complement system are limited to pathogenic cells. Many complement-related disorders and diseases are associated with abnormal destruction of self cells by the complement cascade. In one example, subjects suffering from paroxysmal nocturnal hemoglobinuria (PNH) are unable to synthesize functional versions of the complement regulatory proteins CD55 and CD59 on hematopoietic stem cells. This results in complement-mediated hemolysis and a variety of downstream complications. Other complement-related disorders and diseases include, but are not limited to autoimmune diseases and disorders, neurological diseases and disorders, blood diseases and disorders and infectious diseases and disorders. Experimental evidence suggests that many complement-related disorders are alleviated through inhibition of complement activity. Therefore, there is a need for the development of compounds capable of selectively blocking complement-mediated cell destruction.

SUMMARY

[0009] In one aspect, the present invention refers to a polypeptide of the formula R1-Xaa1-Xaa2-Xaa3-Xaa4-Xaa5-Xaa6-Xaa7-Xaa8-Xaa9-Xaa10-Xaa11-Xaa12-Xaa13-Xaa14-Xaa15, wherein: a. R1 is an acetyl group; b. Xaa1 is Lys; c. Xaa2 is Val; d. Xaa3 is Glu; e. Xaa4 is Arg; f. Xaa5 is Phe; g. Xaa6 is Asp; h. Xaa7 is N-methyl-aspartic acid; i. Xaa8 is tert-butylglycine; j. Xaa9 is Tyr; k. Xaa10 is 7-azatryptophan; l. Xaa11 is Glu; m. Xaa12 is Tyr; n. Xaa13 is Pro; o. Xaa14 is cyclohexylglycine; and p. Xaa15 is selected from the group consisting of N-ε-(PEG24-γ-glutamic acid-N-α-hexadecanoyl)lysine (B28), norvaline, Lys, and N-ε-palmitoyl lysine.

The present disclosure describes compounds, including polypeptides (e.g., peptidomimetics, cyclic polypeptides and cyclic peptidomimetics,) small molecules, antibodies, antibody fragments, and aptamers, and methods of using said compounds for the modulation of complement. According to the present invention, polypeptides may have the sequences set forth in SEQ ID NOs 1-201 or 211. They may be linear or cyclic and may comprise a cyclic loop formed by a bridging moiety between two amino acids. The bridging moieties may comprise a feature selected from the group consisting of a disulfide bond, an amide bond (lactam), a thioether bond, an aromatic ring, an unsaturated aliphatic hydrocarbon chain, a saturated aliphatic hydrocarbon chain, a triazole ring or combinations thereof. Furthermore, the cyclic loop may vary in length and may be 1 amino acid, 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9, amino acids, 10 amino acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids, 16 amino acids, or more.

[0010] The bridging moiety may comprise a disulfide between two cysteine resides or an aromatic ring produced by reaction with a poly(bromomethyl)benzene and such poly(bromomethyl)benzene may be selected from the group consisting of 1,2-bis(bromomethyl)benzene, 1,3-bis(bromomethyl)benzene and 1,4-bis(bromomethyl)benzene.

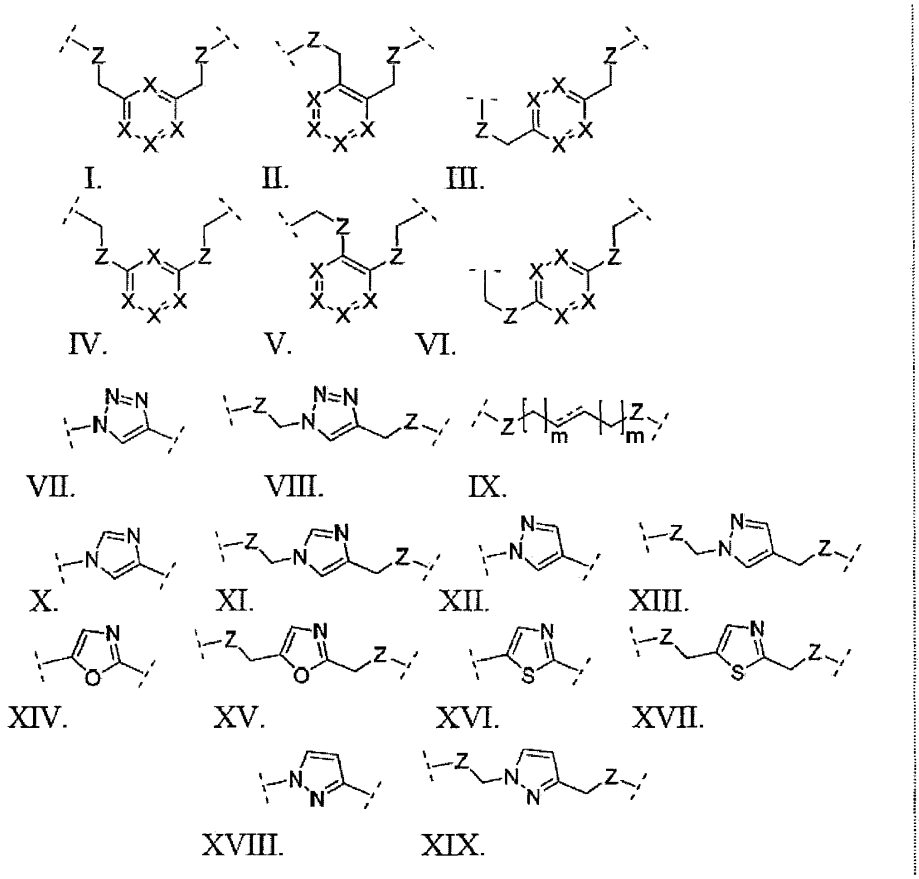
CLAIMS

What is claimed is:

1. A polypeptide of the formula R1-Xaa1-Xaa2-Xaa3-Xaa4-Xaa5-Xaa6-Xaa7-Xaa8-Xaa9-Xaa10-Xaa11-Xaa12-Xaa13-Xaa14-Xaa15, wherein:
    a. R1 is an acetyl group;
    b. Xaa1 is Lys;
    c. Xaa2 is Val;
    d. Xaa3 is Glu;
    e. Xaa4 is Arg;
    f. Xaa5 is Phe;
    g. Xaa6 is Asp;
    h. Xaa7 is N-methyl-aspartic acid;
    i. Xaa8 is tert-butylglycine;
    j. Xaa9 is Tyr;
    k. Xaa10 is 7-azatryptophan;
    l. Xaa11 is Glu;
    m. Xaa12 is Tyr;
    n. Xaa13 is Pro;
    o. Xaa14 is cyclohexylglycine; and
    p. Xaa15 is selected from the group consisting of N-ε-(PEG24-γ-glutamic acid-N-α-hexadecanoyl)lysine (B28), norvaline, Lys, and N-ε-palmitoyl lysine.

2. The polypeptide of claim 1, further comprising a bridging moiety between two amino acids.

3. The polypeptide of claim 2, wherein said bridging moiety comprises a structure selected from the group consisting of structures I-XIX;



wherein each X is independently N or CH, such that no ring contains more than 2 N; each Z is independently a bond, NR, O, S, CH_2, C(O)NR, NRC(O), $S(O)_vNR$, $NRS(O)_v$; each m is independently selected from 0, 1, 2, and 3; each v is independently selected from 1 and 2; each R is independently selected from H and C_1-C_6; and each bridging moiety is connected to the polypeptide by independently selected C_0-C_6 spacers.

4. The polypeptide of claim 2, wherein the bridging moiety comprises a feature selected from the group consisting of a disulfide bond, an amide bond (lactam), a thioether bond, an aromatic ring, an unsaturated aliphatic hydrocarbon chain, a saturated aliphatic hydrocarbon chain and a triazole ring.

5. The polypeptide of any of claims 2-4, wherein the peptide comprises a cyclic loop, wherein the cyclic loop is of a length selected from the group consisting of 1 amino acid, 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9, amino acids, 10 amino acids, 11 amino acids, 12 amino acids, and 13 amino acids.

6. The polypeptide of claim 4, wherein said feature comprises an aromatic ring and wherein said bridging moiety is formed by reaction with a poly(bromomethyl)benzene.

7. The polypeptide of claim 6, wherein the poly(bromomethyl)benzene is selected from the group consisting of 1,2-bis(bromomethyl)benzene, 1,3-bis(bromomethyl)benzene and 1,4-bis(bromomethyl)benzene.

8. The polypeptide of claim 7 wherein the reagent is 1,3-bis(bromomethyl)benzene.

9. The polypeptide of claim 4, wherein said feature comprises an aromatic ring and wherein said bridging moiety is produced by reaction with a compound selected from the group consisting of 2,6-bis(bromomethyl)pyridine, (*E*)-1,4-dibromobut-2-ene and 1,2-bis(bromomethyl)-4-alkylbenzene.

10. The polypeptide of claim 1, wherein said polypeptide is selected from the group consisting of SEQ ID NOs 177, 184 and 194.

11. The polypeptide of any one of claims 1-10, wherein said polypeptide inhibits the cleavage of C5 into C5a and C5b cleavage products.

12. The polypeptide of claim 10 or 11, wherein said polypeptide is SEQ ID NO: 177.

13. The polypeptide of claim 10 or 11, wherein said polypeptide is SEQ ID NO: 184.

14. The polypeptide of claim 10 or 11, wherein said polypeptide is SEQ ID NO: 194.

15. The polypeptide of claim 1, wherein said polypeptide is part of an antibody.

16. A composition comprising the polypeptide of any of claims 1-15 and an acceptable carrier or excipient.

17. The composition of claim 16 comprising an excipient, wherein said excipient comprises a pharmaceutically acceptable excipient.

18. An *in vitro* or *ex vivo* method of inhibiting C5 cleavage in a cellular system, said method comprising contacting said cellular system with the composition of any of claims 16 to 17 or a polypeptide of any of claims 1 to 15.

19. The method of claim 18, wherein said polypeptide inhibits the cleavage of C5 with an IC_{50} of less than 50 nM.

20. Use of the composition of any of claims 16 to 17 or the polypeptide of any of claims 1 to 15 in the manufacture of a medicament for inhibiting C5 cleavage in the treatment of a subject suffering from a complement-related disease, disorder and/or condition, wherein said complement-related disease, disorder and/or condition is selected from the group consisting of sterile inflammation, systemic inflammatory response, sepsis, multi organ failure, acute respiratory distress syndrome, periodontitis, stroke, myocardial infarction, atherosclerosis, diabetes, osteoporosis, thrombotic microangiopathy, vascular thrombosis, endothelial cell damage, thrombocytopenia, hemolysis, disseminated intravascular coagulation, vasculitis, neurodegenerative disease, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's disease, kidney disease, kidney infection, renal transplantation, lupus nephritis, systemic lupus nephritis, membranous glomerulonephritis, hemodialysis complications, chronic inflammation, a wound, an injury, an autoimmune disease, an ocular disease, paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

21. The use of claim 20, wherein said polypeptide inhibits the cleavage of C5 with an IC_{50} of less than 50 nM.

22. The composition of any of claims 16 to 17 or the polypeptide of any of claims 1 to 15 for use in therapy.