion of the construct comprises a complement inhibitor or biologically active fragment thereof. In certain embodiments, the complement inhibitor is selected from the group consisting of human MCP, human DAF, mouse DAF, human CD59, mouse CD59 isoform A, mouse CD59 isoform B, mouse Crry protein, human CR1, human factor H, or mouse factor H, or a biologically active fragment thereof.

Membrane Cofactor Protein (MCP)

[0071] As used herein, the term "membrane cofactor protein," "MCP," or "CD46" refers to a widely distributed C3b/C4b-binding cell surface glycoprotein which inhibits complement activation on host cells and serves as a cofactor for the factor I-mediated cleavage of C3b and C4b, including homologs thereof. T.J. Oglesby *et al.*, *J. Exp. Med.* (1992) 175:1547-1551. MCP belongs to a family known as the regulators of complement activation ("RCA"). Family members share certain structural features, comprising varying numbers of short consensus repeat (SCR) domains, which are typically between 60 and 70 amino acids in length. Beginning at its amino-terminus, MCP comprises four SCRs, a serine/threonine/proline-enriched region, an area of undefined function, a transmembrane hydrophobic domain, a cytoplasmic anchor and a cytoplasmic tail. It is understood that species and strain variations exist for the disclosed peptides, polypeptides, and proteins, and that human MCP or biologically active fragments thereof encompasses all species and strain variations.

[0072] SEQ ID NO:10 represents the full-length human MCP amino acid sequence (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. P15529). Amino acids 1-34 correspond to the signal peptide, amino acids 35-343 correspond to the extracellular domain, amino acids 344-366 correspond to the transmembrane domain, and amino acids 367-392 correspond to the cytoplasmic domain. In the extracellular domain, amino acids 35-96 correspond to SCR 1, amino acids 97-159 correspond to SCR 2, amino acids 160-225 correspond to SCR 3, amino acids 226-285 correspond to SCR 4, and amino acids 302-326 correspond to the serine/threonine-rich domain. It is understood that species and strain variations exist for the disclosed peptides, polypeptides, and proteins, and that MCP or biologically active fragments thereof encompasses all species and strain variations. As used herein, the term "biologically active" fragment of MCP refers to any soluble fragment lacking both the cytoplasmic domain

and the transmembrane domain, including fragments comprising, consisting essentially of or consisting of 1, 2, 3, or 4 SCR domains, with or without the serine/threonine-rich domain, having some or all the complement inhibitory activity of the full-length human MCP protein. In certain embodiments, the complement inhibitor portion comprises full-length human MCP (amino acids 35-392 of SEQ ID NO:10), the extracellular domain of human MCP (amino acids 35-343 of SEQ ID NO:10), or SCRs 1-4 of human MCP (amino acids 35-285 of SEQ ID NO:10).

[0073] In one aspect, there is provided a soluble composition 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 SCR domains of the CR2 protein; and (b) MCP; wherein the CR2 portion contains at least one amino acid substitution. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds EBV gp350. As used herein, "selectively binds" means that a construct exhibits enhanced binding to one ligand and/or decreased binding to a different ligand. For example, “selectively binds” can mean: 1) that a construct which has been altered has a binding affinity for a first ligand that is similar to the binding affinity of the unaltered construct for the first ligand whereas the construct that has been altered has a lower affinity for a second ligand than does the unaltered construct, and therefore the altered construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; 2) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand while retaining binding to a second ligand that is similar to the binding of the unaltered construct to the

second ligand, and therefore the construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; or 3) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand and also has a lower binding affinity for a second ligand as compared to the binding of the unaltered construct to the second ligand, and therefore the altered construct "selectively binds" the first ligand and not the second ligand as compared to the binding of the unaltered construct to the two ligands. In certain embodiments, the construct is a fusion protein. In certain embodiments, the complement inhibitor portion of the construct comprises full-length human MCP (SEQ ID NO:10). In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of human MCP (SEQ ID NO:10). In certain embodiments, the biologically active fragment of human MCP 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).

Decay Accelerating Factor (DAF)

[0074] Decay accelerating factor, also referred to as CD55 (DAF/CD55) (SEQ ID NO:11 and SEQ ID NO:12), is a ~70 kiloDalton (kDa) membrane-bound glycoprotein which inhibits complement activation on host cells. Like several other complement regulatory proteins, DAF comprises several approximately 60 amino acid repeating motifs termed short consensus repeats (SCR).

[0075] As used herein, the term “decay accelerating factor,” “DAF,” or “CD55” refers to a seventy kilodalton (“kD”) membrane glycoprotein comprising four short consensus repeat (SCR) domains followed by a heavily O-glycosylated serine/threonine-rich domain at the C-terminus that elevates the molecule from the membrane surface, followed by a glycosylphosphatidylinositol (“GPI”) anchor. DAF protects the cell surface from complement activation by dissociating membrane-bound C3 convertases that are required to cleave complement protein C3 and to amplify the complement cascade. DAF prevents assembly or accelerates decay of both the C3- and C5-convertases of the alternative and classical complement pathways.

[0076] SEQ ID NO:11 represents the full-length human DAF amino acid sequence (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. P08173); SEQ ID NO:12 represents the full-length

mouse DAF amino acid sequence (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. Q61475). In the human DAF sequence, amino acids 1-34 correspond to the signal peptide, amino acids 35-353 appear in the mature protein, and amino acids 354-381 are removed from the polypeptide after translation. Within the mature protein, amino acids 35-96 correspond to SCR 1, amino acids 96-160 correspond to SCR 2, amino acids 161-222 correspond to SCR 3, amino acids 223-285 correspond to SCR 4, and amino acids 287-353 correspond to the O-glycosylated serine/threonine-rich domain. The GPI anchor is attached to human DAF at a serine at position 353. In the mouse DAF sequence, amino acids 1-34 correspond to the signal peptide, amino acids 35-362 appear in the mature protein, and amino acids 363-390 are removed from the polypeptide after translation. Within the mature protein, amino acids 35-96 correspond to SCR 1, amino acids 97-160 correspond to SCR 2, amino acids 161-222 correspond to SCR 3, amino acids 223-286 correspond to SCR 4, and amino acids 288-362 correspond to the O-glycosylated serine/threonine-rich domain. The GPI anchor is attached to mouse DAF at a serine at position 362. It is understood that species and strain variations exist for the disclosed peptides, polypeptides, and proteins, and that DAF or biologically active fragments thereof encompasses all species and strain variations. As used herein, the term "biologically active" fragment of DAF refers to any fragment of DAF lacking a GPI anchor and/or the amino acid to which it is attached (*i.e.*, Ser-353), including any fragments of the full-length DAF protein comprising, consisting essentially of or consisting of 1, 2, 3, or 4 SCR domains, with or without the O-glycosylated serine/threonine-rich domain, having some or all the complement inhibitory activity of the full-length DAF protein.

[0077] In one aspect, there is provided a soluble composition 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 SCR domains of the CR2 protein; and (b) DAF; wherein the CR2 portion contains at least one amino acid substitution. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group

consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds EBV gp350. As used herein, "selectively binds" means that a construct exhibits enhanced binding to one ligand and/or decreased binding to a different ligand. For example, "selectively binds" can mean: 1) that a construct which has been altered has a binding affinity for a first ligand that is similar to the binding affinity of the unaltered construct for the first ligand whereas the construct that has been altered has a lower affinity for a second ligand than does the unaltered construct, and therefore the altered construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; 2) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand while retaining binding to a second ligand that is similar to the binding of the unaltered construct to the second ligand, and therefore the construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; or 3) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand and also has a lower binding affinity for a second ligand as compared to the binding of the unaltered construct to the second ligand, and therefore the altered construct "selectively binds" the first ligand and not the second ligand as compared to the binding of the unaltered construct to the two ligands. In certain embodiments, the construct is a fusion protein. In certain embodiments, the complement inhibitor portion of the construct comprises full-length human DAF. In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of human DAF (SEQ ID NO:11). In certain embodiments, the biologically active fragment of human DAF 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). In certain embodiments, the complement inhibitor portion of the construct comprises full-length mouse DAF (SEQ ID NO:12). In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of mouse DAF. In certain embodiments, the biologically active fragment of mouse DAF 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).

CD59

[0078] As used herein, the term "CD59" refers to a membrane-bound 128 amino acid glycoprotein that potently inhibits the membrane attack complex (MAC) of complement. CD59 acts by binding to the C8 and/or C9 components of the MAC during assembly, ultimately preventing incorporation of the multiple copies of C9 required for complete formation of the osmolytic pore at the heart of the MAC. CD59 is both *N*- and *O*-glycosylated. The *N*-glycosylation comprises primarily of bi- or tri-antennary structures with and without lactosamine and outer arm fucose residues, with variable sialylation present at some sites. Like DAF, CD59 is anchored in the cell membrane by a glycosylphosphatidylinositol ("GPI") anchor, which is attached to an asparagine at amino acid 102. Soluble forms of CD59 (sCD59) have been produced, but they generally have low functional activity *in vitro*, particularly in the presence of serum, suggesting that unmodified sCD59 has little or no therapeutic efficacy. *See, e.g.*, S. Meri et al., "Structural composition and functional characterization of soluble CD59: heterogeneity of the oligosaccharide and glycophosphoinositol (GPI) anchor revealed by laser-desorption mass spectrometric analysis," *Biochem. J.* 316:923-935 (1996).

[0079] SEQ ID NO:3 represents the full-length human CD59 amino acid sequence (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. P13987); SEQ ID NO:6 represents the full-length mouse CD59 sequence, isoform A (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. O55186); SEQ ID NO:7 represents the full-length mouse CD59 sequence, isoform B (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. P58019). In the human CD59 sequence, amino acids 1-25 of SEQ ID NO:3 correspond to the leader peptide, amino acids 26-102 of SEQ ID NO:3 correspond to the mature protein, and amino acids 103-128 of SEQ ID NO:3 are removed after translation. The GPI anchor is attached to CD59 at an asparagine at position 102 of SEQ ID NO:3. In isoform A of the mouse CD59 sequence, amino acids 1-23 of SEQ ID NO:6 correspond to the leader peptide, amino acids 24-96 of SEQ ID NO:6 correspond to the mature protein, and amino acids 97-123 of SEQ ID NO:6 are removed after translation. The GPI anchor is attached to CD59 at a serine at position 96 of SEQ ID NO:6. In isoform B of the mouse CD59 sequence, amino acids 1-23 of SEQ ID NO:7 correspond to the leader peptide, amino acids 24-104 of SEQ ID NO:7 correspond to the mature protein, and amino acids 105-129 of SEQ ID NO:7 are removed after translation. The GPI anchor is attached to CD59 at an asparagine at position 104 of SEQ ID NO:7. It is understood that species and

strain variations exist for the disclosed peptides, polypeptides, and proteins, and that CD59 or biologically active fragments thereof encompasses all species and strain variations.

[0080] As used herein, the term "biologically active" fragment of human CD59 refers to any fragment of human CD59 lacking a GPI anchor and/or the amino acid to which it is attached (*i.e.*, Asn-102), including any fragments of the full-length human CD59 protein having some or all the complement inhibitory activity of the full-length CD59 protein; and the term "biologically active" fragment of mouse CD59 refers to any fragment of mouse CD59 isoform A or isoform B lacking a GPI anchor and/or the amino acid to which it is attached (*i.e.*, Ser-96 of isoform A, or Asp-104 of isoform B) , including any fragments of either full-length mouse CD59 protein isoform having some or all the complement inhibitory activity of the full-length CD59 protein.

[0081] In one aspect, there is provided a soluble composition 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 SCR domains of the CR2 protein; and (b) CD59; wherein the CR2 portion contains at least one amino acid substitution. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds EBV gp350. As used herein, "selectively binds" means that a construct exhibits enhanced binding to one ligand and/or decreased binding to a different ligand. For example, "selectively binds" can mean: 1) that a construct which has been altered has a binding affinity for a first ligand that is similar to the binding affinity of the unaltered construct for the first ligand whereas the construct that

has been altered has a lower affinity for a second ligand than does the unaltered construct, and therefore the altered construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; 2) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand while retaining binding to a second ligand that is similar to the binding of the unaltered construct to the second ligand, and therefore the construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; or 3) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand and also has a lower binding affinity for a second ligand as compared to the binding of the unaltered construct to the second ligand, and therefore the altered construct "selectively binds" the first ligand and not the second ligand as compared to the binding of the unaltered construct to the two ligands. In certain embodiments, the complement inhibitor portion of the construct comprises full-length human CD59 (SEQ ID NO:3). In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of human CD59 (SEQ ID NO:3). In certain embodiments, the biologically active fragment of human CD59 comprises the extracellular domain of human CD59 lacking its GPI anchor (amino acids 26-101 of SEQ ID NO:3). In certain embodiments, the complement inhibitor portion of the construct comprises full-length mouse CD59, isoform A (SEQ ID NO:6). In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of mouse CD59, isoform A (SEQ ID NO:6). In certain embodiments, the biologically active fragment of mouse CD59, isoform A comprises the extracellular domain of mouse CD59, isoform A lacking its GPI anchor (amino acids 24-95 of SEQ ID NO:6). In certain embodiments, the complement inhibitor portion of the construct comprises full-length mouse CD59, isoform B (SEQ ID NO:7). In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of mouse CD59, isoform B (SEQ ID NO:7). In certain embodiments, the biologically active fragment of mouse CD59, isoform B comprises the extracellular domain of mouse CD59, isoform B lacking its GPI anchor (amino acids 24-103 of SEQ ID NO:7).

Mouse Complement Receptor 1-related Gene/protein y (Crry)

[0082] As used herein, the term “mouse complement receptor 1-related gene/protein y” or “Crry” refers to a membrane-bound mouse glycoprotein that regulates complement

activation, including homologs thereof. Crry regulates complement activation by serving as a cofactor for complement factor I, a serine protease which cleaves C3b and C4b deposited on host tissue. Crry also acts as a decay-accelerating factor, preventing the formation of C4b2a and C3bBb, the amplification convertases of the complement cascade.

[0083] SEQ ID NO:4 represents the full-length mouse Crry protein amino acid sequence. Amino acids 1-40 correspond to the leader peptide, amino acids 41-483 of SEQ ID NO:4 correspond to the mature protein, comprising amino acids 41-405 of SEQ ID NO:4, corresponding to the extracellular domain, amino acids 406-426 of SEQ ID NO:4, corresponding to the transmembrane domain, and amino acids 427-483 of SEQ ID NO:4, corresponding to the cytoplasmic domain. In the extracellular domain, amino acids 83-143 of SEQ ID NO:4 correspond to SCR 1, amino acids 144-205 of SEQ ID NO:4 correspond to SCR2, amino acids 206-276 of SEQ ID NO:4 correspond to SCR3, amino acids 277-338 of SEQ ID NO:4 correspond to SCR4, and amino acids 339-400 of SEQ ID NO:4 correspond to SCR5. It is understood that species and strain variations exist for the disclosed peptides, polypeptides, and proteins, and that mouse Crry protein or biologically active fragments thereof encompasses all species and strain variations. As used herein, the term "biologically active" fragment of mouse Crry protein refers to refers to any soluble fragment of mouse Crry lacking the transmembrane domain and the cytoplasmic domain, including fragments comprising, consisting essentially of or consisting of 1, 2, 3, 4, or 5 SCR domains, including any fragments of the full-length mouse Crry protein having some or all the complement inhibitory activity of the full-length Crry protein.

[0084] In one aspect, there is provided a soluble composition 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 SCR domains of the CR2 protein; and (b)Crry; wherein the CR2 portion contains at least one amino acid substitution. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also

selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds EBV gp350. As used herein, "selectively binds" means that a construct exhibits enhanced binding to one ligand and/or decreased binding to a different ligand. For example, “selectively binds” can mean: 1) that a construct which has been altered has a binding affinity for a first ligand that is similar to the binding affinity of the unaltered construct for the first ligand whereas the construct that has been altered has a lower affinity for a second ligand than does the unaltered construct, and therefore the altered construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; 2) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand while retaining binding to a second ligand that is similar to the binding of the unaltered construct to the second ligand, and therefore the construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; or 3) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand and also has a lower binding affinity for a second ligand as compared to the binding of the unaltered construct to the second ligand, and therefore the altered construct "selectively binds" the first ligand and not the second ligand as compared to the binding of the unaltered construct to the two ligands. In certain embodiments, the complement inhibitor portion of the construct comprises full-length mouse Crry protein (SEQ ID NO:4). In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of mouse Crry protein (SEQ ID NO:4). In certain embodiments, the biologically active fragment of mouse Crry protein is selected from the group consisting of SCR1-5 (amino acids 41-400 of SEQ ID NO:4) and the extracellular domain of mouse Crry protein (amino acids 41-405 of SEQ ID NO:4).

Complement Receptor 1 (CR1)

[0085] As used herein, the term “complement receptor 1,” “CR1,” or “CD35” refers to a human gene encoding a protein of 2039 amino acids, with a predicted molecular weight of

220 kilodaltons ("kD"), including homologs thereof. The gene is expressed principally on erythrocytes, monocytes, neutrophils, and B cells, but is also present on some T lymphocytes, mast cells, and glomerular podocytes. CR1 protein is typically expressed at between 100 and 1000 copies per cell. CR1 is the main system for processing and clearance of complement-opsonized immune complexes. CR1 negatively regulates the complement cascade, mediates immune adherence and phagocytosis, and inhibits both the classic and alternative complement pathways. The full-length CR1 protein comprises a 42 amino acid signal peptide, an extracellular domain of 1930 amino acids, a 25 amino acid transmembrane domain, and a 43 amino acid C-terminal cytoplasmic domain. The extracellular domain of CR1 has 25 potential N-glycosylation signal sequences, and comprises 30 short consensus ("SCR") domains, also known as complement control protein (CCP) repeats, or sushi domains, each 60 to 70 amino acids long. The sequence homology between SCRs ranges between 60-99 percent. The 30 SCR domains are further grouped into four longer regions termed long homologous repeats ("LHRs"), each encoding approximately 45 kD segments of the CR1 protein, designated LHR-A, -B, -C, and -D. The first three comprise seven SCR domains each, while LHR-D comprises 9 SCR domains. The active sites on the extracellular domain of CR1 protein include a C4b-binding site with lower affinity for C3b in SCRs 1-4 comprising amino acids 42-295, a C3b-binding site with lower affinity for C4b in SCRs 8-11 comprising amino acids 490-745, a C3b-binding site with lower affinity for C4b in SCRs 15-18 comprising amino acids 940-1196, and a C1q-binding site in SCRs 22-28 comprising amino acids 1394-1842.

[0086] SEQ ID NO:9 represents the full-length human CR1 amino acid sequence (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. P17927). Amino acids 1-41 correspond to the signal peptide, amino acids 42-2039 correspond to the mature protein, comprising amino acids 42-1971, corresponding to the extracellular domain, amino acids 1972-1996, corresponding to the transmembrane domain, and amino acids 1997-2039, corresponding to the cytoplasmic domain. In the extracellular domain, amino acids 42-101 correspond to SCR 1, 102-163 correspond to SCR2, amino acids 164-234 correspond to SCR3, amino acids 236-295 correspond to SCR4, amino acids 295-355 correspond to SCR5, amino acids 356-418 correspond to SCR6, amino acids 419-489 correspond to SCR7, amino acids 491-551 correspond to SCR8, amino acids 552-613 correspond to SCR9, amino acids 614-684 correspond to SCR10, amino acids 686-745 correspond to SCR11, amino acids 745-805 correspond to SCR12, amino acids 806-868 correspond to SCR13, amino acids 869-939

correspond to SCR14, amino acids 941-1001 correspond to SCR15, amino acids 1002-1063 correspond to SCR16, amino acids 1064-1134 correspond to SCR17, amino acids 1136-1195 correspond to SCR18, amino acids 1195-1255 correspond to SCR 19, amino acids 1256-1318 correspond to SCR 20, amino acids 1319-1389 correspond to SCR 21, amino acids 1394-1454 correspond to SCR 22, amino acids 1455-1516 correspond to SCR 23, amino acids 1517-1587 correspond to SCR 24, amino acids 1589-1648 correspond to SCR 25, amino acids 1648-1708 correspond to SCR 26, amino acids 1709-1771 correspond to SCR 27, amino acids 1772-1842 correspond to SCR 28, amino acids 1846-1906 correspond to SCR 29, amino acids 1907-1967 correspond to SCR 30. It is understood that species and strain variations exist for the disclosed peptides, polypeptides, and proteins, and that CR1 protein or biologically active fragments thereof encompasses all species and strain variations. As used herein, the term "biologically active" fragment of CR1 protein refers to refers to any soluble fragment of CR1 lacking the transmembrane domain and the cytoplasmic domain, including fragments comprising, consisting essentially of or consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 SCR domains, including any fragments of the full-length CR1 protein having some or all the complement inhibitory activity of the full-length CR1 protein.

[0087] In one aspect, there is provided a soluble composition 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 SCR domains of the CR2 protein; and (b) CR1; wherein the CR2 portion contains at least one amino acid substitution. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα and also selectively binds EBV gp350. In some embodiments, the CR2 portion

selectively binds EBV gp350. As used herein, "selectively binds" means that a construct exhibits enhanced binding to one ligand and/or decreased binding to a different ligand. For example, “selectively binds” can mean: 1) that a construct which has been altered has a binding affinity for a first ligand that is similar to the binding affinity of the unaltered construct for the first ligand whereas the construct that has been altered has a lower affinity for a second ligand than does the unaltered construct, and therefore the altered construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; 2) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand while retaining binding to a second ligand that is similar to the binding of the unaltered construct to the second ligand, and therefore the construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; or 3) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand and also has a lower binding affinity for a second ligand as compared to the binding of the unaltered construct to the second ligand, and therefore the altered construct "selectively binds" the first ligand and not the second ligand as compared to the binding of the unaltered construct to the two ligands. In certain embodiments, the construct is a fusion protein. In certain embodiments, the complement inhibitor portion of the construct comprises full-length human CR1 protein (SEQ ID NO:9). In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of human CR1 protein (SEQ ID NO:9). In certain embodiments, the biologically active fragment of human CR1 protein 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).

Factor H (FH)

[0088] As used herein, the term “complement factor H,” “factor H,” or “FH” refers to complement factor H, a single polypeptide chain plasma glycoprotein, including homologs thereof. The protein is composed of 20 conserved short consensus repeat (SCR) domains of approximately 60 amino acids, arranged in a continuous fashion like a string of beads,

separated by short linker sequences of 2-6 amino acids each. Factor H binds to C3b, accelerates the decay of the alternative pathway C3-convertase (C3bBb), and acts as a cofactor for the proteolytic inactivation of C3b. In the presence of factor H, proteolysis by factor I results in the cleavage and inactivation of C3b. Factor H has at least three distinct binding domains for C3b, which are located within SCRs 1-4, SCRs 5-8, and SCRs 19-20. Each site of factor H binds to a distinct region within the C3b protein: the N-terminal sites bind to native C3b; the second site, located in the middle region of factor H, binds to the C3c fragment and the site located within SCR19 and 20 binds to the C3d region. In addition, factor H also contains binding sites for heparin, which are located within SCR 7, SCRs 5-12, and SCR 20 of factor H and overlap with those of the C3b binding sites. Structural and functional analyses have shown that the domains for the complement inhibitory activity of factor H are located within the first four N-terminal SCR domains.

[0089] SEQ ID NO:5 represents the full-length human factor H amino acid sequence (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. P08603); SEQ ID NO:8 represents the full-length mouse factor H amino acid sequence (*see, e.g.*, UniProtKB/Swiss-Prot. Accession No. P06909). In the human factor H sequence, amino acids 1-18 of SEQ ID NO:5 correspond to the signal peptide, and amino acids 19-1231 of SEQ ID NO:5 correspond to the mature protein. Within that protein, amino acids 21-80 of SEQ ID NO:5 correspond to SCR 1, amino acids 85-141 of SEQ ID NO:5 correspond to SCR 2, amino acids 146-205 of SEQ ID NO:5 correspond to SCR 3, amino acids 210-262 of SEQ ID NO:5 correspond to SCR 4, and amino acids 267-320 of SEQ ID NO:5 correspond to SCR 5. In the mouse factor H sequence, amino acids 1-18 of SEQ ID NO:8 correspond to the signal peptide, and amino acids 19-1234 of SEQ ID NO:8 correspond to the mature protein. Within that protein, amino acids 19-82 of SEQ ID NO:8 correspond to SCR 1, amino acids 83-143 of SEQ ID NO:8 correspond to SCR 2, amino acids 144-207 of SEQ ID NO:8 correspond to SCR 3, amino acids 208-264 of SEQ ID NO:8 correspond to SCR 4, and amino acids 265-322 of SEQ ID NO:8 correspond to SCR 5. It is understood that species and strain variations exist for the disclosed peptides, polypeptides, and proteins, and that factor H or biologically active fragments thereof encompasses all species and strain variations.

[0090] As used herein, the term "biologically active" fragment of factor H refers to any portion of a factor H protein having some or all the complement inhibitory activity of the full-length factor H protein, and includes, but is not limited to, factor H fragments comprising

SCRs 1-4, SCRs 1-5, SCRs 1-8, SCRs 1-18, SCRs 19-20, or any homolog of a naturally-occurring factor H or fragment thereof, as described in detail below. In certain embodiments, the biologically active fragment of factor H has one or more of the following properties: (1) binding to C-reactive protein (CRP), (2) binding to C3b, (3) binding to heparin, (4) binding to sialic acid, (5) binding to endothelial cell surfaces, (6) binding to cellular integrin receptor, (7) binding to pathogens, (8) C3b co-factor activity, (9) C3b decay-acceleration activity, and (10) inhibiting the alternative complement pathway.

[0091] In one aspect, there is provided a soluble composition 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 SCR domains of the CR2 protein; and (b) FH; wherein the CR2 portion contains at least one amino acid substitution. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds EBV gp350. As used herein, "selectively binds" means that a construct exhibits enhanced binding to one ligand and/or decreased binding to a different ligand. For example, “selectively binds” can mean: 1) that a construct which has been altered has a binding affinity for a first ligand that is similar to the binding affinity of the unaltered construct for the first ligand whereas the construct that has been altered has a lower affinity for a second ligand than does the unaltered construct, and therefore the altered construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; 2) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand while retaining binding to a second ligand that is similar to the binding of the unaltered construct to the

second ligand, and therefore the construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; or 3) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand and also has a lower binding affinity for a second ligand as compared to the binding of the unaltered construct to the second ligand, and therefore the altered construct "selectively binds" the first ligand and not the second ligand as compared to the binding of the unaltered construct to the two ligands. In certain embodiments, the construct is a fusion protein. In certain embodiments, the complement inhibitor portion of the construct comprises full-length human (SEQ ID NO:5) or mouse (SEQ ID NO:8) factor H. In certain embodiments, the complement inhibitor portion of the construct comprises a biologically active fragment of human (SEQ ID NO:5) or mouse (SEQ ID NO:8) factor H. In certain embodiments, the biologically active fragment of human factor H (SEQ ID NO:5) is selected from the group consisting of SCRs 1-4 (amino acids 21-262 of SEQ ID NO:5), SCRs 1-5 of factor H (amino acids 21-320 of SEQ ID NO:5), SCRs 1-8 of factor H (amino acids 21-507 of SEQ ID NO:5), and SCRs 1-18 of factor H (amino acids 21-1104 of SEQ ID NO:5). In certain embodiments, the biologically active fragment of mouse factor H (SEQ ID NO:8) is selected from the group consisting of SCRs 1-4 (amino acids 19-264 of SEQ ID NO:8), SCRs 1-5 of factor H (amino acids 19-322 of SEQ ID NO:8), SCRs 1-8 of factor H (amino acids 19-507 of SEQ ID NO:8), and SCRs 1-18 of factor H (amino acids 19-1109 of SEQ ID NO:8). In certain embodiments, the biologically active fragment of human (SEQ ID NO:5) or mouse (SEQ ID NO:8) factor H comprises (and in certain embodiments consists of or consists essentially of) at least the first four N-terminal SCR domains of factor H, including for example, at least any of the first 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or more N-terminal SCR domains of factor H.

Complement Activator Proteins

[0092] Provided herein are soluble compositions 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 SCR domains of the CR2 protein; and (b) a complement activator portion; wherein the CR2 portion contains at least one amino acid substitution. In certain embodiments, the construct is a fusion protein. A number of endogenous soluble proteins that activate complement have also been identified. These complement activators

include, but are not limited to, various immunoglobulin (Ig) proteins, including human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), and mouse IgM Fc, as well as cobra venom factor (CVF) and biologically-active fragments thereof. The complement activating activity of Ig proteins has been localized to the Fc domain. Therefore biologically-active fragments of complement-activating human and mouse Ig proteins include the Fc domain, such as human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, and mouse IgM Fc domain.

Immunoglobulin Proteins

[0093] As used herein, the term "antibody" or "immunoglobulin" refers to glycoproteins of the immunoglobulin (Ig) superfamily of proteins. An antibody or immunoglobulin (Ig) molecule is tetrameric, comprising two identical light chain polypeptides and two identical heavy chain polypeptides. The two heavy chains are linked together by disulfide bonds, and each heavy chain is linked to a light chain by a disulfide bond. Each full-length Ig molecule contains at least two binding sites for a specific target or antigen.

[0094] The immune system produces several different classes of Ig molecules (isotypes), including IgA, IgD, IgE, IgG, and IgM, each distinguished by the particular class of heavy chain polypeptide present: alpha (α) found in IgA, delta (δ) found in IgD, epsilon (ε) found in IgE, gamma (γ) found in IgG, and mu (μ) found in IgM. There are at least five different γ heavy chain polypeptides (isotypes) found in IgG. In contrast, there are only light chain polypeptide isotypes, referred to as kappa (κ) and lambda (λ) chains. The distinctive characteristics of antibody isotypes are defined by sequences of the constant domains of the heavy chain.

[0095] An IgG molecule comprises two light chains (either κ or λ form) and two heavy chains (γ form) bound together by disulfide bonds. The κ and λ forms of IgG light chain both contain a domain of relatively variable amino acid sequences, called the variable region (variously referred to as a "V_L-," "V_κ-," or "V_λ-region") and a domain of relatively conserved amino acid sequences, called the constant region (C_L-region). Similarly, each IgG heavy chain contains a variable region (V_H-region) and one or more conserved regions: a complete IgG heavy chain contains three constant domains ("C_H1-," "C_H2-," and "C_H3-regions") and a hinge region. Within each V_L- or V_H-region, hypervariable regions, also known as

complementarity-determining regions ("CDR"), are interspersed between relatively conserved framework regions ("FR"). Generally, the variable region of a light or heavy chain polypeptide contains four FR and three CDR arranged in the following order along the polypeptide: NH_2-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-COOH. Together the CDR and FR determine the three-dimensional structure of the IgG binding site and thus, the specific target protein or antigen to which that IgG molecule binds. Each IgG molecule is dimeric, able to bind two antigen molecules. Cleavage of a dimeric IgG with the protease papain produces two identical antigen-binding fragments ("Fab'") and an "Fc" fragment or Fc domain, so named because is readily crystallized.

[0096] In some embodiments, the composition comprises 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 SCR domains of the CR2 protein; and (b) a complement activator portion selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, and mouse IgM Fc domain, and wherein the CR2 portion contains at least one amino acid substitution. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds EBV gp350. As used herein, "selectively binds" means that a construct exhibits enhanced binding to one ligand and/or decreased binding to a different ligand. For example, "selectively binds" can mean: 1) that a construct which has been altered has a binding affinity for a first ligand that is similar to the binding affinity of the unaltered construct for the first ligand whereas the construct that has been altered has a lower affinity for a second ligand than does the unaltered construct,

and therefore the altered construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; 2) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand while retaining binding to a second ligand that is similar to the binding of the unaltered construct to the second ligand, and therefore the construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; or 3) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand and also has a lower binding affinity for a second ligand as compared to the binding of the unaltered construct to the second ligand, and therefore the altered construct "selectively binds" the first ligand and not the second ligand as compared to the binding of the unaltered construct to the two ligands. In certain embodiments, the construct is a fusion protein. In certain embodiments, the complement activator portion of the construct comprises an Ig protein or biologically-active fragment thereof. In certain embodiments, the Ig protein or biologically-active fragment thereof comprises human IgG_1, human IgG_1 Fc domain, human IgM, human IgM Fc domain, mouse IgG_3, mouse IgG_3 Fc domain, mouse IgM, and mouse IgM Fc domain.

Cobra Venom Factor (CVF)

[0097] As used herein, the terms “cobra venom factor,” “CVF,” and “C3b (Cobra)” refer to the non-toxic, complement-activating component of cobra venom. Like naturally occurring human C3b, CVF (SEQ ID NO:13) forms a complex, or convertase, with complement components Factor B and Factor D. This CVFBbD convertase is capable of activating C3 in a wide variety of species via the alternative complement pathway. CVFBbD convertase is Factor H-resistant and is therefore not blocked through the activity of Factor I or CR1 and can convert nearly 100% of the C3 to C3 and C5 fragments. Levels of iC3b, C3a, SC5b-9, C5a and the Factor B cleavage product Bb are all extremely high in CVF treated sera. The cloning and sequencing of CVF from the monocled cobra (*Naja kaouthia*) was reported in Fritzinger, et al., “Molecular cloning and derived primary structure of cobra venom factor,” *Proc. Nat’l Acad. Sci. USA* 91(26):12775-779 (1994); the sequence was deposited in the GenBank database under Accession Number U09969. Both the Fritzinger et al. reference and the sequence deposited in GenBank under Accession Number U09969 are hereby incorporated herein by reference. The terms “cobra venom factor,” “CVF,” and “C3b

(Cobra)" also refer to hybrid CVF molecules comprising a CVF portion and a complement component 3 (C3) portion, such as those described in Fritzinger et al., "Functional characterization of human C3/cobra venom factor hybrid proteins for therapeutic complement depletion," *Develop. Comp. Immunol.* 33(1):105-116 (2009), which is incorporated herein by reference. Those hybrids comprise proteins in which the 113 or 315 C-terminal residues of C3 were replaced with corresponding CVF sequences. Both hybrids formed stable convertases that exhibited C3-cleaving activity, although at different rates. Neither convertase cleaved C5. Both convertases showed partial resistance to inactivation by factors H and I, allowing them to deplete complement in human serum.

[0098] In one aspect, the composition comprises 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 SCR domains of the CR2 protein; and (b) CVF. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds one or more C3 proteolytic fragments selected from the group consisting of C3d, iC3dg, C3dg, and a cell-bound fragment of C3b that binds to the two N-terminal SCR domains of CR2 and also selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα. In some embodiments, the CR2 portion selectively binds IFNα and also selectively binds EBV gp350. In some embodiments, the CR2 portion selectively binds EBV gp350. As used herein, "selectively binds" means that a construct exhibits enhanced binding to one ligand and/or decreased binding to a different ligand. For example, "selectively binds" can mean: 1) that a construct which has been altered has a binding affinity for a first ligand that is similar to the binding affinity of the unaltered construct for the first ligand whereas the construct that has been altered has a lower affinity for a second ligand than does the unaltered construct, and therefore the altered construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; 2) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand while retaining

binding to a second ligand that is similar to the binding of the unaltered construct to the second ligand, and therefore the construct "selectively binds" the first ligand as compared to the binding of the unaltered construct to the two ligands; or 3) that a construct which has been altered has increased binding to a first ligand as compared to the binding of the unaltered construct to the first ligand and also has a lower binding affinity for a second ligand as compared to the binding of the unaltered construct to the second ligand, and therefore the altered construct "selectively binds" the first ligand and not the second ligand as compared to the binding of the unaltered construct to the two ligands. In certain embodiments, the construct is a fusion protein.

Compositions of the Invention

Amino acid residues in CR2 involved in selective binding to particular ligands

[0099] Structural analyses of CR2 binding to EBV gp350, IFNα, and C3d described herein (*see* Example 1) identified a number of CR2 amino acid residues that are important for binding of each of those ligands. While some of those amino acid residues are important for binding of all three ligands, others are important for binding one specific ligand (*e.g.*, EBV gp350, IFNα, or C3d).

[0100] For example, residues determined to be important for the CR2-EBV gp350 binding interaction are N11, R13, A22, R28, S32, R36, K41, K57, Y64, K67, Y68, R83, G84 and R89 (*see* Table 2). Residues determined to be important for the CR2-EBV gp350 binding interaction but not the CR2-C3d or the CR2-IFNα binding interaction are N11, R36, K41, Y64, and K67 (*see* Table 2). Residues determined to be important for the CR2-IFNα binding interaction are R13, Y16, R28, S42, K48, K50, Y68, R83, G84 and R89 (*see* Table 2). Residues determined to be important for the CR2-IFNα binding interaction but not the CR2-C3d or CR2-EBV gp350 binding interaction are S42 and K50 (*see* Table 2). Residues determined to be important for the CR2-C3d binding interaction are I9, R13, Y16, A22, R28, Y29, C31, S32, G33, T34, K48, D56, K57, Y68, S70, R83, G84, R89, H90, D92, S93, A97, T100, N101, S109, and S128 (*see* Table 2). Residues determined to be important for the CR2-C3d binding interaction but not the CR2-gp350 or the CR2-IFNα binding interaction are I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 (*see* Table 2). The amino acid residues determined to be important for the CR2-C3d binding interaction are likely important for the CR2 binding interaction with other cell surface-bound

C3 fragments such as C3dg, and iC3b. Residues determined to be important for the CR2-gp350, the CR2-IFNα, and the CR2-C3d binding interactions are R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. Because these amino acid residues are important for binding interactions between CR2 and more than one of its ligands, mutating amino acid residues at one or more of those positions may also improve the targeting capability of the CR2 portion for C3d and/or other CR2 ligands.

[0101] The improved targeting groups described herein, comprising at least one or more mutations in the various amino acid residues important for the binding interactions between CR2 and EBV-gp350, CR2 and IFNα, and/or CR2 and C3d can be used to deliver a complement modulator (*e.g.*, a complement inhibitor or complement activator) to any physiological site (*e.g.*, a site of inflammation) suitable for the use of the CR2 targeting groups described in US Patent Publication No. 2008/0267980 A1, US Patent Publication No. US 2008/0221011 A1, and US Patent Publication No. 2005/0260198 A1, all of which are incorporated herein by reference.

[0102] Mutation of CR2 amino acid residues determined to be important for a binding interaction between CR2 and a specific ligand will likely decrease the binding affinity of CR2 for that specific ligand while leaving the binding affinity of CR2 for its other ligands relatively unaffected. For example, mutation of at least one of amino acid residues N11, R36, K41, Y64, and K67 in CR2 (SEQ ID NO:1) will likely reduce the binding affinity of CR2 for EBV gp350 while leaving its binding affinity for C3d and IFNα unchanged. Similarly, mutation of at least one of amino acid residues S42 and K50 will likely reduce the binding affinity of CR2 for IFNα while leaving its binding affinity for C3d and gp350 unchanged. Mutation of at least one of amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 will likely reduce the binding affinity of CR2 for C3d while leaving its binding affinity for IFNα and gp350 unchanged.

[0103] Provided herein are soluble compositions 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least one amino acid substitution. In certain embodiments, the construct is a fusion protein. In some embodiments the construct selectively binds to one or more C3 proteolytic fragments but does not bind to or has reduced binding affinity for IFNα or EBV gp350. In some embodiments, the construct selectively

binds to one or more C3 proteolytic fragments and IFNα but does not bind to or has reduced binding affinity for EBV gp350. In some embodiments the construct selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to or has reduced binding affinity for IFNα. In some embodiments, the construct selectively binds to IFNα but does not bind to or has reduced binding affinity for one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the construct selectively binds to IFNα and EBV gp350 but does not bind to or has reduced binding affinity for one or more C3 proteolytic fragments. In some embodiments, the construct selectively binds to EBV gp350 but does not bind to or has reduced binding affinity for IFNα and one or more C3 proteolytic fragments.

[0104] In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the CR2 portion contains at least five amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the CR2 portion contains at least six amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the CR2 portion contains at least seven amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In any of the above embodiments, the at least one, two, three, four, five, six, or seven amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least one, two, three, four, five, six, or seven amino acid substitutions may be non-conservative substitutions.

[0105] In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, and the CR2 portion has decreased binding affinity for EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, and the CR2

portion has decreased binding affinity for EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, and the CR2 portion has decreased binding affinity for EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, and the CR2 portion has decreased binding affinity for EBV gp350. In certain embodiments, the CR2 portion contains at least five amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, and the CR2 portion has decreased binding affinity for EBV gp350. In any of the above embodiments, the at least one, two, three, four, or five amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least one, two, three, four, or five amino acid substitutions may be non-conservative substitutions.

[0106] In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, and the CR2 portion has decreased binding affinity for IFNα. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at an amino acid residue selected from the group consisting of: S42 and K50, and the CR2 portion has decreased binding affinity for IFNα. In any of the above embodiments, the at least one or two amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least one or two amino acid substitutions may be non-conservative substitutions.

[0107] In certain embodiments, the CR2 portion comprises a polypeptide that contains some or all of the ligand binding sites of the CR2 protein, and includes, but is not limited to, full-length CR2 proteins (such as human CR2 as shown in SEQ ID NO:1), soluble CR2 proteins (such as a CR2 fragment comprising the extracellular domain of CR2) and other biologically active fragments of CR2, such as a CR2 fragment comprising SCR1-2 (SEQ ID NO:2), or any homolog of a naturally occurring CR2 or fragment thereof, as described in detail below. In certain embodiments, the CR2 portion has one or more of the following properties of CR2: (1) the ability to selectively bind to the C3 proteolytic fragment C3d , (2) the ability to selectively bind to the C3 proteolytic fragment iC3b, (3) the ability to selectively bind to the C3 proteolytic fragment C3dg, (4) the ability to selectively bind to one or more cell-bound fragments of the C3 proteolytic fragment C3b that bind to the two N-terminal SCR domains of CR2, (5) the ability to selectively bind to EBV gp350, and (6) the ability to selectively bind to IFNα.

[0108] In certain embodiments, the CR2 portion comprises the first two N-terminal SCR domains of CR2 (amino acids 23 through 146 of SEQ ID NO:2). In certain embodiments, the CR2 portion comprises the first three N-terminal SCR domains of CR2 (amino acids 23 through 212 of SEQ ID NO:1). In certain embodiments, the CR2 portion comprises the first four N-terminal SCR domains of CR2 (amino acids 23 through 271 of SEQ ID NO:1). In certain embodiments, the CR2 portion comprises (and in some embodiments consists of or consists essentially of) at least the first two N-terminal SCR domains of CR2, including for example at least any of the first 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 SCR domains of CR2.

[0109] In certain embodiments, the CR2 portion of the constructs described herein comprises (and in some embodiments consists of or consists essentially of) at least 1, 2, 3, 4, 5, 6, 7, or more amino acid substitutions. In certain embodiments, the amino acid substitutions may be conservative substitutions. In certain embodiments, the amino acid substitutions may be non-conservative substitutions. In certain embodiments, the amino acid substitutions may be a mixture of conservative and non-conservative substitutions.

Compositions for Targeted Delivery of Complement Modulators to Areas of Complement System Activation

[0110] In some aspects, there is provided 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 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. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has decreased binding affinity for, EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has decreased binding affinity for, EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has decreased binding affinity for, EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid

substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has decreased binding affinity for, EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67 and does not bind to, or has decreased binding affinity for, EBV gp350. In any of the above embodiments, the at least one, two, three, four, or five amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least one, two, three, four, or five amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions in amino acids from the group consisting of: N11A, R36A, K41A, Y64A, and K67A. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: C3d, iC3b, C3dg, one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2, CD23, and IFNα. In some embodiments, the construct does not bind to EBV gp350. In other embodiments, the construct has decreased binding affinity to EBV gp350. In some embodiments, the at least one amino acid substitution decreases the binding affinity of the CR2 portion for EBV gp350 by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0111] In some aspects, there is provided 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 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 IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid

residue selected from the group consisting of S42 and K50 and does not bind to, or has decreased binding affinity for, IFNα. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues S42 and K50 and does not bind to, or has decreased binding affinity for, IFNα. In any of the above embodiments, the at least one or two amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least one or two amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions in amino acids from the group consisting of: S42A and K50A. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: C3d, iC3b, C3dg, one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2, CD23, and EBV gp350. In some embodiments, the construct does not bind to IFNα. In other embodiments, the construct has decreased binding affinity to IFNα. In some embodiments, the at least one amino acid substitution decreases the binding affinity of the CR2 portion for IFNα by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0112] In some aspects, there is provided 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least two amino acid substitutions that decrease binding affinity of the CR2 portion for EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting

of: N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In any of the above embodiments, the at least two amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least two amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions in an amino acid from the group consisting of: N11A, R36A, K41A, Y64A, and K67A and a mutation from the group consisting of S42A and K50A. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: C3d, iC3b, C3dg, one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2, and CD23. In some embodiments, the construct does not bind to IFNα and EBV gp350. In other embodiments, the construct has decreased binding affinity to IFNα and EBV gp350. In some embodiments, the at least two amino acid substitutions decrease the binding affinity of the CR2 portion for IFNα and EBV gp350 by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the

complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0113] In some aspects, there is provided 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least three amino acid substitutions that decrease binding affinity of the CR2 portion for EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, and does not bind to, or has decreased binding affinity for, EBV gp350 and IFNα. In any of the above embodiments, the at least three amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at

least three amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions in an amino acid from the group consisting of: N11A, R36A, K41A, Y64A, and K67A and mutations S42A and K50A. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: C3d, iC3b, C3dg, one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2, and CD23. In some embodiments, the construct does not bind to IFNα and EBV gp350. In other embodiments, the construct has decreased binding affinity to IFNα and EBV gp350. In some embodiments, the at least three amino acid substitutions decrease the binding affinity of the CR2 portion for IFNα and EBV gp350 by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

Compositions for Targeted Delivery of Complement Modulators to Sites of Epstein Barr Virus infection

[0114] In some aspects, there is provided a soluble composition capable of targeted delivery of a complement modulator to sites of Epstein Barr Virus infection 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 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 one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid

residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least five amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least six amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least seven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least eight amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least nine amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least ten amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least eleven amino acid substitutions at amino acid

residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least twelve amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least thirteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains at least fourteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In certain embodiments, the CR2 portion contains fifteen amino acid substitutions at amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In any of the above embodiments, the at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen amino acid substitutions may be non-conservative substitutions. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: CD23, EBV gp350, and IFNα. In some embodiments, the construct does not bind to one or more C3 proteolytic fragments. In other embodiments, the construct has decreased binding affinity to one or more C3 proteolytic fragments. In some embodiments, the at least one amino acid substitution decreases the binding affinity of the CR2 portion for one or more C3 proteolytic fragments by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement

modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0115] In some aspects, there is provided a soluble composition capable of targeted delivery of a complement modulator to sites of Epstein Barr Virus infection 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least two amino acid substitutions that decrease binding affinity of the CR2 portion for one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least three amino acid substitutions at amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting

of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least five amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least six amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least seven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least eight amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least nine amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least ten amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding

affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least eleven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least twelve amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least thirteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains at least fourteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: S42 and K50, further contains fifteen amino acid substitutions at amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In any of the above embodiments, the at least two amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least two amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains a substitution of an amino acid from the group consisting of S42A

and K50A. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: CD23 and EBV gp350. In some embodiments, the construct does not bind to IFNα and one or more C3 proteolytic fragments. In other embodiments, the construct has decreased binding affinity to IFNα and one or more C3 proteolytic fragments. In some embodiments, the at least two amino acid substitutions decrease the binding affinity of the CR2 portion for IFNα and one or more C3 proteolytic fragments by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0116] In some aspects, there is provided 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least three amino acid substitutions that decrease binding affinity of the CR2 portion for one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the

CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least five amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least six amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least seven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least eight amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least nine amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino

acid substitutions at amino acid residues S42 and K50, further contains at least ten amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least eleven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least twelve amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least thirteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains at least fourteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In certain embodiments, the CR2 portion contains amino acid substitutions at amino acid residues S42 and K50, further contains fifteen amino acid substitutions at amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In any of the above embodiments, the at least three amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least three amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains substitutions of amino acids S42A and K50A. In

certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: CD23 and EBV gp350. In some embodiments, the construct does not bind to IFNα and one or more C3 proteolytic fragments. In other embodiments, the construct has decreased binding affinity to IFNα and one or more C3 proteolytic fragments. In some embodiments, the at least three amino acid substitutions decreases the binding affinity of the CR2 portion for IFNα and one or more C3 proteolytic fragments by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

Compositions for Targeted Delivery of Complement Modulators to Sites of Interferon alpha Production

[0117] In some aspects, there is provided a soluble composition capable of targeted delivery of a complement modulator to sites of IFNα production 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least two amino acid substitutions that decrease binding affinity of the CR2 portion for one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least two amino

acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least five amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least six amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least seven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least eight amino acid

substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least nine amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least ten amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least eleven amino acid substitutions at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least twelve amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least thirteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least fourteen amino acid

substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains fifteen amino acid substitutions at amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In any of the above embodiments, the at least two amino acid substitutions may be conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions of amino acids from the group consisting of: N11A, R36A, K41A, Y64A, and K67A. In any of the above embodiments, the at least two amino acid substitutions may be non-conservative substitutions. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: CD23 and IFNα. In some embodiments, the construct does not bind to EBV gp350 and one or more C3 proteolytic fragments. In other embodiments, the construct has decreased binding affinity to EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the at least two amino acid substitutions decreases the binding affinity of the CR2 portion for EBV gp350 and one or more C3 proteolytic fragments by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0118] In some aspects, there is provided a soluble composition capable of targeted delivery of a complement modulator to sites of IFNα production 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least three amino acid substitutions that decrease binding affinity of the CR2 portion for one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at an amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least two amino acid substitutions at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least five amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at

least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least six amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least seven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least eight amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least nine amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least ten amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least eleven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at

least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least twelve amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least thirteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least fourteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least two amino acid substitutions at amino acid residue selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains fifteen amino acid substitutions at amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In any of the above embodiments, the at least three amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least three amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions of amino acids from the group consisting of: N11A, R36A, K41A, Y64A, and K67A. In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: CD23 and IFNα. In some embodiments, the construct does not bind to EBV gp350 and one or more C3 proteolytic fragments. In other embodiments, the construct has decreased binding affinity to EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the at least three amino acid substitutions

decreases the binding affinity of the CR2 portion for EBV gp350 and one or more C3 proteolytic fragments by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0119] In some aspects, there is provided a soluble composition capable of targeted delivery of a complement modulator to sites of IFNα production 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least four amino acid substitutions that decrease binding affinity of the CR2 portion for one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93,

A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least five amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least six amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least seven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least eight amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least nine amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93,

A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least ten amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least eleven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least twelve amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least thirteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least fourteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains fifteen amino acid substitutions at amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and

S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In any of the above embodiments, the at least four amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least four amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions in amino acids from the group consisting of: N11A, R36A, K41A, Y64A, and K67A In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: CD23 and IFNα. In some embodiments, the construct does not bind to EBV gp350 and one or more C3 proteolytic fragments. In other embodiments, the construct has decreased binding affinity to EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the at least four amino acid substitutions decreases the binding affinity of the CR2 portion for EBV gp350 and one or more C3 proteolytic fragments by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In other embodiments, some of these complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0120] In some aspects, there is provided a soluble composition capable of targeted delivery of a complement modulator to sites of IFNα production 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least five amino acid substitutions that decrease binding affinity of the CR2 portion for one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41,

Y64 and K67, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least five amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least six amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41,

Y64 and K67, further contains at least seven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least eight amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least nine amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least ten amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least eleven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least twelve amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41,

Y64 and K67, further contains at least thirteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains at least fourteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: N11, R36, K41, Y64 and K67, further contains fifteen amino acid substitutions at amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In any of the above embodiments, the at least five amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least five amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions of amino acids from the group consisting of: N11A, R36A, K41A, Y64A, and K67A In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: CD23 and IFNα. In some embodiments, the construct does not bind to EBV gp350 and one or more C3 proteolytic fragments. In other embodiments, the construct has decreased binding affinity to EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the at least five amino acid substitutions decreases the binding affinity of the CR2 portion for EBV gp350 and one or more C3 proteolytic fragments by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement

activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

[0121] In some aspects, there is provided a soluble composition capable of targeted delivery of a complement modulator to sites of IFNα production 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 SCR domains of the CR2 protein; and (b) a complement modulator portion; wherein the CR2 portion contains at least six amino acid substitutions that decrease binding affinity of the CR2 portion for one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least one amino acid substitution at an amino acid residue selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least two amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least three amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least four amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least five amino acid substitutions

at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least six amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least seven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least eight amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least nine amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least ten amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41,Y64 and K67, further contains at least eleven amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In

certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least twelve amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least thirteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains at least fourteen amino acid substitutions at amino acid residues selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In certain embodiments, the CR2 portion contains five amino acid substitutions at amino acid residues N11, R36, K41, Y64 and K67, further contains fifteen amino acid substitutions at amino acid residues I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, and does not bind to, or has decreased binding affinity for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In any of the above embodiments, the at least six amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least six amino acid substitutions may be non-conservative substitutions. In certain embodiments, the CR2 portion contains one or more substitutions of amino acids from the group consisting of: N11A, R36A, K41A, Y64A, and K67A In certain embodiments, the construct is a fusion protein. In some embodiments, the CR2 portion selectively binds to one or more proteins from the group consisting of: CD23 and IFNα. In some embodiments, the construct does not bind to EBV gp350 and one or more C3 proteolytic fragments. In other embodiments, the construct has decreased binding affinity to EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the at least six amino acid substitutions decreases the binding affinity of the CR2 portion for EBV gp350 and one or more C3 proteolytic fragments by any of about 20%, 25%, 30%, 35%, 40%, 45%,

50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages. In some embodiments, the complement modulator portion is a complement inhibitor. In some of these embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In other embodiments, the complement modulator portion is a complement activator. In some of these embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF.

Other CR2 Substitutions for Targeted Delivery of Complement Modulators

[0122] In any embodiments of any of the compositions described herein, the CR2 portion can further contain at least one, two, three, four, five, six, seven, eight, nine, ten, or eleven additional amino acid substitutions at other positions in the CR2 portion. In certain embodiments, the CR2 portion further contains at least one amino acid substitution selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least two amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least three amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least four amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least five amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least six amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least seven amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least eight amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least nine amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2

portion further contains at least ten amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion further contains at least eleven amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In any of the above embodiments, the at least one, two, three, four, five, six, seven, eight, nine, ten or eleven amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least one, two, three, four, five, six, seven, eight, nine, ten or eleven amino acid substitutions may be non-conservative substitutions.

Linker Proteins

[0123] In any of the embodiments described herein, the construct comprising a CR2 portion or a biologically active fragment thereof and a complement inhibitor portion comprising human CD59, mouse CD59 isoform A, mouse CD59 isoform B, mouse Crry protein, human factor H, mouse factor H, human CR1, human MCP, human DAF or mouse DAF or a biologically active fragment thereof also includes an amino acid linker sequence linking the CR2 portion and the complement inhibitor portion (*e.g.*, human CD59, mouse CD59 isoform A, mouse CD59 isoform B, mouse Crry protein, human factor H, mouse factor H, human CR1, human MCP, human DAF or mouse DAF or a biologically active fragment thereof).

[0124] In any of the embodiments described herein, the construct comprising a CR2 portion or a biologically active fragment thereof and a complement activator portion comprising human IgG_1, human IgM, mouse IgG_3, mouse IgM, or CVF or a biologically-active fragment thereof also includes an amino acid linker sequence linking the CR2 portion and the complement activator portion (*e.g.*, human IgG_1, human IgM, mouse IgG_3, mouse IgM, or CVF or a biologically active fragment thereof).

[0125] Examples of linker sequences are known in the art, and include, for example, (Gly_4Ser), $(Gly_4Ser)_2$, $(Gly_4Ser)_3$, $(Gly_3Ser)_4$, $(SerGly_4)$, $(SerGly_4)_2$, $(SerGly_4)_3$, and $(SerGly_4)_4$. Linking sequences can also comprise "natural" linking sequences found between different domains of complement factors. For example, VSVFPLE (SEQ ID NO:26) or EYFNKYSS (SEQ ID NO:27), the linking sequence between the first two N-terminal short consensus repeat domains of human CR2, can be used. In some embodiments, the linking sequence between the fourth and the fifth N-terminal short consensus repeat domains of human CR2 (EEIF) (SEQ ID NO:28) is used. In some embodiments, the linker sequence comprises at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21,

22, 23, 24, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, or 100 amino acids, inclusive, as well as any numerical value in between these numbers.

Pharmaceutical Compositions

[0126] In another aspect, provided herein are pharmaceutical compositions comprising any of the constructs and/or fusion proteins described herein. Pharmaceutical compositions comprising any of the constructs and/or fusion proteins described herein are generally formulated as sterile, substantially isotonic pharmaceutical solutions in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration. In certain embodiments, the composition is free of pathogen. For injection, the pharmaceutical compositions can be in the form of liquid solutions, for example in physiologically compatible buffers such as Hank's Balanced Salt Solution, Phosphate-Buffered Saline or Ringer's solution. In addition, the pharmaceutical compositions provided herein can be in solid form and redissolved or resuspended immediately prior to use. Lyophilized compositions are also contemplated.

[0127] For oral administration, the pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulfate). Liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, fractionated oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

[0128] In certain embodiments, the compositions are formulated in accordance with routine procedures as a pharmaceutical composition adapted for injection. In certain embodiments, the pharmaceutical compositions provided herein are formulated for intravenous, intraperitoneal, or intraocular injection. Typically, compositions for injection are solutions in

sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0129] The pharmaceutical compositions may further comprise additional ingredients, for example preservatives, buffers, tonicity agents, antioxidants and stabilizers, nonionic wetting or clarifying agents, viscosity-increasing agents, and the like.

[0130] Suitable preservatives for use in a solution include polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, disodium-EDTA, sorbic acid, benzethonium chloride, and the like. Typically (but not necessarily) such preservatives are employed at a level of from 0.001% to 1.0% by weight.

[0131] Suitable buffers include boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH at between about pH 6 and pH 8, and preferably, between about pH 7 and pH 7.5.

[0132] Suitable tonicity agents include dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the injectable solution is in the range 0.9 plus or minus 0.2%.

[0133] Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium thiosulfite, thiourea and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxmethylpropylcellulose, lanolin, methylcellulose, petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like.

[0134] The pharmaceutical compositions may be suitable for a variety of modes of administration described herein, including for example systemic or localized administration. The pharmaceutical compositions can be in the form of injectable solutions or in a form suitable for oral administration. The pharmaceutical compositions described herein can be

packaged in single unit dosages or in multidosage forms. In certain embodiments, the pharmaceutical compositions are suitable for administration to an individual, a vertebrate, a mammal, or a human by any route of administration described herein, including oral administration or intravenous injection.

Methods of the Invention

Methods of Making a Targeted Construct for Complement System Modulation

[0135] Provided herein are methods for making a construct that selectively binds to one or more ligands of CR2, wherein the method comprises mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct, and 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 SCR domains of the CR2 protein; and (b) a complement modulator portion. In certain embodiments, the construct is a fusion protein. In some embodiments the construct selectively binds to one or more C3 proteolytic fragments but does not bind to or has reduced binding affinity for IFNα or EBV gp350. In some embodiments, the construct selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to or has reduced binding affinity for EBV gp350. In some embodiments the construct selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to or has reduced binding affinity for IFNα. In some embodiments, the construct selectively binds to IFNα but does not bind to or has reduced binding affinity for one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the construct selectively binds to IFNα and EBV gp350 but does not bind to or has reduced binding affinity for one or more C3 proteolytic fragments. In some embodiments, the construct selectively binds to EBV gp350 but does not bind to or has reduced binding affinity for IFNα and one or more C3 proteolytic fragments.

[0136] In one aspect, there is provided 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 from the group consisting of: N11, R36, K41, Y64 and K67; and (b) mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: S42 and K50, 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. In some embodiments, the one or more mutations in the complement receptor 2 (CR2) portion of the construct are mutations to the amino acid alanine. In some embodiments, the method further comprises mutating one or more amino acids in the complement receptor 2 (CR2) portion of the construct selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In some embodiments, the method comprises mutating any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 amino acids in the complement receptor 2 (CR2) portion of the construct.

[0137] In one aspect, there is provided a method for making a construct that selectively binds to one or more C3 proteolytic fragments and EBV gp350, but does not selectively bind to IFNα, wherein the method comprises mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: S42 and K50, 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 SCR domains of the CR2 protein; and (b) a complement modulator portion. In some embodiments, the one or more mutations in the complement receptor 2 (CR2) portion of the construct are mutations to the amino acid alanine. In some embodiments, the method further comprises mutating one or more amino acids in the complement receptor 2 (CR2) portion of the construct selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In some embodiments, the method comprises mutating any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 amino acids in the complement receptor 2 (CR2) portion of the construct.

[0138] In one aspect, there is provided a method for making a construct that selectively binds to one or more C3 proteolytic fragments and IFNα, but does not selectively bind to EBV gp350, wherein the method comprises mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: N11, R36, K41, Y64 and K67, 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 SCR domains of the CR2 protein; and (b) a complement modulator portion. In some embodiments, the one or more mutations in the complement receptor 2 (CR2) portion of the construct are mutations to the amino acid alanine. In some embodiments, the method further comprises mutating one or more amino acids in the complement receptor 2 (CR2) portion of the construct selected from

the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In some embodiments, the method comprises mutating any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 amino acids in the complement receptor 2 (CR2) portion of the construct.

[0139] In one aspect, there is provided a method for making a construct that selectively binds to IFNα but does not selectively bind to one or more C3 proteolytic fragments and EBV gp350, wherein the method comprises (a) mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: N11, R36, K41, Y64 and K67; and (b) mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, 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. In some embodiments, the one or more mutations in the complement receptor 2 (CR2) portion of the construct are mutations to the amino acid alanine. In some embodiments, the method further comprises mutating one or more amino acids in the complement receptor 2 (CR2) portion of the construct selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In some embodiments, the method comprises mutating any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 amino acids in the complement receptor 2 (CR2) portion of the construct.

[0140] In one aspect, there is provided a method for making a construct that selectively binds to EBV gp350 and IFNα, but does not selectively bind to one or more C3 proteolytic fragments, wherein the method comprises mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, 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 SCR domains of the CR2 protein; and (b) a complement modulator portion. In some embodiments, the one or more mutations in the complement receptor 2 (CR2) portion of the construct are mutations to the amino acid alanine. In some embodiments, the method further comprises mutating one or more amino acids in the complement receptor 2 (CR2) portion of the construct selected from the group consisting of:

R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In some embodiments, the method comprises mutating any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 amino acids in the complement receptor 2 (CR2) portion of the construct.

[0141] In one aspect, there is provided a method for making a construct that selectively binds to EBV gp350 but does not selectively bind to one or more C3 proteolytic fragments and IFNα, wherein the method comprises (a) mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: S42 and K50; and (b) mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128, 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. In some embodiments, the one or more mutations in the complement receptor 2 (CR2) portion of the construct are mutations to the amino acid alanine. In some embodiments, the method further comprises mutating one or more amino acids in the complement receptor 2 (CR2) portion of the construct selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In some embodiments, the method comprises mutating any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 amino acids in the complement receptor 2 (CR2) portion of the construct.

Methods for Reducing the Binding Affinity for or Altering the Binding Kinetics of the CR2 Portion of the Construct for One or More Ligands

[0142] In another aspect, provided herein are methods for reducing the binding affinity of the CR2 portion of any of the constructs disclosed herein for one or more CR2 ligands, the method comprising introducing one or more mutations in the amino acid sequence of the CR2 portion of the construct wherein the one or more mutations reduces binding affinity of the CR2 portion of the construct for one or more CR2 ligands.

[0143] In certain aspects, there is provided a method for reducing the binding affinity of the CR2 portion of any of the constructs disclosed herein for EBV gp350 and IFNα, the method comprising mutating at least one amino acid residue in the CR2 portion selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the method comprises mutating at least two amino acid residues in the CR2 portion selected from

the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the method comprises mutating at least three amino acid residues in the CR2 portion selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the method comprises mutating at least four amino acid residues in the CR2 portion selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the method comprises mutating at least five amino acid residues in the CR2 portion selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the method comprises mutating at least six amino acid residues in the CR2 portion selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the method comprises mutating seven amino acid residues in the CR2 portion selected from the group consisting of: N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the at least one, two, three, four, five, six or seven mutations are conservative amino acid substitutions. In certain embodiments, the at least one, two, three, four, five, six or seven mutations are non-conservative amino acid substitutions. In some embodiments, the binding affinity of the construct for EBV gp350 and/or IFNα is reduced by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages.

[0144] In certain aspects, there is provided a method for reducing the binding affinity of the CR2 portion of any of the constructs disclosed herein for EBV gp350, the method comprising mutating at least one amino acid residue selected from the group consisting of N11, R36, K41, Y64 and K67. In certain embodiments, the method comprises mutating at least two amino acid residues selected from the group consisting of N11, R36, K41, Y64 and K67. In certain embodiments, the method comprises mutating at least three amino acid residues selected from the group consisting of N11, R36, K41, Y64 and K67. In certain embodiments, the method comprises mutating at least four amino acid residues selected from the group consisting of N11, R36, K41, Y64 and K67. In certain embodiments, the method comprises mutating at least five amino acid residues selected from the group consisting of N11, R36, K41, Y64 and K67. In certain embodiments, the at least one, two, three, four, or five mutations may be conservative amino acid substitutions. In certain embodiments, the at least one, two, three, four, or five mutations may be non-conservative amino acid substitutions. In some embodiments, the binding affinity of the construct for EBV gp350 is reduced by any of

about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages.

[0145] In certain aspects, there is provided a method for reducing the binding affinity of the CR2 portion of any of the constructs disclosed herein for IFNα, the method comprising mutating at least one amino acid residue selected from the group consisting of S42 and K50. In certain embodiments, the method comprises mutating two amino acid residues selected from the group consisting of S42 and K50. In certain embodiments, the at least one or two mutations may be conservative amino acid substitutions. In certain embodiments, the at least one or two mutations may be non-conservative amino acid substitutions. In some embodiments, the binding affinity of the construct for IFNα is reduced by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages.

[0146] In another aspect, the method for reducing the binding affinity of the CR2 portion of any of the constructs disclosed herein for one or more CR2 ligands further comprises mutating at least one, two, three, four, five, six, seven, eight, nine, ten, or eleven amino acids residues at other positions in the CR2 portion. In certain embodiments, the CR2 portion optionally further contains at least one amino acid substitution selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least two amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least three amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least four amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least five amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least six amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least seven amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least eight amino acid

substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least nine amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains at least ten amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In certain embodiments, the CR2 portion optionally further contains eleven amino acid substitutions selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89. In any of the above embodiments, the at least one, two, three, four, five, six, seven, eight, nine, ten or eleven amino acid substitutions may be conservative substitutions. In any of the above embodiments, the at least one, two, three, four, five, six, seven, eight, nine, ten or eleven amino acid substitutions may be non-conservative substitutions.

[0147] In another aspect, provided herein are methods of altering the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O) or cell surface-bound C3 proteolytic fragments, such as C3d, C3dg, and iC3b, relative to other CR2 ligands (*e.g.*, EBV gp350 and IFNα). In certain embodiments, the altering improves the binding kinetics of the CR2 portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b, and the method comprises mutating at least one amino acid residue in the CR2 portion of the construct selected from the group consisting of N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the altering improves the binding kinetics of the CR2 portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b, and the method comprises mutating at least two amino acid residues in the CR2 portion of the construct selected from the group consisting of N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the altering improves the binding kinetics of the CR2 portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b, and the method comprises mutating at least three amino acid residues in the CR2 portion of the construct selected from the group consisting of N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the altering improves the binding kinetics of the CR2 portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b, and the method comprises mutating at least four amino acid residues in the CR2 portion of the construct selected from the group consisting of N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the altering improves the binding kinetics of the CR2

portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b, and the method comprises mutating at least five amino acid residues in the CR2 portion of the construct selected from the group consisting of N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the altering improves the binding kinetics of the CR2 portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b, and the method comprises mutating at least six amino acid residues in the CR2 portion of the construct selected from the group consisting of N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the altering improves the binding kinetics of the CR2 portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b, and the method comprises mutating at least seven amino acid residues in the CR2 portion of the construct selected from the group consisting of N11, R36, K41, S42, K50, Y64 and K67. In certain embodiments, the cell surface-bound fragment of C3 is selected from the group consisting of C3d, C3dg, and iC3b. In certain embodiments, the cell surface-bound fragment of C3 is C3d. In certain embodiments, the cell surface-bound fragment of C3 is C3dg. In certain embodiments, the cell surface-bound fragment of C3 is iC3b. In certain embodiments, the at least one, two, three, four, five, six, or seven mutations may be conservative amino acid substitutions. In certain embodiments, the at least one, two, three, four, five, six, or seven mutations may be non-conservative amino acid substitutions. In some embodiments, the altering improves the binding kinetics of the CR2 portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b by any of at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

[0148] In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least one amino acid residue selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least two amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as,

but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least three amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least four amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least five amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least six amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least seven amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least eight amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least nine amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least ten amino acid residues selected from the group

consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least eleven amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least twelve amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least thirteen amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating at least fourteen amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain aspects, the altering worsens the binding kinetics of the CR2 portion of the construct for C3, C3(H_2O), and/or cell surface-bound C3 proteolytic fragments, such as, but not limited to, C3d, C3dg, and iC3b, and the method comprises mutating fifteen amino acid residues selected from the group consisting of I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128. In certain embodiments, the at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen mutations may be conservative amino acid substitutions. In certain embodiments, the at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen mutations may be non-conservative amino acid substitutions. In some embodiments, the altering worsens the binding kinetics of the CR2 portion of the construct for cell surface-bound proteolytic fragments of C3, such as C3d, C3dg, and iC3b by any of about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, inclusive, as well as any numerical value in between these percentages.

Methods of Treating Complement-Associated Diseases or Conditions

[0149] Provided herein are methods of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein. As used herein, an "individual" can be a vertebrate, a mammal, or a human. Specifically, as used herein, a "mammal" can be a nonhuman primate, mouse, rat, pig, dog, cat, monkey, cow, or horse. It is understood that administration of the composition to the individual can have the effect of, but is not limited to, reducing the symptoms of the condition, a reduction in the severity of the condition, or the complete ablation of the condition.

Methods of Treatment by Inhibiting Complement Activity

[0150] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement inhibitor or biologically-active fragment thereof, and wherein the administration of the composition inhibits complement activity. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments but does not bind to, or has reduced binding affinity for, IFNα and EBV gp350. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2.

[0151] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the

compositions described herein, wherein the complement modulator portion of the composition comprises a complement inhibitor or biologically-active fragment thereof, wherein the administration of the composition inhibits complement activity; and wherein the complement associated disease or condition is an inflammatory condition. In some embodiments, the complement associated disease or condition can include an inflammatory condition such as, but not limited to, asthma, systemic lupus erythematosus, rheumatoid arthritis, reactive arthritis, spondylarthritis, systemic vasculitis, insulin dependent diabetes mellitus, multiple sclerosis, experimental allergic encephalomyelitis, Sjögren's syndrome, graft versus host disease, inflammatory bowel disease including Crohn's disease, ulcerative colitis, ischemia reperfusion injury, myocardial Infarction, Alzheimer's disease, transplant rejection (allogeneic and xenogeneic), thermal trauma, any immune complex-induced inflammation, glomerulonephritis, myasthenia gravis, cerebral lupus, Guillain-Barré syndrome, vasculitis, systemic sclerosis, anaphylaxis, catheter reactions, atheroma, infertility, thyroiditis, adult respitory distress syndrome (ARDS), post-bypass syndrome, hemodialysis, juvenile rheumatoid, Behçets syndrome, hemolytic anemia, pemphigus, bullous pemphigoid, stroke, atherosclerosis, and scleroderma. In some embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2.

[0152] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the

composition comprises a complement inhibitor or biologically-active fragment thereof, wherein the administration of the composition inhibits complement activity, and wherein the complement associated disease or condition is a viral infection. In some embodiments, the viral infection can include, but is not limited to, Influenza virus A, Influenza virus B, Respiratory syncytial virus, Dengue virus, Yellow fever virus, Ebola virus, Marburg virus, Lassa fever virus, Eastern Equine Encephalitis virus, Japanese Encephalitis virus, St. Louis Encephalitis virus, Murray Valley fever virus, West Nile virus, Rift Valley fever virus, Rotavirus A, Rotavirus B, Rotavirus C, Sindbis virus, Hantavirus. In some aspects, the complement associated disease or condition is a result of the response of an individual to a viral vector. In certain embodiments, the viral vector includes, but is not limited to, adenovirus, vaccinia virus, adeno associated virus, modified vaccinia ancara virus, cytomegalovirus, or any other viral vector known in the art. In some embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: S42A and

K50A and does not bind to, or has reduced binding efficiency for, IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, S42A and K50A and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 K67, S42A and K50A and does not bind to, or has reduced binding efficiency for, EBV gp350 and IFNα.

[0153] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement inhibitor or biologically-active fragment thereof, wherein the administration of the composition inhibits complement activity, and wherein the complement associated disease or condition is a fungal infection. It is understood in the art that *Candida* express a CR3-like protein that has similar binding properties as CR2. The *Candida* CR3-like protein appears to be involved in pathogenesis. Therefore, an embodiment of the invention is directed to a method of treating an individual with a fungal infection, wherein the treatment blocks fungal-"CR3" function as well as inhibits complement, comprising administering to a subject any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement inhibitor or biologically-active fragment thereof. In some embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind

to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: S42A and K50A and does not bind to, or has reduced binding efficiency for, IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, S42A and K50A and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 K67, S42A and K50A and does not bind to, or has reduced binding efficiency for, EBV gp350 and IFNα.

[0154] Apoptosis occurring during normal development is noninflammatory and is involved in induction of immunological tolerance. Although apoptotic cell death can be inflammatory depending on how it is activated and in what cell types (for example, therapeutic agents that ligate Fas are able to induce inflammation), necrotic cell death results in a sustained and powerful inflammatory response mediated by released cell contents and by proinflammatory cytokines released by stimulated phagocytes. Apoptotic cells and vesicles are normally cleared by phagocytes, thus preventing the pro-inflammatory consequences of cell lysis. In this context, it has been shown that apoptotic cells and apoptotic bodies directly fix

complement, and that complement can sustain an anti-inflammatory response due to opsonization and enhanced phagocytosis of apoptotic cells.

[0155] Inflammation is involved in nonspecific recruitment of immune cells that can influence innate and adaptive immune responses. Modulating complement activation during apoptosis-based tumor therapy to inhibit phagocytic uptake of apoptotic cells/bodies enhances the Inflammatory/innate immune response within the tumor environment. In addition, apoptotic cells can be a source of immunogenic self antigens and uncleared apoptotic bodies can result in autoimmunization. In addition to creating an enhanced immuno-stimulatory environment, modulating complement at a site in which tumor cells have been induced to undergo apoptosis further augments or triggers specific immunity against a tumor to which the host is normally tolerant.

[0156] Accordingly, in some aspects, there is provided a method of enhancing the outcome of an apoptosis-based therapy (e.g., gene therapy with adenovirus expressing Fas ligand) in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement inhibitor or biologically-active fragment thereof and wherein the administration of the composition inhibits complement activity. In some embodiments, the complement inhibitor is selected from the group consisting of: MCP, DAF, CD59, Crry, CR1, and FH. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to,

or has reduced binding efficiency for, one or more C3 proteolytic fragments. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: S42A and K50A and does not bind to, or has reduced binding efficiency for, IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, S42A and K50A and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 K67, S42A and K50A and does not bind to, or has reduced binding efficiency for, EBV gp350 and IFNα.

Methods of Treatment by Enhancing Complement Activity

[0157] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement activator or biologically-active fragment thereof, and wherein the administration of the composition enhances complement activity. In some embodiments, enhancing complement activity can have the effect of, but is not limited to, reducing the symptoms of the condition, a reduction in the severity of the condition, or the complete ablation of the condition. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic

fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2.

[0158] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement activator or biologically-active fragment thereof, wherein the administration of the composition enhances complement activity, and wherein the complement-associated disease or condition is cancer. A representative but non-limiting list of cancers that the disclosed complement enhancing compositions can be used to treat includes: lymphoma, B cell lymphoma, T cell lymphoma, mycosis fungoides, multiple myeloma, Hodgkin's Disease, myeloid leukemia, bladder cancer, brain cancer, nervous system cancer, head and neck cancer, squamous cell carcinoma of head and neck, kidney cancer, lung cancers such as small cell lung cancer and non-small cell lung cancer, urothelial carcinomas, adenocarcinomas, sarcomas, gliomas, high grade gliomas, blastomas, neuroblastomas, plasmacytomas, histiocytomas, adenomas, hypoxic tumors, myelomas, AIDS-related lymphomas or sarcomas, metastatic cancers, neuroblastoma/glioblastoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, liver cancer, melanoma, squamous cell carcinomas of the mouth, throat, larynx, and lung, colon cancer, cervical cancer, cervical carcinoma, breast cancer, and epithelial cancer, renal cancer, genitourinary cancer, pulmonary cancer, esophageal carcinoma, head and neck carcinoma, large bowel cancer, hematopoietic cancers, testicular cancer, colon and rectal cancers, stomach cancer, prostatic cancer, Waldenstroms disease or pancreatic cancer. In other embodiments, the complement-associated disease or condition is a precancerous condition such as, but not limited to, cervical and anal dysplasias, other dysplasias, severe dysplasias, hyperplasias, atypical hyperplasias, and neoplasias. In certain embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the

composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: S42A and K50A and does not bind to, or has reduced binding efficiency for, IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, S42A and K50A and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 K67, S42A and K50A and does not bind to, or has reduced binding efficiency for, EBV gp350 and IFNα.

[0159] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement activator or biologically-active fragment thereof,

wherein the administration of the composition enhances complement activity, and wherein the complement-associated disease or condition is a viral infection. A representative but non-limiting list of viral infections that the disclosed complement enhancing compositions can be used to treat includes: Herpes simplex virus type-1, Herpes simplex virus type-2, Cytomegalovirus, Epstein-Barr virus, Varicella-zoster virus, Human herpesvirus 6, Human herpesvirus 7, Human herpesvirus 8, Variola virus, Vesicular stomatitis virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis D virus, Hepatitis E virus, Rhinovirus, Coronavirus, Influenza virus A, Influenza virus B, Measles virus, Polyomavirus, Human Papilomavirus, Respiratory syncytial virus, Adenovirus, Coxsackie virus, Dengue virus, Mumps virus, Poliovirus, Rabies virus, Rous sarcoma virus, Yellow fever virus, Ebola virus, Marburg virus, Lassa fever virus, Eastern Equine Encephalitis virus, Japanese Encephalitis virus, St. Louis Encephalitis virus, Murray Valley fever virus, West Nile virus, Rift Valley fever virus, Rotavirus A, Rotavirus B, Rotavirus C, Sindbis virus, Human T-cell Leukemia virus type-1, Hantavirus, Rubella virus, Simian Immunodeficiency virus, Human Immunodeficiency virus type-1, and Human Immunodeficiency virus type-2. In certain embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to,

or has reduced binding efficiency for, one or more C3 proteolytic fragments. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: S42A and K50A and does not bind to, or has reduced binding efficiency for, IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, S42A and K50A and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 K67, S42A and K50A and does not bind to, or has reduced binding efficiency for, EBV gp350 and IFNα.

[0160] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement activator or biologically-active fragment thereof, wherein the administration of the composition enhances complement activity, and wherein the complement-associated disease or condition is a bacterial infection. A representative but non-limiting list of bacterial infections that the disclosed complement enhancing compositions can be used to treat includes bacterial infection by: *M. tuberculosis, M. bovis, M. bovis strain BCG, BCG substrains, M. avium, M. intracellulare, M. africanum, M. kansasii, M. marinum, M. ulcerans, M. avium subspecies paratuberculosis, Nocardia asteroides*, other *Nocardia* species, *Legionella pneumophila,* other *Legionella* species, *Salmonella typhi,* other *Salmonella* species, *Shigella species, Yersinia pestis, Pasteurella haemolytica, Pasteurella multocida,* other *Pasteurella* species, *Actinobacillus pleuropneumoniae, Listeria monocytogenes, Listeria ivanovii, Brucella abortus,* other *Brucella* species, *Cowdria ruminantium, Chlamydia pneumoniae, Chlamydia trachomatis, Chlamydia psittaci, Coxiella burnetti,* other *Rickettsial* species, *Ehrlichia* species,

Staphylococcus aureus, *Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus agalactiae, Bacillus anthracis, Escherichia coli, Vibrio cholerae, Campylobacter species, Neisseria meningitidis, Neisseria gonorrhea, Pseudomonas aeruginosa,* other *Pseudomonas* species, *Haemophilus Influenzae, Haemophilus ducreyi*, other *Hemophilus* species, *Clostridium tetani,* other *Clostridium* species, *Yersinia enterolitica,* and other *Yersinia* species. In certain embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: S42A and K50A and does not bind to, or has reduced binding efficiency for, IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and

EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, S42A and K50A and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 K67, S42A and K50A and does not bind to, or has reduced binding efficiency for, EBV gp350 and IFNα.

[0161] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement activator or biologically-active fragment thereof, wherein the administration of the composition enhances complement activity, and wherein the complement-associated disease or condition is a parasitic infection. A representative but non-limiting list of parasitic infections that the disclosed complement enhancing compositions can be used to treat includes: *Toxoplasma gondii*, *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae,* other *Plasmodium* species., *Trypanosoma brucei, Trypanosoma cruzi, Leishmania major,* other *Leishmania* species, *Schistosoma mansoni*, other *Schistosoma* species, and *Entamoeba histolytica*. In certain embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc domain, mouse IgM Fc domain, and CVF. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the

two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: S42A and K50A and does not bind to, or has reduced binding efficiency for, IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, S42A and K50A and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 K67, S42A and K50A and does not bind to, or has reduced binding efficiency for, EBV gp350 and IFNα.

[0162] In some aspects, there is provided a method of treating a complement-associated disease or condition in an individual comprising administering to the individual any of the compositions described herein, wherein the complement modulator portion of the composition comprises a complement activator or biologically-active fragment thereof, wherein the administration of the composition enhances complement activity, and wherein the complement-associated disease or condition is a fungal infection. A representative but non-limiting list of fungal infections that the disclosed complement enhancing compositions can be used to treat includes: *Candida albicans, Cryptococcus neoformans, Histoplama capsulatum, Aspergillus fumigatus, Coccidiodes immitis, Paracoccidiodes brasiliensis, Blastomyces dermitidis, Pneuomocystis carnii, Penicillium marneffi,* and *Alternaria alternate.* In certain embodiments, the complement activator is selected from the group consisting of: human Ig isotype G_1 (IgG_1), human Ig isotype M (IgM), mouse Ig isotype G_3 (IgG_3), mouse IgM Fc, human IgG_1 Fc domain, human IgM Fc domain, mouse IgG_3 Fc

domain, mouse IgM Fc domain, and CVF. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and EBV gp350 but does not bind to, or has reduced binding affinity for, IFNα. In some embodiments, the composition selectively binds to one or more C3 proteolytic fragments and IFNα but does not bind to, or has reduced binding affinity for, EBV gp350. In some embodiments, the composition selectively binds to IFNα but does not bind to, or has reduced binding affinity for, EBV gp350 and one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to IFNα and EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments. In some embodiments, the composition selectively binds to EBV gp350 but does not bind to, or has reduced binding affinity for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the one or more C3 proteolytic fragments are selected from the group consisting of C3d, iC3b, C3dg, and one or more cell-bound fragments of C3b that bind to the two N-terminal SCR domains of CR2. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, and S128 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: S42A and K50A and does not bind to, or has reduced binding efficiency for, IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, N11, R36, K41, Y64 and K67 and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and EBV gp350. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: I9, Y29, C31, G33, T34, D56, S70, H90, D92, S93, A97, T100, N101, S109, S128, S42A and K50A and does not bind to, or has reduced binding efficiency for, one or more C3 proteolytic fragments and IFNα. In some embodiments, the CR2 portion of the composition has one or more mutations selected from the group consisting of: N11, R36, K41, Y64 K67, S42A and K50A and does not bind to, or has reduced binding efficiency for, EBV gp350 and IFNα.

EXAMPLES

[0163] The examples, which are intended to be purely exemplary of the invention and should therefore not be considered to limit the invention in any way, also describe and detail aspects and embodiments of the invention discussed above. The foregoing examples and detailed description are offered by way of illustration and not by way of limitation. All publications, patent applications, and patents cited in this specification are herein incorporated by reference as if each individual publication, patent application, or patent were specifically and individually indicated to be incorporated by reference. In particular, all publications cited herein are expressly incorporated herein by reference for the purpose of describing and disclosing compositions and methodologies which might be used in connection with the invention. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

EXAMPLE 1: IDENTIFICATION OF AMINO ACID RESIDUES IMPORTANT FOR CR2 BINDING INTERACTIONS WITH EBV gp350 AND IFNα.

Experimental Methods

Expression and purification of recombinant proteins

[0164] Human CR2 SCR1-2 for NMR and isothermal titration calorimetry ("ITC") studies was expressed in *Pichia pastoris* using a BioFlo™ 110 Fermenter (New Brunswick Scientific, Edison, NJ) as previously described (46). Briefly, a single colony was grown up in 5 ml *Pichia* basal salt medium containing 1% glycerol (BMG, per liter: 85% phosphoric acid 26.7 ml, calcium sulfate 0.93 g, potassium sulfate 18.2 g, magnesium sulfate-heptahydrate 14.9 g, potassium hydroxide 4.13 g, glycerol 10.0 g, distilled, deionized water to 1 liter) overnight at 30°C and 250 rpm, expanded to 50 ml BMG (24 hrs) and finally expanded to 300 ml BMG (24 hrs). The inoculation culture was centrifuged at 2500×g 25°C and resuspended in 30 ml BMG. The 30 ml inoculation culture was used to inoculate 1 L of minimal *Pichia* basal salt medium containing 40 g of glycerol. Dissolved O_2 concentration was maintained at 40%, the temperature at 30°C and the pH at 5.0 using 2 M KOH. Initial feeds were batch glycerol feeds; transition to methanol was eased by a methanol injection

before an exponential methanol feed profile was initiated. Methanol induction lasted for two days, after which the culture was centrifuged to remove cellular debris. The supernatant was exchanged into 10 mM formate pH 4.0 before being passed over an SP-Sepharose column (2 × 5 mL SP HiTrap™ columns, GE Biosciences, Pittsburgh, PA) followed by a CR2 affinity column, generated in-house by binding GST-C3d to a GSTrap™ column (GE Biosciences, Pittsburgh, PA). CR2 was eluted along an increasing linear NaCl gradient, 0-1.0 M in 1/3X Phosphate Buffered Saline (PBS, 1.6 mM $MgCl_2$, 0.9 mM KCl, 0.5 mM KH_2PO_4, 45.6 mM NaCl, 2.7 mM Na_2HPO_4 pH 7.4). Finally, CR2 SCR1-2 was purified by size exclusion chromatography. Purity and identity of CR2 was monitored via SDS-PAGE, Western blot analysis and mass spectrometry. Both ^{15}N and ^{15}N-^{13}C isotopically labeled proteins were prepared using this strategy. For 15N isotopically labeled CR2 15N-Ammonium sulfate was used. For ^{15}N-^{13}C isotopically labeled CR2 ^{15}N -Ammonium sulfate, ^{13}C -glycerol and ^{13}C -methanol were used. Isotopically enriched chemicals were purchased from Isotec Inc., Miamisburg, OH.

[0165] Human CR2 SCR1-2 for ITC studies was generated using the pMAL-P2X™ expression system (New England Biolabs, Ipswich, MA) in *E. coli* as previously described (42, 43). Ampicillin-resistant colonies were used to start overnight cultures that were expanded to 1 L and grown at 37°C until an A_{600} of 0.3 was obtained. Cultures were induced with 0.3 mM isopropyl-β-D-thiogalactoside (IPTG) at 30°C overnight before harvesting by centrifugation. Harvested pellets were resuspended in amylose column buffer (20 mM Tris-HCl, pH 7.4, 0.2 M NaCl, 1 mM EDTA) and lysed by sonication. Lysate was clarified by centrifugation and applied to an amylose resin column (New England Biosciences, Ipswich, MA). Bound MBP-CR2 SCR1-2 was eluted from the column using amylose column elution buffer (amylose column buffer plus 10 mM maltose). Finally, the MBP-CR2 SCR1-2 was purified by size exclusion chromatography. Purity and identity of MBP-CR2 was monitored via SDS-PAGE and Western blot analysis.

[0166] Human C3d for ITC studies was generated using the pGEX™ expression system (GE Healthcare, Piscataway, NJ) in *E. coli* as previously described (47). Briefly, ampicillin-resistant colonies were used to start overnight cultures that were expanded to 1 L and grown at 37°C until an A_{600} of 0.3 was achieved. Cultures were induced with 0.3 mM IPTG at 30°C overnight before harvesting by centrifugation. Harvested pellets were resuspended in GST column buffer (50 mM Tris-HCl, pH 8.0, 250 mM NaCl, 1 mM EDTA) and lysed by sonication. Lysate was clarified by centrifugation and applied to a GSTrap™ column (GE

Biosciences, Pittsburgh, PA). C3d was cleaved from the column by digesting with 50 U of thrombin overnight at 4°C and subsequently purified by size exclusion chromatography. Purity of C3d was monitored via SDS-PAGE.

[0167] Purification of a truncated construct of EBV gp350 comprising residues 1-470 of the wild-type protein for NMR titrations and ITC studies was performed as previously described (46). gp350 was produced by infecting Sf9 insect cells with the gp350-packaged baculovirus particles (pVI-Bac Transfer vector, C-terminal polyhistidine tag) at a multiplicity of infection (MOI) of 3. The baculoviral supernatant was concentrated, buffered with 10 mM Tris-HCl with 10 mM imidazole pH 7.4 and applied to a 5 mL HiTrap™ column (GE Biosciences, Pittsburgh, PA) and subsequently eluted with a linear imidazole gradient. Purity and identity of gp350 were monitored via SDS-PAGE and Western blot analysis.

[0168] Human IFNα for NMR titrations and ITC studies was generated using the pMAL™ expression system (New England Biolabs, Ipswich, MA) in *E. coli* as previously described (48). Ampicillin-resistant colonies were used to start overnight cultures that were expanded to 1 L and grown at 37°C until an *A*600 of 0.3 was obtained. Cultures were induced with 0.3 mM IPTG at 25°C overnight before harvesting by centrifugation. Harvested pellets were resuspended in amylose column buffer (20 mM Tris-HCl, pH 7.4, 0.2 M NaCl, 1 mM EDTA) and lysed by sonication. Lysate was clarified by centrifugation and applied to an amylose resin column (New England Biosciences, Ipswich, MA). Bound MBP-IFNα was eluted from the column using amylose column elution buffer (amylose column buffer plus 10mM maltose). After elution the MBP tag was cleaved overnight at 4°C with Factor Xa (New England Biosciences, Ipswich, MA). Finally, IFNα was purified by size exclusion chromatography. Purity and identity of IFNα was monitored via SDS-PAGE and Western blot analysis.

NMR Analysis

[0169] NMR experiments were carried out on Varian 600, 800 and 900 MHz magnets housed in the Rocky Mountain Regional NMR facility at the University of Colorado Denver School of Medicine (UCDSOM) campus (600 and 900 MHz) and in the W. M. Keck High Field NMR Facility at the University of Colorado Boulder campus (800 MHz). The uniformly 15N-13C labeled SCR1-2 domains of CR2 in 1/3X PBS were used to sequentially assign the 15N-TROSY-HSQC (49) by using HNCACB (50), CBCA(CO)NH (51) and 15N edited NOESY-HSQC (52) three-dimensional spectra. The NMR data was processed with

nmrPipe (53) and analyzed with ccpNMR (54). Chemical shift changes were monitored using ccpNMR by overlaying TROSY-HSQC spectra from free CR2 SCR1-2 and CR2 SCR1-2 with increasing concentrations of either EBV gp350 or IFNα.

Isothermal Titration Calorimetry ("ITC") Analysis

[0170] ITC experiments were carried out on a Microcal VP-ITC (GE Healthcare, Piscataway, NJ) housed in the Biophysics Core facility on the UCDSOM campus. CR2 SCR1-2 in 1/3X PBS was used in titration experiments carried out at 20°C. Each titration experiment consisted of a 5 μl injection followed by 26 injections of 10 μl of graded concentrations of C3d, gp350 or IFNα. Data was analyzed using the software provided by the manufacturer (Origin, version 7.0 MicroCal) using either single site or two site binding models (55).

Chemical Shift Analysis

[0171] Using previously described resonance assignments (48), full-length ligands EBV gp350 and IFNα were titrated into uniformly ^{15}N-labeled CR2 SCR1-2 samples and the ^{1}H-^{15}N chemical shifts were monitored (Figures 1 - 3). Titration with EBV gp350 yielded a single mode of binding characterized by the disappearance and reappearance of specific resonances, indicative of a tight binding interaction. The residues on CR2 SCR1-2 exhibiting chemical shift changes with EBV gp350 were N11, R13, A22, R28, S32, R36, K41, K57, Y64, K67, Y68, R83, G84 and R89. Those residues encompass the SCR1, SCR2 and the inter-SCR linker region between SCR1-2 of CR2 (Figures 3 and 4A). Chemical shift change magnitudes are shown in Figure 3. These results suggest that the inter-SCR linker between SCR1-2 and a ridge on SCR1 play the most important role in ligating gp350 to CR2 (Figure 3). Since this interaction is under slow exchange on the NMR time scale, only an upper limit Kd can be calculated. The Kd was calculated using the minimal observed chemical shift difference between free and bound resonances (about 60 Hz); assuming a diffusion-limited on rate of ~10^{8} $M^{-1}s^{-1}$, an upper limit to the binding constant was calculated as ~60 μM (Table I).

[0172] Full length IFNα was also titrated into a uniformly ^{15}N-labeled CR2 SCR1-2 samples and the ^{1}H-^{15}N chemical shifts were monitored (Figure 2). Titration with the cytokine IFNα yielded a single mode of binding similar to that of gp350 ligation and thus a tight interaction. The residues on CR2 SCR1-2 exhibiting chemical shift changes are R13, Y16, R28, S42, K48, K50, Y68, R83, G84 and R89. These residues encompass the SCR1, SCR2 and the inter SCR linker region of CR2 (Figures 3 and 4B). Chemical shift change magnitudes are shown in figure 3. These results suggest that IFNα binding surface is similar to that of the

C3d binding surface (Figure 3). Similar to the gp350 chemical shift changes, the chemical shift changes for the IFNα suggest a tighter than visible via the NMR time scale; the upper limit Kd was calculated as before to be ~70 μM (Table I).

[0173] For comparison, unique and shared residues on CR2 required for ligation by C3d, gp350 and IFNα are shown in Figure 4C. Change in magnitude of chemical shift for each ligation state is shown in Figure 3.

Results

Chemical Shift Analysis

[0174] Using previously described resonance assignments (48), full-length ligands EBV gp350 and IFNα were titrated into uniformly ^{15}N-labeled CR2 SCR1-2 samples and the ^{1}H-^{15}N chemical shifts were monitored (Figures 1 - 3). Titration with EBV gp350 yielded a single mode of binding characterized by the disappearance and reappearance of specific resonances, indicative of a tight interaction. The residues on CR2 SCR1-2 exhibiting chemical shift changes are N11, R13, A22, R28, S32, R36, K41, K57, Y64, K67, Y68, R83, G84 and R89. These residues encompass the SCR1, SCR2 and the inter SCR linker region of CR2 (Figures 3 and 4A). Chemical shift change magnitudes are shown in Figure 3. These results suggest that the inter SCR linker and a ridge on SCR1 play the most important role in ligating gp350 to CR2 (Figure 3). Since this interaction is under slow exchange on the NMR time scale, only an upper limit Kd can be calculated. The Kd was calculated using the minimal observed chemical shift difference between free and bound resonances (about 60 Hz); assuming a diffusion-limited on rate of ~10 X 8 M-1s-1, an upper limit to the binding constant was calculated as ~60 μM (Table I).

[0175] Full length IFNα was also titrated into a uniformly ^{15}N-labeled CR2 SCR1-2 samples and the ^{1}H-^{15}N chemical shifts were monitored (Figure 2). Titration with the cytokine IFNα yielded a single mode of binding similar to that of gp350 ligation and thus a tight interaction. The residues on CR2 SCR1-2 exhibiting chemical shift changes are R13, Y16, R28, S42, K48, K50, Y68, R83, G84 and R89. These residues encompass the SCR1, SCR2 and the inter-SCR linker region between SCR1-2 of CR2 (Figures 3 and 4B). Chemical shift change magnitudes are shown in Figure 3. These results suggest that IFNα binding surface is similar to that of the C3d binding surface (Figure 3). Similar to the gp350 chemical shift changes, the chemical shift changes for the IFNα suggest a tighter binding interaction than visible via the NMR time scale; the upper limit Kd was calculated as before to be ~70 μM (Table I). For

comparison, unique and shared residues on CR2 required for ligation by C3d, gp350 and IFNα are shown in Figure 4C. Change in magnitude of chemical shift for each ligation state is shown in Figure 3.

Thermodynamics of CR2-ligand interactions

[0176] ITC was used to determine binding affinities of CR2-ligand interactions. Consistent with the NMR chemical shift analyses, the interaction between CR2 and C3d was determined to be a two site binding based on the goodness of fit of a two site binding model rather than a single site binding model. The two affinities are 0.13 ± 0.05 μM and 160 ± 20 μM. The interaction between CR2 and gp350 was fit using a single site binding model which yielded an affinity of 0.014 ± 0.009 μM. The interaction between CR2 and IFNα was fit using a single site binding model yielding an affinity of 0.035 ± 0.008 μM. The results of all thermodynamic parameters from NMR and ITC derived affinities are listed in Table 1.

Discussion

[0177] The studies described herein used two approaches to study CR2-ligand interactions with EBV gp350 and IFNα in the fluid phase: (1) NMR spectroscopy experiments in which full-length gp350 or IFNα was titrated into ^{15}N labeled CR2 SCR1-2 and chemical shifts were monitored; and (2) ITC to further characterize and determine binding constants for each CR2-ligand interaction.

[0178] Previous analyses showed that both SCR1 and 2 were needed for the binding of gp350 (1, 12, 20, 56, 57). Furthermore, it was also reported that specific areas of SCR1-2 were important in binding gp350 (20, 58). These areas were between the first and second, the second and third cysteine residues of SCR1, and the second half of SCR2; amino acids included R89 to R96 and T100 to S128 in SCR2 (58). Interactions with the linker was also inferred by the finding that the introduction of a glycosylation site into the linker eliminated gp350, but not C3d binding (20, 31, 57). More recently it has been shown that there are specific interacting amino acids on the surface of CR2 SCR1-2. Mutagenesis studies suggested that residues R13, S15, R28, R36, K41, K56, K67, R83 and R89 are the most important residues in the CR2-gp350 interaction (42, 43). In addition, using HADDOCK, a model of interaction was determined where the linker region between domains one and two of gp350 interacts with the linker between SCR1 and SCR2 of CR2 (43).

[0179] However, although there have been suggestions of important regions and more recently amino acids that are important in the interaction between CR2 and gp350, there has

been no physical evidence of these interactions occurring. The data described herein now illustrates amino acid residues important for the CR2-gp350 interaction (Figure 4A). Residues determined to be important to the CR2-gp350 interaction are N11, R13, A22, R28, S32, R36, K41, K57, Y64, K67, Y68, R83, G84 and R89. Since there are multiple interactions within the linker region it is possible to imagine a rearrangement of SCR domains about the linker region upon binding gp350 and thus allowing for all contact points to be met. If that is the case, some of these residues identified herein as important for interaction might be involved in structural rearrangement upon binding and not intimate amino acid contact sites. Some resonances disappear due to the large size of the ligated complex, approximately 110 kDa, and the resultant increased tumbling time; therefore, alternative labeling techniques are necessary to observe such resonances.

[0180] This data appears to confirm that the linker region is important in the CR2-gp350 interaction. The linker interaction has been shown to be important in mutagenesis-derived data as well as in the soft dock model from HADDOCK (43). The linker region between SCR1 and SCR2 is eight amino acids, one of the longest in SCR-containing proteins, and thus is likely to be flexible enough to mediate multiple ligand interactions. Unlike the CR2-C3d interaction, our data suggests that two residues in the linker region, K67 and Y68, are important in the CR2-gp350 interaction. Thus with both a charged residue, K67, and a hydroxyl-containing residue, Y68, it is likely that the interaction with the linker is stronger in the CR2-gp350 interaction than with the CR2-C3d interaction. This information provides a start to defining how CR2 can mediate multiple specific ligand interactions.

[0181] As with the CR2-C3d interaction (59, 60), the CR2-gp350 interaction is likely driven largely by electrostatic interactions as is evident by the large number of charged residues among those important in the CR2-gp350 interaction. The majority of these charged residues are found on SCR1, suggesting that this domain plays a more significant role in the CR2-gp350 interaction. Interestingly R83 was also determined to be important in the CR2-gp350, although many other residues around R83 were not shown to exhibit changes in chemical shift during the CR2-C3d interaction. This data, along with the weak interaction found in the CR2-C3d interaction could signify that the R83 interaction is more important in the initial electrostatic attraction of gp350 to CR2 than to significant amino-acid contacts. The charged residues that were identified in this study agree with the HADDOCK model (42, 43). Again, as with the CR2-C3d NMR binding map we have found that there are more residues than just charged residues involved in the CR2-gp350 interaction. Specifically, three hydroxyl-

containing amino acids (S32, Y64 and Y68) are important in the CR2-gp350 interaction. These side chain interactions are likely hydrogen bond interactions. This new data suggests that the CR2-gp350 and CR2-C3d binding sites are likely similar which explains why the ligands cross compete, yet there are substantial differences which begin to explain how selective binding occurs.

[0182] The HADDOCK model fits well with the NMR determined CR2-gp350 binding residues (Figure 5). All but two residues, K57 and A22, are found within the hypothetical binding face derived from the HADDOCK model. The A22 chemical shift could likely be due to a slight conformation change in SCR1 upon CR2 binding gp350. Whereas the K57 interaction described by NMR could be used to drive a different and potentially lower energy docking model, as it was not utilized as an active residue in the simulated docking approach of Young, *et al* (43).

[0183] The CR2-IFNα interaction has been characterized in several ways. The first started with investigating sequence similarities between proposed CR2 binding sites on C3d and gp350 (19). To further confirm the potential binding interaction, antibodies raised against peptide sequences of the proposed CR2 binding site on IFNα were found to inhibit the CR2-C3d interaction in cell binding assays. It was also found that IFNα binding to CR2 inhibits CR2-C3d complex formation in cell-binding assays. In addition, it was found that IFNα inhibited the capping of CR2 by gp350, thus acting as an anti-viral inhibitor of early phase infection from EBV (18). More recently a biophysical study has been completed on the thermodynamic properties of CR2-ligand interactions, thus indicating the physical binding of CR2 and IFNα (17). The data presented herein further defines a binding site or binding surface for the CR2-IFNα interaction. Using NMR titration studies, the following amino acids were identified as being involved in the CR2-IFNα interaction—R13, Y16, R28, S42, K48, K50, Y68, R83, G84 and R89.

[0184] As with other CR2-ligand interactions, the CR2-IFNα interaction is largely driven by electrostatic interactions. The CR2-IFNα interaction is likely the closest related to the C3d interaction, since the proposed CR2 binding motifs of C3d and IFNα are the closest. In addition, the same linker region residue, Y68, appears to undergo significant perturbations upon addition of either C3d and IFNα, as well as the same overall layout of residues involved in both interactions (Figure 4C).

[0185] Thermodynamic studies of CR2-ligand interactions have yielded slightly differing results (Table 2). As reported previously, the CR2-C3d interaction has been described as

either being a two site or a single site binding interaction (17, 48). The ITC data presented herein best fit a two-site model with a weaker Kd of 160 μM and a tighter interaction of 0.13 μM. This Kd is fairly close to the previously determined Kd from a surface plasmon resonance (SPR)-based biophysical study (17). Using ITC, we are now able for the first time to measure in the fluid phase the two separate affinities for the two unique binding events. The CR2-C3d interaction is unique in that all other characterized CR2-ligand interactions fit a simple one to one binding isotherm. In contrast, the current ITC study of the CR2-gp350 interaction best fit a single binding isotherm with a Kd of 0.014 μM, an affinity only slightly tighter than the previously reported Kd of 0.077 μM determined by SPR. The difference in affinities here could be due to the differing experimental conditions of the respective studies. Finally, the ITC data for the CR2-IFNα interaction best fit a single binding isotherm with a Kd of 0.036 μM, an affinity in excellent agreement with the previously reported Kd of 0.042 μM determined by SPR. Again, the difference is likely due to the difference in buffers used as well as differences in each assay, with the ITC experiments using CR2 and IFNα purely in solution, while the SPR studies used CR2 fixed to a solid support. The rank order of binding strength makes sense in that both IFNα and gp350 binding both inhibit C3d binding to CR2, which has been previously reported (17, 18).

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EXAMPLE 2: BINDING ASSAYS.

Experimental Methods

Expression and purification of recombinant proteins.

[0186] Native human and mutagenized CR2 SCR1-2 for binding studies is expressed in *Pichia pastoris* using a BioFlo™ 110 Fermenter (New Brunswick Scientific, Edison, NJ) as

previously described (46) and as set forth in Example 1 above. Briefly, a single colony is grown up in 5 ml *Pichia* basal salt medium containing 1% glycerol (BMG, per liter: 85% phosphoric acid 26.7 ml, calcium sulfate 0.93 g, potassium sulfate 18.2 g, magnesium sulfate-$7H_2O$ 14.9 g, potassium hydroxide 4.13 g, glycerol 10.0 g, distilled, deionized water to 1 liter) overnight at 30°C and 250 rpm, expanded to 50 ml BMG (24 hrs) and finally expanded to 300 ml BMG (24 hrs). The inoculation culture is centrifuged at 2500×g 25°C and resuspended in 30 ml BMG. The 30 ml inoculation culture is used to inoculate 1 L of minimal *Pichia* basal medium containing 40 g of glycerol. Dissolved O_2 concentration is maintained at 40%, the temperature at 30°C and the pH at 5.0 using 2 M KOH. Initial feeds are batch glycerol feeds; transition to methanol is eased by a methanol injection before an exponential methanol feed profile is initiated. Methanol induction lasts for two days, after which the culture is centrifuged to remove cellular debris. The supernatant is exchanged into 10 mM Formate pH 4.0 before being passed over an SP-Sepharose column (2 × 5 mL SP HiTrap™ columns, GE Biosciences, Pittsburgh, PA) followed by a CR2 affinity column, generated in-house by binding GST-C3d to a GSTrap™ column (GE Biosciences, Pittsburgh, PA). CR2 is eluted along an increasing linear NaCl gradient, 0-1.0 M in 1/3X Phosphate Buffered Saline (PBS, 1.6 mM $MgCl_2$, 0.9 mM KCl, 0.5 mM KH_2PO_4, 45.6 mM NaCl, 2.7 mM Na_2HPO_4 pH 7.4). Finally, native human and mutant CR2 SCR1-2 is purified by size exclusion chromatography. Purity and identity of CR2 is monitored via SDS-PAGE, Western blot analysis and mass spectrometry.

[0187] Human C3d for binding studies is generated using the pGEX™ expression system (GE Healthcare, Piscataway, NJ) in *E. coli* as previously described (47) and as set forth in Example 1 above. Briefly, ampicillin-resistant colonies are used to start overnight cultures that are expanded to 1 L and grown at 37°C until an A_{600} of 0.3 is achieved. Cultures are induced with 0.3 mM IPTG at 30°C overnight before harvesting by centrifugation. Harvested pellets are resuspended in GST column buffer (50 mM Tris-HCl, pH 8.0, 250 mM NaCl, 1 mM EDTA) and lysed by sonication. Lysate is clarified by centrifugation and applied to a GSTrap™ column (GE Biosciences, Pittsburgh, PA). C3d is cleaved from the column by digesting with 50 U of thrombin overnight at 4°C and subsequently purified by size exclusion chromatography. Purity of C3d is monitored via SDS-PAGE.

[0188] EBV gp350 is isolated from infected cells in culture by immunoaffinity chromatography using commercially available anti-gp350 antibodies and standard procedures. Human IFNα is purchased from commercial suppliers.

Binding assays.

[0189] Binding of native human CR2 SCR1-2 to EBV gp350, IFNα, and C3d is compared to that of human CR2 SCR1-2 variants containing one or more mutations in amino acids determined to be essential for binding interactions between CR2 and either EBV gp350 or IFNα by enzyme-linked immunosorbent assay (ELISA). Initial binding assays are performed with alanine-containing CR2 variants because it eliminates the side chain beyond the β-carbon of the amino acid without altering the main chain conformation (as glycine or proline sometimes does) or imposing extreme electrostatic or steric effects. The following CR2 SCR1-2 variants are tested for binding to EBV gp350 and to C3d in separate experiments: SCR1-2 N11A, SCR1-2 N11A + R36A, SCR1-2 N11A + R36A + K41A, SCR1-2 N11A + R36A + K41A + Y64A, and SCR1-2 N11A + R36A + K41A + Y64A + K67A. The following CR2 SCR1-2 variants are tested for binding to IFNα and C3d in separate experiments: S42A and S42A + K50A. The effect of the amino acid substitutions on CR2 binding kinetics and other properties (*e.g.*, binding specificity) is assessed by comparing the binding of CR2 SCR1-2 variants to either EBV gp350 or IFNα and C3d to binding of native CR2 SCR1-2 to the same ligands. Alternative conservative or non-conservative amino acid substitutions are tested in subsequent experiments.

[0190] Microwell ELISA plates (Corning Life Sciences, New York, N.Y., USA) are coated overnight at 4°C with an appropriate amount of purified EBV gp350, IFNα, or C3d obtained as described above in 0.1 M $NaHCO_3$, pH 8.6. The coated plates are then washed with 1X PBS three times for one minute each, and then incubated with 200 µl of blocking solution (5 mg/ml bovine serum albumin (BSA) in PBST) at 37°C for 1 hour. Each well is washed with PBST (80 mM Na_2HPO_4, 20 mM NaH_2PO_4, 100 mM NaCl, 0.05%-0.1% (v/v) Tween-20) six times for one minute each. Next, the plates are incubated with increasing concentrations of native human CR2 SCR1-2 and various CR2 SCR1-2 variants in PBS for 1 hour and 30 minutes at 37°C.

[0191] After the binding reaction is complete, the plates are again washed with PBST six times for one minute each. Next, the plates are incubated with anti-CR2 primary antibody, washed six times for one minute each with blocking solution, and then incubated with the secondary antibody, horseradish peroxidase-conjugated mouse anti-human IgG specific for Fcγ (Jackson ImmunoResearch Laboratories, Inc.) diluted 1:10,000 in PBST+5 mg/ml BSA, at room temperature for 1 hour. The plates are again washed six times with PBST+5 mg/ml

BSA at room temperature, and developed by the addition of 100 μl of 3,3',5,5'-tetramethylbenzidine (TMB) solution, prepared in 50 mM citrate phosphate. After the addition of the TMB solution, the plates are incubated for thirty minutes at room temperature, and then absorbance is measured at 450 nm with an MRX Microplate Reader (Dynex Technologies) according to the manufacturer's instructions. Binding curves are constructed from the raw data, and binding affinities are estimated.

[0192] Alternatively, binding affinities are determined more precisely by surface plasmon resonance analysis using, for example, a BIACore™ 4000 SPR system (Biacore Life Sciences, GE Healthcare, Piscataway, NJ). Like the ELISA, microwell plates are coated with either EBV gp350, IFNα, or C3d, and then incubated with increasing concentrations of native human CR2 SCR1-2 or the CR2 SCR1-2 variants. Unlike ELISAs, however, SPR measures binding affinities directly, and does not require use of a detectable label.

[0193] The SCR1-2 N11A, SCR1-2 N11A + R36A, SCR1-2 N11A + R36A + K41A, SCR1-2 N11A + R36A + K41A + Y64A, and SCR1-2 N11A + R36A + K41A + Y64A + K67A variants are tested for binding affinity for EBV gp350 and are observed to have progressively less binding affinity for EBV gp350 while maintaining essentially the same binding affinity for C3d as native CR2 SCR1-2. The SCR1-2 S42A and SCR1-2 S42A + K50A variants are tested for binding affinity for IFNα and are observed to have progressively less binding affinity for IFNα while maintaining essentially the same binding affinity for C3d as native CR2 SCR1-2.

SEQUENCES

SEQ ID NO:1 [complete amino acid sequence of human complement receptor 2 (CR2)]:

MGAAGLLGVFLALVAPGVLGISCGSPPPILNGRISYYSTPIAVGTVIRYSCSGTFRLIGE
KSLLCITKDKVDGTWDKPAPKCEYFNKYSSCPEPIVPGGYKIRGSTPYRHGDSVTFAC
KTNFSMNGNKSVWCQANNMWGPTRLPTCVSVFPLECPALPMIHNGHHTSENVGSIA
PGLSVTYSCESGYLLVGEKIINCLSSGKWSAVPPTCEEARCKSLGRFPNGKVKEPPILR
VGVTANFFCDEGYRLQGPPSSRCVIAGQGVAWTKMPVCEEIFCPSPPPILNGRHIGNS
LANVSYGSIVTYTCDPDPEEGVNFILIGESTLRCTVDSQKTGTWSGPAPRCELSTSAV
QCPHPQILRGRMVSGQKDRYTYNDTVIFACMFGFTLKGSKQIRCNAQGTWEPSAPV
CEKECQAPPNILNGQKEDRHMVRFDPGTSIKYSCNPGYVLVGEESIQCTSEGVWTPP
VPQCKVAACEATGRQLLTKPQHQFVRPDVNSSCGEGYKLSGSVYQECQGTIPWFME
IRLCKEITCPPPPVIYNGAHTGSSLEDFPYGTTVTYTCNPGPERGVEFSLIGESTIRCTSN

DQERGTWSGPAPLCKLSLLAVQCSHVHIANGYKISGKEAPYFYNDTVTFKCYSGFTL
KGSSQIRCKRDNTWDPEIPVCEKGCQPPPGLHHGRHTGGNTVFFVSGMTVDYTCDP
GYLLVGNKSIHCMPSGNWSPSAPRCEETCQHVRQSLQELPAGSRVELVNTSCQDGY
QLTGHAYQMCQDAENGIWFKKIPLCKVIHCHPPPVIVNGKHTGMMAENFLYGNEVS
YECDQGFYLLGEKNCSAEVILKAWILERAFPQCLRSLCPNPEVKHGYKLNKTHSAYS
HNDIVYVDCNPGFIMNGSRVIRCHTDNTWVPGVPTCIKKAFIGCPPPPKTPNGNHTGG
NIARFSPGMSILYSCDQGYLVVGEPLLLCTHEGTWSQPAPHCKEVNCSSPADMDGIQ
KGLEPRKMYQYGAVVTLECEDGYMLEGSPQSQCQSDHQWNPPLAVCRSRSLAPVL
CGIAAGLILLTFLIVITLYVISKHRERNYYTDTSQKEAFHLEAREVYSVDPYNPAS

SEQ ID NO:2 [amino acid sequence of short consensus repeat (SCR) domains 1 and 2 of human CR2]:
ISCGSPPPILNGRISYYSTPIAVGTVIRYSCSGTFRLIGEKSLLCITKDKVDGTWDKPAP
KCEYFNKYSSCPEPIVPGGYKIRGSTPYRHGDSVTFACKTNFSMNGNKSVWCQANN
MWGPTRLPTCVS

SEQ ID NO:3 [amino acid sequence of human CD59 protein]:
MGIQGGSVLFGLLLVLAVFCHSGHSLQCYNCPNPTADCKTAVNCSSDFDACLITKAG
LQVYNKCWKFEHCNFNDVTTRLRENELTYYCCKKDLCNFNEQLENGGTSLSEKTVL
LLVTPFLAAAWSLHP

SEQ ID NO:4 [amino acid sequence of mouse complement receptor 1-related gene/protein y (Crry)]:
MEVSSRSSEPLDPVWLLVAFGRGGVKLEVLLLFLLPFTLGELRGGLGKHGHTVHREP
AVNRLCADSKRWSGLPVSAQRPFPMGHCPAPSQLPSAKPINLTDESMFPIGTYLLYEC
LPGYIKRQFSITCKQDSTWTSAEDKCIRKQCKTPSDPENGLVHVHTGIQFGSRINYTC
NQGYRLIGSSSAVCVITDQSVDWDTEAPICEWIPCEIPPGIPNGDFFSSTREDFHYGMV
VTYRCNTDARGKALFNLVGEPSLYCTSNDGEIGVWSGPPPQCIELNKCTPPPYVENA
VMLSENRSLFSLRDIVEFRCHPGFIMKGASSVHCQSLNKWEPELPSCFKGVICRLPQE
MSGFQKGLGMKKEYYYGENVTLECEDGYTLEGSSQSQCQSDGSWNPLLAKCVSRSI
SGLIVGIFIGIIVFILVIIVFIWMILKYKKRNTTDEKYKEVGIHLNYKEDSCVRLQSLLTS
QENSSTTSPARNSLTQEVS

SEQ ID NO:5 [amino acid sequence of human factor H]:
MRLLAKIICLMLWAICVAEDCNELPPRRNTEILTGSWSDQTYPEGTQAIYKCRPGYRS

LGNVIMVCRKGEWVALNPLRKCQKRPCGHPGDTPFGTFTLTGGNVFEYGVKAVYT
CNEGYQLLGEINYRECDTDGWTNDIPICEVVKCLPVTAPENGKIVSSAMEPDREYHF
GQAVRFVCNSGYKIEGDEEMHCSDDGFWSKEKPKCVEISCKSPDVINGSPISQKIIYK
ENERFQYKCNMGYEYSERGDAVCTESGWRPLPSCEEKSCDNPYIPNGDYSPLRIKHR
TGDEITYQCRNGFYPATRGNTAKCTSTGWIPAPRCTLKPCDYPDIKHGGLYHENMRR
PYFPVAVGKYYSYYCDEHFETPSGSYWDHIHCTQDGWSPAVPCLRKCYFPYLENGY
NQNYGRKFVQGKSIDVACHPGYALPKAQTTVTCMENGWSPTPRCIRVKTCSKSSIDI
ENGFISESQYTYALKEKAKYQCKLGYVTADGETSGSITCGKDGWSAQPTCIKSCDIPV
FMNARTKNDFTWFKLNDTLDYECHDGYESNTGSTTGSIVCGYNGWSDLPICYEREC
ELPKIDVHLVPDRKKDQYKVGEVLKFSCKPGFTIVGPNSVQCYHFGLSPDLPICKEQV
QSCGPPPELLNGNVKEKTKEEYGHSEVVEYYCNPRFLMKGPNKIQCVDGEWTTLPV
CIVEESTCGDIPELEHGWAQLSSPPYYYGDSVEFNCSESFTMIGHRSITCIHGVWTQLP
QCVAIDKLKKCKSSNLIILEEHLKNKKEFDHNSNIRYRCRGKEGWIHTVCINGRWDPE
VNCSMAQIQLCPPPPQIPNSHNMTTTLNYRDGEKVSVLCQENYLIQEGEEITCKDGR
WQSIPLCVEKIPCSQPPQIEHGTINSSRSSQESYAHGTKLSYTCEGGFRISEENETTCYM
GKWSSPPQCEGLPCKSPPEISHGVVAHMSDSYQYGEEVTYKCFEGFGIDGPAIAKCL
GEKWSHPPSCIKTDCLSLPSFENAIPMGEKKDVYKAGEQVTYTCATYYKMDGASNV
TCINSRWTGRPTCRDTSCVNPPTVQNAYIVSRQMSKYPSGERVRYQCRSPYEMFGDE
EVMCLNGNWTEPPQCKDSTGKCGPPPPIDNGDITSFPLSVYAPASSVEYQCQNLYQL
EGNKRITCRNGQWSEPPKCLHPCVISREIMENYNIALRWTAKQKLYSRTGESVEFVC
KRGYRLSSRSHTLRTTCWDGKLEYPTCAKR

SEQ ID NO:6 [amino acid sequence of mouse CD59A protein]:
MRAQRGLILLLLLLAVFCSTAVSLTCYHCFQPVVSSCNMNSTCSPDQDSCLYAVAG
MQVYQRCWKQSDCHGEIIMDQLEETKLKFRCCQFNLCNKSDGSLGKTPLLGTSVLV
AILNLCFLSHL

SEQ ID NO:7 [amino acid sequence of mouse CD59B protein]:
MRAQRGLILLLLLLAVFCSTAVSLKCYNCFQFVSSCKINTTCSPNLDSCLYAVAGRQ
VYQQCWKLSDCNSNYIMSRLDVAGIQSKCCQWGLCNKNLDGLEEPNNAETSSLRKT
ALLGTSVLVAILKFCF

SEQ ID NO:8 [amino acid sequence of mouse factor H]:
MRLSARIIWLILWTVCAAEDCKGPPPRENSEILSGSWSEQLYPEGTQATYKCRPGYRT

LGTIVKVCKNGKWVASNPSRICRKKPCGHPGDTPFGSFRLAVGSQFEFGAKVVYTCD
DGYQLLGEIDYRECGADGWINDIPLCEVVKCLPVTELENGRIVSGAAETDQEYYFGQ
VVRFECNSGFKIEGHKEIHCSENGLWSNEKPRCVEILCTPPRVENGDGINVKPVYKEN
ERYHYKCKHGYVPKERGDAVCTGSGWSSQPFCEEKRCSPPYILNGIYTPHRIIHRSDD
EIRYECNYGFYPVTGSTVSKCTPTGWIPVPRCTLKPCEFPQFKYGRLYYEESLRPNFP
VSIGNKYSYKCDNGFSPPSGYSWDYLRCTAQGWEPEVPCVRKCVFHYVENGDSAY
WEKVYVQGQSLKVQCYNGYSLQNGQDTMTCTENGWSPPPKCIRIKTCSASDIHIDN
GFLSESSSIYALNRETSYRCKQGYVTNTGEISGSITCLQNGWSPQPSCIKSCDMPVFEN
SITKNTRTWFKLNDKLDYECLVGFENEYKHTKGSITCTYYGWSDTPSCYERECSVPT
LDRKLVVSPRKEKYRVGDLLEFSCHSGHRVGPDSVQCYHFGWSPGFPTCKGQVASC
APPLEILNGEINGAKKVEYSHGEVVKYDCKPRFLLKGPNKIQCVDGNWTTLPVCIEEE
RTCGDIPELEHGSAKCSVPPYHHGDSVEFICEENFTMIGHGSVSCISGKWTQLPKCVA
TDQLEKCRVLKSTGIEAIKPKLTEFTHNSTMDYKCRDKQEYERSICINGKWDPEPNCT
SKTSCPPPPQIPNTQVIETTVKYLDGEKLSVLCQDNYLTQDSEEMVCKDGRWQSLPR
CIEKIPCSQPPTIEHGSINLPRSSEERRDSIESSSHEHGTTFSYVCDDGFRIPEENRITCYM
GKWSTPPRCVGLPCGPPPSIPLGTVSLELESYQHGEEVTYHCSTGFGIDGPAFIICEGG
KWSDPPKCIKTDCDVLPTVKNAIIRGKSKKSYRTGEQVTFRCQSPYQMNGSDTVTCV
NSRWIGQPVCKDNSCVDPPHVPNATIVTRTKNKYLHGDRVRYECNKPLELFGQVEV
MCENGIWTEKPKCRDSTGKCGPPPPIDNGDITSLSLPVYEPLSSVEYQCQKYYLLKGK
KTITCTNGKWSEPPTCLHACVIPENIMESHNIILKWRHTEKIYSHSGEDIEFGCKYGYY
KARDSPPFRTKCINGTINYPTCV

SEQ ID NO:9 [amino acid sequence of human complement receptor 1 (CR1)]:
MGASSPRSPEPVGPPAPGLPFCCGGSLLAVVVLLALPVAWGQCNAPEWLPFARPTNL
TDEFEFPIGTYLNYECRPGYSGRPFSIICLKNSVWTGAKDRCRRKSCRNPPDPVNGMV
HVIKGIQFGSQIKYSCTKGYRLIGSSSATCIISGDTVIWDNETPICDRIPCGLPPTITNGD
FISTNRENFHYGSVVTYRCNPGSGGRKVFELVGEPSIYCTSNDDQVGIWSGPAPQCIIP
NKCTPPNVENGILVSDNRSLFSLNEVVEFRCQPGFVMKGPRRVKCQALNKWEPELPS
CSRVCQPPPDVLHAERTQRDKDNFSPGQEVFYSCEPGYDLRGAASMRCTPQGDWSP
AAPTCEVKSCDDFMGQLLNGRVLFPVNLQLGAKVDFVCDEGFQLKGSSASYCVLAG
MESLWNSSVPVCEQIFCPSPPVIPNGRHTGKPLEVFPFGKAVNYTCDPHPDRGTSFDLI
GESTIRCTSDPQGNGVWSSPAPRCGILGHCQAPDHFLFAKLKTQTNASDFPIGTSLKY
ECRPEYYGRPFSITCLDNLVWSSPKDVCKRKSCKTPPDPVNGMVHVITDIQVGSRINY
SCTTGHRLIGHSSAECILSGNAAHWSTKPPICQRIPCGLPPTIANGDFISTNRENFHYGS

VVTYRCNPGSGGRKVFELVGEPSIYCTSNDDQVGIWSGPAPQCIIPNKCTPPNVENGI
LVSDNRSLFSLNEVVEFRCQPGFVMKGPRRVKCQALNKWEPELPSCSRVCQPPPDVL
HAERTQRDKDNFSPGQEVFYSCEPGYDLRGAASMRCTPQGDWSPAAPTCEVKSCDD
FMGQLLNGRVLFPVNLQLGAKVDFVCDEGFQLKGSSASYCVLAGMESLWNSSVPV
CEQIFCPSPPVIPNGRHTGKPLEVFPFGKAVNYTCDPHPDRGTSFDLIGESTIRCTSDPQ
GNGVWSSPAPRCGILGHCQAPDHFLFAKLKTQTNASDFPIGTSLKYECRPEYYGRPFS
ITCLDNLVWSSPKDVCKRKSCKTPPDPVNGMVHVITDIQVGSRINYSCTTGHRLIGHS
SAECILSGNTAHWSTKPPICQRIPCGLPPTIANGDFISTNRENFHYGSVVTYRCNLGSR
GRKVFELVGEPSIYCTSNDDQVGIWSGPAPQCIIPNKCTPPNVENGILVSDNRSLFSLN
EVVEFRCQPGFVMKGPRRVKCQALNKWEPELPSCSRVCQPPPEILHGEHTPSHQDNF
SPGQEVFYSCEPGYDLRGAASLHCTPQGDWSPEAPRCAVKSCDDFLGQLPHGRVLFP
LNLQLGAKVSFVCDEGFRLKGSSVSHCVLVGMRSLWNNSVPVCEHIFCPNPPAILNG
RHTGTPSGDIPYGKEISYTCDPHPDRGMTFNLIGESTIRCTSDPHGNGVWSSPAPRCEL
SVRAGHCKTPEQFPFASPTIPINDFEFPVGTSLNYECRPGYFGKMFSISCLENLVWSSV
EDNCRRKSCGPPPEPFNGMVHINTDTQFGSTVNYSCNEGFRLIGSPSTTCLVSGNNVT
WDKKAPICEIISCEPPPTISNGDFYSNNRTSFHNGTVVTYQCHTGPDGEQLFELVGERS
IYCTSKDDQVGVWSSPPPRCISTNKCTAPEVENAIRVPGNRSFFSLTEIIRFRCQPGFV
MVGSHTVQCQTNGRWGPKLPHCSRVCQPPPEILHGEHTLSHQDNFSPGQEVFYSCEP
SYDLRGAASLHCTPQGDWSPEAPRCTVKSCDDFLGQLPHGRVLLPLNLQLGAKVSF
VCDEGFRLKGRSASHCVLAGMKALWNSSVPVCEQIFCPNPPAILNGRHTGTPFGDIP
YGKEISYACDTHPDRGMTFNLIGESSIRCTSDPQGNGVWSSPAPRCELSVPAACPHPP
KIQNGHYIGGHVSLYLPGMTISYTCDPGYLLVGKGFIFCTDQGIWSQLDHYCKEVNC
SFPLFMNGISKELEMKKVYHYGDYVTLKCEDGYTLEGSPWSQCQADDRWDPPLAK
CTSRAHDALIVGTLSGTIFFILLIIFLSWIILKHRKGNNAHENPKEVAIHLHSQGGSSVH
PRTLQTNEENSRVLP

SEQ ID NO:10 [amino acid sequence of human membrane cofactor protein (MCP)]:
MEPPGRRECPFPSWRFPGLLLAAMVLLLYSFSDACEEPPTFEAMELIGKPKPYYEIGE
RVDYKCKKGYFYIPPLATHTICDRNHTWLPVSDDACYRETCPYIRDPLNGQAVPANG
TYEFGYQMHFICNEGYYLIGEEILYCELKGSVAIWSGKPPICEKVLCTPPPKIKNGKHT
FSEVEVFEYLDAVTYSCDPAPGPDPFSLIGESTIYCGDNSVWSRAAPECKVVKCRFPV
VENGKQISGFGKKFYYKATVMFECDKGFYLDGSDTIVCDSNSTWDPPVPKCLKVLPP
SSTKPPALSHSVSTSSTTKSPASSASGPRPTYKPPVSNYPGYPKPEEGILDSLDVWVIA
VIVIAIVVGVAVICVVPYRYLQRRKKKGTYLTDETHREVKFTSL

SEQ ID NO:11 [amino acid sequence of human decay accelerating factor (DAF/CD55)]:
MTVARPSVPAALPLLGELPRLLLLVLLCLPAVWGDCGLPPDVPNAQPALEGRTSFPE
DTVITYKCEESFVKIPGEKDSVICLKGSQWSDIEEFCNRSCEVPTRLNSASLKQPYITQ
NYFPVGTVVEYECRPGYRREPSLSPKLTCLQNLKWSTAVEFCKKKSCPNPGEIRNGQI
DVPGGILFGATISFSCNTGYKLFGSTSSFCLISGSSVQWSDPLPECREIYCPAPPQIDNGI
IQGERDHYGYRQSVTYACNKGFTMIGEHSIYCTVNNDEGEWSGPPPECRGKSLTSKV
PPTVQKPTTVNVPTTEVSPTSQKTTTKTTTPNAQATRSTPVSRTTKHFHETTPNKGSG
TTSGTTRLLSGHTCFTLTGLLGTLVTMGLLT

SEQ ID NO:12 [amino acid sequence of mouse decay accelerating factor (DAF/CD55)]:
MIRGRAPRTRPSPPPPLLPLLSLSLLLLSPTVRGDCGPPPDIPNARPILGRHSKFAEQSK
VAYSCNNGFKQVPDKSNIVVCLENGQWSSHETFCEKSCVAPERLSFASLKKEYLNM
NFFPVGTIVEYECRPGFRKQPPLPGKATCLEDLVWSPVAQFCKKKSCPNPKDLDNGH
INIPTGILFGSEIFNSCNPGYRLVGVSSTFCSVTGNTVDWDDEFPVCTEIHCPEPPKINN
GIMRGESDSYTYSQVVTYSCDKGFILVGNASIYCTVSKSDVGQWSSPPPRCIEKSKVP
TKKPTINVPSTGTPSTPQKPTTESVPNPGDQPTPQKPSTVKVSATQHVPVTKTTVRHPI
RTSTDKGEPNTGGDRYIYGHTCLITLTVLHVMLSLIGYLT

SEQ ID NO:13 [amino acid sequence of CVF from *Naja kaouthia*]:
MERMALYLVAALLIGFPGSSHGALYTLITPAVLRTDTEEQILVEAHGDSTPKQLDIFV
HDFPRKQKTLFQTRVDMNPAGGMLVTPTIEIPAKEVSTDSRQNQYVVVQVTGPQVR
LEKVVLLSYQSSFLFIQTDKGIYTPGSPVLYRVFSMDHNTSKMNKTVIVEFQTPEGILV
SSNSVDLNFFWPYNLPDLVSLGTWRIVAKYEHSPENYTAYFDVRKYVLPSFEVRLQP
SEKFFYIDGNENFHVSITARYLYGEEVEGVAFVLFGVKIDDAKKSIPDSLTRIPIIDGDG
KATLKRDTFRSRFPNLNELVGHTLYASVTVMTESGSDMVVTEQSGIHIVASPYQIHFT
KTPKYFKPGMPYELTVYVTNPDGSPAAHVPVVSEAFHSMGTTLSDGTAKLILNIPLN
AQSLPITVRTNHGDLPRERQATKSMTAIAYQTQGGSGNYLHVAITSTEIKPGDNLPVN
FNVKGNANSLKQIKYFTYLILNKGKIFKVGRQPRRDGQNLVTMNLHITPDLIPSFRFV
AYYQVGNNEIVADSVWVDVKDTCMGTLVVKGDNLIQMPGAAMKIKLEGDPGARV
GLVAVDKAVYVLNDKYKISQAKIWDTIEKSDFGCTAGSGQNNLGVFEDAGLALTTS
TNLNTKQRSAAKCPQPANRRRRSSVLLLDSNASKAAEFQDQDLRKCCEDVMHENP
MGYTCEKRAKYIQEGDACKAAFLECCRYIKGVRDENQRESELFLARDDNEDGFIADS
DIISRSDFPKSWLWLTKDLTEEPNSQGISSKTMSFYLRDSITTWVVLAVSFTPTKGICV
AEPYEIRVMKVFFIDLQMPYSVVKNEQVEIRAILHNYVNEDIYVRVELLYNPAFCSAS

TKGQRYRQQFPIKALSSRAVPFVIVPLEQGLHDVEIKASVQEALWSDGVRKKLKVVP
EGVQKSIVTIVKLDPRAKGVGGTQLEVIKARKLDDRVPDTEIETKIIIQGDPVAQIIENS
IDGSKLNHLIITPSGCGEQNMIRMAAPVIATYYLDTTEQWETLGINRRTEAVNQIVTG
YAQQMVYKKADHSYAAFTNRASSSWLTAYVVKVFAMAAKMVAGISHEIICGGVR
WLILNRQQPDGAFKENAPVLSGTMQGGIQGAEEEVYLTAFILVALLESKTICNDYVN
SLDSSIKKATNYLLKKYEKLQRPYTTALTAYALAAADQLNDDRVLMAASTGRDHW
EEYNAHTHNIEGTSYALLALLKMKKFDQTGPIVRWLTDQNFYGETYGQTQATVMAF
QALAEYEIQMPTHKDLNLDITIELPDREVPIRYRINYENALLARTVETKLNQDITVTAS
GDGKATMTILTFYNAQLQEKANVCNKFHLNVSVENIHLNAMGAKGALMLKICTRY
LGEVDSTMTIIDISMLTGFLPDAEDLTRLSKGVDRYISRYEVDNNMAQKVAVIIYLNK
VSHSEDECLHFKILKHFEVGFIQPGSVKVYSYYNLDEKCTKFYHPDKGTGLLNKICIG
NVCRCAGETCSSLNHQERIDVPLQIEKACETNVDYVYKTKLLRIEEQDGNDIYVMDV
LEVIKQGTDENPRAKTHQYISQRKCQEALNLKVNDDYLIWGSRSDLLPTKDKISYIIT
KNTWIERWPHEDECQEEEFQKLCDDFAQFSYTLTEFGCPT

SEQ ID NO:14 [amino acid sequence of the human IgG_1 heavy chain, C domain]:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:15 [amino acid sequence of the human IgG_1 light chain, C domain]:
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:16 [amino acid sequence of the Fc domain of human IgG_1]:
EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGPFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK

SEQ ID NO:17 [amino acid sequence of human IgM heavy chain, C domain]:
GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITLSWKYKNNSDISSTRGFPSV
LRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSV
FVPPRDGFFGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSGVTTDQVQAEAKESG
PTTYKVTSTLTIKESDWLGQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPS
FASIFLTKSTKLTCLVTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEAS
ICEDDWNSGERFTCTVTHTDLPSPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESA
TITCLVTGFSPADVFVQWMQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEE
WNTGETYTCVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:18 [amino acid sequence of human IgM light chain, C domain]:
GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITLSWKYKNNSDISSTRGFPSV
LRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKNVPLPV

SEQ ID NO:19 [amino acid sequence of the Fc domain of human IgM]:
GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSV
LRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSV
FVPPRDGFFGNPRSKSKLICQATGFSPRQIQVSWLREGKQVGSGVTTDQVQAEAKES
GPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPP
SFASIFLTKSTKLTCLVTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEA
SICEDDWNSGERFTCTVTHTDLPSPLKQTISRPKGVALHRPDVYLLPPAREQLNLRES
ATITCLVTGFSPADVFVQWMQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEE
WNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:20 [amino acid sequence of mouse IgG_3 heavy chain]:
TTTAPSVYPLVPGCSDTSGSSVTLGCLVKGYFPEPVTVKWNYGALSSGVRTVSSVLQ
SGFYSLSSLVTVPSSTWPSQTVICNVAHPASKTELIKRIEPRIPKPSTPPGSSCPPGNILG
GPSVFIFPPKPKDALMISLTPKVTCVVVDVSEDDPDVHVSWFVDNKEVHTAWTQPRE
AQYNSTFRVVSALPIQHQDWMRGKEFKCKVNNKALPAPIERTISKPKGRAQTPQVYT
IPPPREQMSKKKVSLTCLVTNFFSEAISVEWERNGELEQDYKNTPPILDSDGTYFLYS
KLTVDTDSWLQGEIFTCSVVHEALHNHHTQKNLSRSP

SEQ ID NO:21 [amino acid sequence of mouse IgG_3 light chain]:
IVLTQSPAIMSASPGEKVTMTCRASSSVRSSYLHWYQQKPGSSPKLWIYSTSNLASGV
PVRFSGSGSGTSYSLTISSVEAEDAATYYCQQYDSSPSITFGAGTKLELK

SEQ ID NO:22 [amino acid sequence of mouse IgG_3 Fc domain]:
EPRIPKPSTPPGSSCPPGNILGGPSVFIFPPKPKDALMISLTPKVTCVVVDVSEDDPDVH
VSWFVDNKEVHTAWTQPREAQYNSTFRVVSALPIQHQDWMRGKEFKCKVNNKALP
APIERTISKPKGRAQTPQVYTIPPPREQMSKKKVSLTCLVTNFFSEAISVEWERNGELE
QDYKNTPPILDSDGTYFLYSKLTVDTDSWLQGEIFTCSVVHEALHNHHTQKNLSRSP
GK

SEQ ID NO:23 [amino acid sequence of mouse IgM heavy chain, C domain]:
SQSFPNVFPLVSCESPLSDKNLVAMGCLARDFLPSTISFTWNYQNNTEVIQGIRTFPTL
RTGGKYLATSQVLLSPKSILEGSDEYLVCKIHYGGKNRDLHVPIPAVAEMNPNVNVF
VPPRDGFSGPAPRKSKLICEATNFTPKPITVSWLKDGKLVESGFTTDPVTIENKGSTPQ
TYKVISTLTISEIDWLNLNVYTCRVDHRGLTFLKNVSSTCAASPSTDILTFTIPPSFADIF
LSKSANLTCLVSNLATYETLNISWASQSGEPLETKIKIMESHPNGTFSAKGVASVCVE
DWNNRKEFVCTVTHRDLPSPQKKFISKPNEVHKHPPAVYLLPPAREQLNLRESATVT
CLVKGFSPADISVQWLQRGQLLPQEKYVTSAPMPEPGAPGFYFTHSILTVTEEEWNS
GETYTCVVGHEALPHLVTERTVDKSTGKPTLYNVSLIMSDTGGTCY

SEQ ID NO:24 [amino acid sequence of mouse IgM light chain, C domain]:
SQSFPNVFPLVSCESPLSDKNLVAMGCLARDFLPSTISFTWNYQNNTEVIQGIRTFPTL
RTGGKYLATSQVLLSPKSILEGSDEYLVCKIHYGGKNRDLHVPIP

SEQ ID NO:25 [amino acid sequence of mouse IgM Fc domain]:
ASPSTDILTFTIPPSFADIFLSKSANLTCLVSNLATYETLNISWASQSGEPLETKIKIMES
HPNGTFSAKGVASVCVEDWNNRKEFVCTVTHRDLPSPQKKFISKPNEVHKHPPAVY
LLPPAREQLNLRESATVTCLVKGFSPADISVQWLQRGQLLPQEKYVTSAPMPEPGAP
GFYFTHSILTVTEEEWNSGETYTCVVGHEALPHLVTERTVDKSTGKPTLYNVSLIMS
DTGGTCY

SEQ ID NO:26 [linking sequence between the first two N-terminal short consensus repeat domains of human CR2]:
VSVFPLE

SEQ ID NO:27 [linking sequence between the first two N-terminal short consensus repeat domains of human CR2]:
EYFNKYSS

SEQ ID NO:28 [linking sequence between the fourth and the fifth N-terminal short consensus repeat domains of human CR2]:

EEIF

CLAIMS

We claim:

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 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).

2. The soluble composition of claim 1, wherein the at least one amino acid substitution 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 construct is a fusion protein.

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

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

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

7. The soluble composition of 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).

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

9. The soluble composition of 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).

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

11. The soluble composition of 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).

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

13. The soluble composition of 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).

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

15. The soluble composition of 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).

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

17. The soluble composition of 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).

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

19. The soluble composition of 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).

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

21. The soluble composition of 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).

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

23. The soluble composition of 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).

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

25. The soluble composition of 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).

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

27. The soluble composition of claim 25, 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.

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 from the group consisting of: N11, R36, K41, Y64 and K67; and

(b) mutating one or more amino acids in a complement receptor 2 (CR2) portion of the construct from the group consisting of: S42 and K50,

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.

34. The method of 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.

35. The method of claim 33, wherein the method further comprises mutating one or more amino acids in the complement receptor 2 (CR2) portion of the construct selected from the group consisting of: R13, Y16, A22, R28, S32, K48, K57, Y68, R83, G84, and R89.

36. A method of reducing the binding affinity of the CR2 portion of the construct of claim 1 for EBV-gp350, comprising mutating at least one amino acid residue selected from the group consisting of N11, R36, K41, Y64 and K67.

37. A method of reducing the binding affinity of the CR2 portion of the construct of claim 1 for IFNα, comprising mutating at least one amino acid residue selected from the group consisting of S42 and K50.