CLAIMS

1. A fusion construct comprising at least a first, second, and third component, wherein the first component comprises a wild type CFI or variant thereof (CFI variant), wherein the second component comprises a FH or CR1, and the third component comprises a FH or CR1,

wherein the CFI variant comprises at least one modification with respect to a wild type CFI, wherein the CFI variant is capable of modulating the complement system, wherein the CFI variant has at least one improved characteristic as compared to the wild type CFI, and wherein the variant is selected from those presented in Table 2 or Table 3.

2. The fusion construct of claim 1, wherein the first component:

(a) comprises a wild type CFI, comprising an amino acid sequence set forth in SEQ ID NO: 5, and/or optionally wherein the construct comprises albumin, optionally wherein the albumin is human serum albumin, optionally wherein human serum albumin comprises an amino acid sequence set forth in SEQ ID NO: 7; or

(b) comprises a CFI variant.

3. The fusion construct of any one of claims 1-2, wherein;

(a) the improved characteristic is selected from an increase in half-life or bioavailability, or an increase or decrease in any one or more of activity, substrate specificity, potency, substrate affinity, cofactor affinity and catalytic capability, optionally wherein the improved characteristic:

(i) is an increase in activity, optionally wherein the increase in activity comprises an increase in the cleavage of C3b and/or C4b, optionally wherein the increase in activity comprises:

(A) an increase in the cleavage of C3b and does not comprise an increase in the cleavage of C4b, and/or optionally wherein the increase in the cleavage of C3b is increased at least or about 1.5-fold, at least or about 2-fold, at least or about 3-fold, at least or about 4-fold, at least or about 5-fold, at least or about 10-fold, at least or about 20-fold, at least or about 30-fold, at least or about 40-fold, at least or about 50-fold, at least or about 100-fold, at least or about 150-fold, at least or about 500-fold, or at least or about 1000-fold as compared to a wild type CFI not part of a fusion construct, or compared to a fusion construct comprising a wild type CFI; or

(B) an increase in the cleavage of C4b as compared to the wild type CFI, and does not comprise an increase in the cleavage of C3b; or

(ii) is a decrease in activity.

4. The fusion construct of any one claims 3(i) and 3(B), wherein the increase in the cleavage of C4b is increased at least or about 1.5-fold, at least or about 2-fold, at least or about 3-fold, at least or about 4-fold, at least or about 5-fold, at least or about 10-fold, at least or about 20-fold, at least or about 30-fold, at least or about 40-fold, at least or about 50-fold, at least or about 100-fold, at least or about 150-fold, at least or about 500-fold, or at least or about 1000-fold as compared to a wild type CFI not part of a fusion construct, or compared to a fusion construct comprising a wild type CFI.

5. The fusion construct of any one of claims 3(i)-3(A) and 4, wherein the increase in activity comprises:

(a) an increase in generation of iC3b;

(b) an increase in the generation of C3dg from iC3b; and/or

(c) a reduction in the levels of C3b α-chain.

6. The fusion construct of any one of claims 3(i)-5, wherein the increase in activity comprises an increase in the hydrolysis of a peptide substrate or proteolysis of a macromolecular protein substrate.

7. The fusion construct of any one of claims 1-6, wherein the fusion construct:

(a) has at least one improved characteristic as compared to a free wild type CFI, without the presence of Factor H and/or without the presence of CR1; or

(b) has at least one improved characteristic as compared to a free wild type CFI, and wherein the at least one improved characteristic is further improved by the presence of exogenous Factor H and/or exogenous CR1.

8. The fusion construct of any of claims 1 to 7, wherein the CFI variant comprises at least one modification corresponding to a wild type CFI having the amino acid sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 5.

9. The fusion construct of any of claims 1 to 8, wherein the CFI variant is a chimera comprising one or more domains from a human CFI, and wherein the human CFI further comprises a substitution of one or more amino acid residues for amino acid residues of a corresponding region from a non-human species CFI.

10. The fusion construct of any of claims 1 to 9, wherein the CFI variant is a chimera, and wherein the modification comprises the substitution of one or more amino acid residues of the CFI with amino acid residues from a corresponding region of a non-CFI serine protease.

11. The fusion construct of any of claims 1 to 10, wherein the CFI variant comprises:

(a) an A chain and a B chain, wherein the CFI variant comprises one or more modifications at the interface of the A chain and the B chain;

(b) one or more modifications at a C-terminal region of the CFI variant; or

(c) one or more modifications at one or more N-linked glycosylation sites of the CFI variant;

(d) one or more modifications in the SPD domain of the CFI, optionally comprising one or more modifications at any one or more of the autolysis loop, the 99 loop, the S1 pocket entrance, or the activation loop of SPD, or any one or more of the domains presented in FIG. 1;

(e) a substitution of an autolysis loop of the CFI (REKDNERVFS, SEQ ID NO: 9) for an autolysis loop of trypsin (NTASSGADYPDE, SEQ ID NO: 10), wherein the autolysis loop occurs between positions corresponding to position 456 and position 465 in a CFI having the amino acid sequence set forth in SEQ ID NO: 5;

(f) one or more modifications at an active site of the CFI;

(g) an A chain and a B chain, wherein the CFI variant comprises a structural arrangement from N-terminus to C-terminus as (A chain)-(optional linker)-(B chain);

(h) an A chain and a B chain, wherein the CFI variant comprises a structural arrangement from N-terminus to C-terminus as (B chain)-(optional linker)-(A chain); or

(i) each one of the SPD, the FIMAC domain, the SRCR domain, the LDLr1 domain, and the LDLr2 domain, and any other domains presented in FIG. 1.

12. The fusion construct of any of claims 1 to 11, wherein the CFI variant does not comprise all of the SPD, the FIMAC domain, the SRCR domain, the LDLr1 domain, and the LDLr2 domain.

13. The fusion construct of claim 12, wherein the CFI variant comprises the SPD, optionally wherein the CFI variant comprises the amino acid sequence set forth in SEQ ID NO: 12.

14. The fusion construct of any of claims 1 to 13, wherein the CFI variant is sialylated.

15. The fusion construct of any of claims 1 to 14, wherein the CFI variant is active, optionally wherein the CFI variant is activated by furin or a variant thereof.

16. The fusion construct of any of claims 1 to 15, wherein the second component is a half-life extender selected from albumin, PEG, a non-biodegradable polymer, a biodegradable polymer, and Fc.

17. A fusion construct comprising any of the fusion constructs of Table 3.

18. A pharmaceutical composition comprising any one of the fusion constructs of claims 1-17, and optionally a pharmaceutically acceptable excipient.

19. A method of modulating the complement system, comprising contacting a sample *in vitro* with any one of the fusion constructs of claims 1-17.

20. Use of the fusion construct of any one of claims 1-17 in the manufacture of a medicament for modulating the complement factor system, wherein a tissue is to be contacted in vivo with the fusion construct.

21. The method of claim 19, or the use according to claim 20, wherein the method or use results in:

(a) the increase in the cleavage of C3b, C4b, generation of iC3b, generation of C3dg, and/or C4c;

(b) a decrease in hemolysis;

(c) the reduction or level of MAC;

(d) the reduction of the amplification of the complement system; or

(e) the increase in the hydrolysis of a peptide substrate, or an increase in the proteolysis of a macromolecular protein substrate.

22. Use of a therapeutically effective amount of any one of the fusion constructs of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating a non-ocular condition.

23. The use according to claim 22, wherein the non-ocular condition:

(a) is characterized by a deficiency of CFI;

(b) is characterized by dysregulation of the complement system; and/or

(c) is:

(i) a systemic acute indication, optionally wherein the non-ocular condition is a systemic acute indication selected from the group consisting of: acute glomerulonephritis, acute renal injury, acute respiratory distress syndrome, bacterial meningitis, brain hemorrhage, burns, coronavirus infection, Epstein-Barr virus infection, hematopoietic stem cell transplantation, ischemia reperfusion injury, Lyme disease, myocardial infarction, organ transplantation, periodontitis, pneumonia, pre-eclampsia, schistosomiasis, sepsis, stroke, thromboembolism, ischemia-reperfusion injury and traumatic brain injury;

(ii) a systemic chronic indication, optionally wherein the non-ocular condition is a systemic chronic indication selected from the group consisting of: Alzheimer's disease, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, antiphospholipid syndrome, asthma, atherosclerosis, atypical hemolytic uremic syndrome (aHUS), autoimmune hemolytic anemia, bullous pemphigoid (BP), C3 glomerulopathy, chronic kidney failure, chronic obstructive pulmonary disease, Crohn's disease, diabetic neuropathy, generalized myasthenia gravis (gMG), Granulomatosis with Polyangiitis (GPA), Guillain-Barré Syndrome (GBS), hereditary angioedema (HAE), hidradenitis suppurativa (HS), IgA nephropathy, lupus nephritis (LN), membranous glomerulonephritis (MN), microscopic polyangiitis (MPA), motor neuron disease, multifocal motor neuropathy (MMN), multiple sclerosis (MS), non-insulin dependent diabetes, osteoarthritis, pancreatitis, Parkinson's disease, paroxysmal nocturnal hemoglobinuria, post-transplant lymphoproliferative disease, protein losing enteropathy, psoriasis, pyoderma gangrenosum, rheumatoid arthritis, schizophrenia (SZ), systemic lupus erythematosus (SLE), immune thrombocytopenia (ITP), ulcerative colitis, Amyotrophic lateral sclerosis (ALS), warm autoimmune hemolytic anemia (wAIHA), cold agglutinin disease (CAD), and Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN), Lampert-Eaton myasthenic syndrome (LEMS), CHAPLE syndrome (CD55 deficiency), thrombotic microangiography (TMA), Huntington's disease and chronic inflammatory demyelinating polyneuropathy (CIDP);

(iii) non-oncological; or

(iv) oncological, optionally wherein the non-ocular condition is characterized by solid tumors, or by liquid tumors, optionally wherein the non-ocular condition is characterized by;

(A) solid tumors, and is selected from the group consisting of: colorectal tumors, hormone-refractory prostate cancer, melanoma, metastatic breast cancer, metastatic colorectal cancer, metastatic esophageal cancer, metastatic pancreas cancer, metastatic stomach cancer, nasopharyngeal carcinoma, non-small cell lung cancer, pancreas tumors, squamous cell carcinoma, and stomach tumors; or

(B) liquid tumors, and is selected from the group consisting of: acute myelogenous leukemia, B-cell lymphoma, and Hodgkin's disease.

24. The pharmaceutical composition of claim 18, the method of claim 19, or the use according to any one of claims 20-23, wherein the fusion construct, or the pharmaceutical composition is to be administered to the subject subcutaneously, or intravenously, optionally wherein the administration is a subcutaneous administration, optionally wherein the subcutaneous administration is a daily, or weekly, or every other week.

25. Use of a therapeutically effective amount of any one of the fusion constructs of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating an ocular condition.

26. The use according to claim 25, wherein the ocular condition:

(a) is characterized by a deficiency of CFI;

(b) is characterized by dysregulation of the complement system;

(c) is selected from the group consisting of: diabetic macular edema (DME), diabetic retinopathy, dry age-related macular degeneration (AMD), glaucoma, keratoconjunctivitis, neuromyelitis optica spectrum disorder (NMOSD), open angle glaucoma, polypoidal choroidal vasculopathy, Stargardt Disease, uveitis, and vitreoretinopathy; and/or

(d) is non-oncological.