and/or fostering development of a more favorable environment in the host organism (Kotwal, GJ, *Immunology Today*, 21(5), 242-248, 2000). VCCPs are among these proteins. Poxvirus complement control proteins are members of the complement control protein (CCP) superfamily and typically contain 4 SCR modules. These proteins possess features that make them particularly advantageous for treatment and prevention of macular degeneration related conditions and for treatment and prevention of choroidal neovascularization.

[00180] Thus in certain embodiments of the invention one or both of the therapeutic agents is a poxvirus complement control protein (PVCCP). The PVCCP can comprise a sequence encoded by, e.g., vaccinia virus, variola major virus, variola minor virus, cowpox virus, monkeypox virus, ectromelia virus, rabbitpox virus, myxoma virus, Yaba-like disease virus, or swinepox virus. In other embodiments the VCCP is a herpesvirus complement control protein (HVCCP). The HVCCP can comprise a sequence encoded by a *Macaca fuscata* rhadinovirus, cercopithecine herpesvirus 17, or human herpes virus 8. In other embodiments the HVCCP comprises a sequence encoded by herpes simplex virus saimiri ORF 4 or ORF 15 (Albrecht, JC. & Fleckenstein, B., J. Virol., 66, 3937-3940, 1992; Albrecht, J., et al., Virology, 190, 527-530, 1992).

[00181] The VCCP may inhibit the classical complement pathway, the alternate complement pathway, the lectin pathway, or any combination of these. In certain embodiments of the invention the VCCP, e.g., a PVCCP, binds to C3b, C4b, or both. In certain embodiments of the invention the PVCCP comprises one or more putative heparin binding sites (K/R-X-K/R) and/or possesses an overall positive charge. Preferably the PVCCP comprises at least 3 SCR modules (e.g., modules 1-3), preferably 4 SCR modules. The PVCCP protein can be a precursor of a mature PVCCP (i.e., can include a signal sequence that is normally cleaved off when the protein is expressed in virus-infected cells) or can be a mature form (i.e., lacking the signal sequence).

[00182] Vaccinia complement control protein (VCP) is a virus-encoded protein secreted from vaccinia infected cells. VCP is 244 amino acids in length, contains 4 SCRs, and is naturally produced by intracellular cleavage of a 263 amino acid precursor. VCP runs as an ~35 kD protein in a 12% SDS/polyacrylamide gel under reducing conditions and has a predicted molecular mass of about 28.6 kD. VCP is described in U.S. Patent Nos. 5,157,110 and 6,140,472, and in Kotwal, GK, et al., *Nature*, 355, 176-178, 1988. Figures 3A and 3B show the sequence of the precursor and mature VCP proteins, respectively. VCP has been shown to inhibit the classical pathway of complement activation via its ability to bind to C3 and C4 and act as a cofactor for factor I mediated cleavage of these components as well as promoting decay of existing convertase (Kotwal, GK, et al., *Science*, 250, 827-830, 1990; McKenzie et al., *J.*

Infect. Dis., 1566, 1245-1250, 1992). It has also been shown to inhibit the alternative pathway by causing cleavage of C3b into iC3b and thereby preventing formation of the alternative pathway C3 convertase (Sahu, A, et al., *J. Immunol.*, 160, 5596-5604, 1998). VCP thus blocks complement activation at multiple steps and reduces levels of the proinflammatory chemotactic factors C3a, C4a, and C5a.

[00183] VCP also possesses the ability to strongly bind heparin in addition to heparan sulfate proteoglycans. VCP contains two putative heparin binding sites located in modules 1 and 4 (Jha, P and Kotwal, GJ, and references therein). VCP is able to bind to the surface of endothelial cells, possibly via interaction with heparin and/or heparan sulfate at the cell surface, resulting in decreased antibody binding (Smith, SA, et al., *J. Virol.*, 74(12), 5659-5666, 2000). VCP can be taken up by mast cells and possibly persist in tissue for lengthy periods of time, thereby potentially prolonging its activity (Kotwal, GJ, et al., *In* GP. Talwat, et al. (eds), 10th International Congress of Immunology., Monduzzi Editore, Bologna, Italy, 1998). In addition, VCP can reduce chemotactic migration of leukocytes by blocking chemokine binding (Reynolds, D, et al., in S. Jameel and L. Villareal (ed., *Advances in animal virology*. Oxford and IBN Publishing, New Delhi, India, 1999).

[00184] Variola virus major and minor encode proteins that are highly homologous to VCP and are referred to as smallpox inhibitor of complement enzymes (SPICE) (Rosengard, AM, et al., *Proc. Natl. Acad. Sci.*, 99(13), 8803-8813. U.S. Pat. No. 6,551,595). SPICE from various variola strains sequenced to date differs from VCP by about 5% (e.g., about 11 amino acid differences). Similarly to VCP, SPICE binds to C3b and C4b and causes their degradation, acting as a cofactor for factor I. However, SPICE degrades C3b approximately 100 times as fast as VCP and degrades C4b approximately 6 times as fast as VCP. The amino acid sequence of SPICE is presented in Figure 6 and can be described as follows. Referring to Figure 6, a signal sequence extends from amino acid 1 to about amino acid 19. Four SCRs extend from about amino acid 20 to amino acid 263. Each SCR is characterized by four cysteine residues. The four cysteine residues form two disulfide bonds in the expressed protein. The boundaries of each SCR are best defined by the first and fourth cysteine residues in the sequence that forms the disulfide bonds of the SCR. An invariant tryptophan residue is present between cysteine 3 and cysteine 4 of each SCR. SCR1 extends from amino acid 20 or 21 to amino acid 81. Both residues are cysteines that may be involved in disulfide bonding. SCR2 extends from amino acid 86 to amino acid 143. SCR3 extends from amino acid 148 to amino acid 201. SCR4 extends from amino acid 206 to amino acid 261. The SCRs include the complement binding locations of SPICE. SPICE or any of the portions thereof that inhibit complement activation, e.g., SPICE and

SPICE-related polypeptides containing four SCRs, such as those described in U.S. Pat. No. 6,551,595, are of use in the present invention.

[00185] Complement control proteins from cowpox virus (referred to as inflammation modulatory protein, IMP) and monkeypox virus (referred to herein as monkeypox virus complement control protein, MCP) have also been identified and sequenced (Miller, CG, et al., *Virology*, 229, 126-133, 1997 and Uvarova, EA and Shchelkunov, SN, *Virus Res.*, 81(1-2), 39-45, 2001). MCP differs from the other PVCCPs described herein in that it contains a truncation of the C-terminal portion of the fourth SCR.

[00186] It will be appreciated that the exact sequence of complement control proteins identified in different virus isolates may differ slightly. Such proteins fall within the scope of the present invention. Complement control proteins from any such isolate may be used, provided that the protein has not undergone a mutation that substantially abolishes its activity. Thus the sequence of a VCCP such as SPICE or VCP may differ from the exact sequences presented herein or under the accession numbers listed in Table 1. It will also be appreciated that a number of amino acid alterations, e.g., additions, deletions, or substitutions such as conservative amino acid substitutions, may be made in a typical polypeptide such as a VCCP without significantly affecting its activity, such that the resulting protein is considered equivalent to the original polypeptide. For example, up to about 10% of the amino acids, or up to about 20% of the amino acids may frequently be changed without significantly altering the activity. Also, of course, domains known to have similar functions can be substituted for one another. Such domains may be found within a single polypeptide (e.g., repeated domains) or within different, homologous polypeptides. The effect of any particular amino acid alteration(s) or domain substitutions can readily be determined.

[00187] Figure 4 shows a sequence alignment of a variety of poxvirus complement control proteins from isolates of variola major and minor, vaccinia, cowpox virus, and monkeypox virus. Figure 5 shows a comparison of the SCR domain structure of a number of complement control proteins and fragments thereof, the number of K+R residues, %K+R residues, pI, number of putative heparin binding sites, and ability to inhibit hemolysis (indicative of complement inhibiting activity) and/or bind to heparin.

[00188] Without limitation, any of the viral polypeptides identified by accession number in Table 2 below is of use in various embodiments of the invention.

[00189] Table 2: Representative Viral Complement Control Proteins

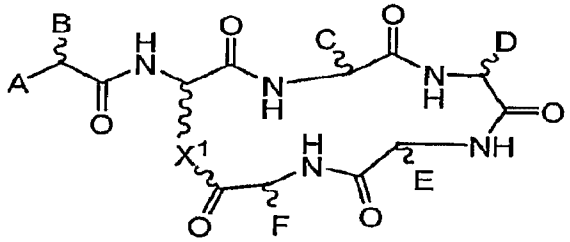
Virus	Protein	Accession	Virus Type
Variola	D12L	NP_042056	Orthopoxvirus
	D15L (SPICE)	AAA69423	Orthopoxvirus
Vaccinia	VCP	AAO89304	Orthopoxvirus
Cowpox	CPXV034	AAM13481	Orthopoxvirus
	C17L	CAA64102	Orthopoxvirus
Monkeypox	D14L	AAV84857	Orthopoxvirus
Ectromelia virus	Complement control protein	CAE00484	Orthopoxvirus
Rabbitpox	RPXV017	AAS49730	Orthopoxvirus
Macaca fuscata rhadinovirus	JM4	AAS99981	Rhadinavirus (Herpesvirus)
Cercopithecine herpesvirus 17	Complement binding protein (ORF4)	NP_570746	Herpesvirus
Human herpes virus 8	Complement binding protein (ORF4)	AAB62602	Herpesvirus

[00190] ***Compounds that Inhibit C5 Activation or Activity***

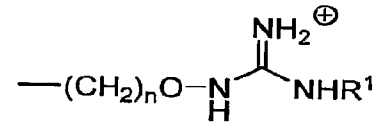
[00191] In certain embodiments the complement inhibitor inhibits activation of C5. For example, the complement inhibitor may bind to C5. Exemplary agents include antibodies, antibody fragments, polypeptides, small molecules, and aptamers. Exemplary antibodies are described in U.S. Pat. No. 6,534,058. Exemplary compounds that bind to and inhibit C5 are described in U.S. Pat. Pub. Nos. 20050090448 and 20060115476. In certain embodiments the complement inhibitor is an antibody, small molecule, aptamer, or polypeptide that binds to substantially the same binding site on C5 as an antibody described in U.S. Pat. No. 6,534,058 or a peptide described in USSN 10/937,912. U.S. Pat. Pub. No. 20060105980 discloses aptamers that bind to and inhibit C5. Also of use are RNAi agents that inhibit expression of C5 or C5R.

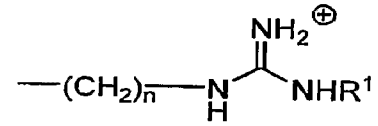
[00192] In other embodiments the agent is an antagonist of a C5a receptor (C5aR). Exemplary C5a receptor antagonists include a variety of small cyclic peptides such as those described in U.S. Pat. No. 6,821,950; USSN 11/375,587; and/or PCT/US06/08960 (WO2006/099330).

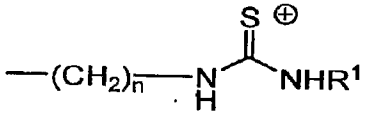
For example, the therapeutic agent may be a compound of general formula I below:

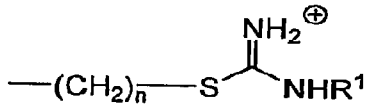


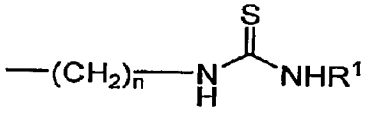
[00193] where A is H, alkyl, aryl, NH_2, NHalkyl, $N(alkyl)_2$, NHaryl or NHacyl; B is an alkyl, aryl, phenyl, benzyl, naphthyl or indole group, or the side chain of a D- or L-amino acid selected from the group consisting of phenylalanine, homophenylalanine, tryptophan, homotryptophan, tyrosine, and homotyrosine; C is the side chain of a D-, L- or homo-amino acid selected from the group consisting of proline, alanine, leucine, valine, isoleucine, arginine, histidine, aspartate, glutamate, glutamine, asparagine, lysine, tyrosine, phenylalanine, cyclohexylalanine, norleucine, tryptophan, cysteine and methionine; D is the side chain of a D- or L-amino acid selected from the group consisting of cyclohexylalanine, homocyclohexylalanine, leucine, norleucine, homoleucine, homonorleucine and tryptophan; E is the side chain of a D- or L-amino acid selected from the group consisting of tryptophan and homotryptophan; F is the side chain of a D- or L-amino acid selected from the group consisting of arginine, homoarginine, lysine and homolysine or is one of the following side-chains











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