[00016] In addition to or in lieu of high concentration and long acting delivery, increased bioavailability (e.g., ocular residence time) of the drug can be achieved, or facilitated, by post-translational modifications, wherein the protein drug is covalently conjugated with natural or synthetic polymers such as polysialylation, HESylation (conjugation with hydroxyethyl starch) and PEGylation. Chen et al (2011) Expert. Opin. Drug Deliv. 8:1221-36; Kontermann (2009) BioDrugs 23:93-109. PEGylation, the covalent attachment of polymer polyethylene glycol (PEG) to a protein, is a well-established technology especially useful for extending the half-life of antibody fragment therapeutics. Jevsevar et al. (2010) *Biotech. J.* 5:113-128.

[00017] The conditions that a drug is exposed to vary depending on the delivery system used. For incorporation into solid PLGA implants, lyophilized or spray-dried drug is used. Implants are produced using a hot-melt extrusion process such that the drug is briefly exposed to temperatures approaching 90°C. Although the drug remains in solid state for the duration of release, degradation of PLGA may expose the drug to a low pH environment. In contrast, drug delivered with the PDS is maintained at high concentration in liquid state and exposed to vitreous which is characterized as a reducing environment at physiological ionic strength and pH.

[00018] Thus, there exists great needs for anti-factor D antibodies with improved stabilities, preferably suitable for high concentration formulation and/or long acting delivery.

Summary ~~of the Invention~~

[00019] The present ~~invention~~disclosure is based in part on the discovery that targeted amino acid substitutions of identified hot spots in an antibody can effectively improve the antibody's stability and overall potency as a therapeutic.

[00020] In one aspect, ~~the present invention relates to~~there is provided an anti-factor D antibody variant~~s~~ with improved stability. ~~The invention includes anti-factor D antibody variants~~ comprising substitution of at least one target aspartic acid (D or Asp) residue within a hypervariable region (HVR) of a reference anti-Factor D antibody, wherein the target Asp residue is identified as prone to isomerization and the substitution is Asp to Glutamic acid (E or Glu), and wherein the anti-Factor D antibody variant exhibits improved stability without significant loss of Factor D binding affinity when compared to the reference anti-Factor D antibody. In some ~~aspects~~embodiments, the target Asp residue subject to substitution is within an Asp-Xaa motif, wherein Xaa is Asp, Gly, His, Ser or Thr. In one ~~aspect~~embodiment, the target Asp residue is the first Asp of an Asp-Asp (DD) motif. In one ~~aspect~~embodiment, the anti-factor D antibody variants comprise one or more substitutions at

additional Asp sites within a HVR of a reference anti-Factor D antibody, wherein the substitution is Asp to Serine (S or Ser) in order to reduce the overall charges of the antibody, thereby improving the solubility of the antibody. In one ~~aspect~~embodiment, the anti-factor D antibody variants comprise one or more substitutions at asparagine (N or Asn) sites identified as prone to deamidation, wherein the substitution is Asn to Ser in order to reduce or eliminate the antibody's deamidation.

[00021] In one ~~aspect~~embodiment, the reference anti-factor D antibody used to generate the antibody variants of the ~~invention~~disclosure comprises the light chain variable domain sequence of SEQ ID NO:3, the heavy chain variable domain sequence of SEQ ID NO:4, or both. Subsequently, the resulting antibody variants may comprise a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12, or may comprise a light chain HVR3 (HVR-L3) sequence of SEQ ID NO:13, or may comprise a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12, or may comprise a heavy chain HVR3 (HVR-H3) sequence of SEQ ID NO:15.

[00022] In one ~~aspect~~embodiment, the anti-factor D antibody variant of the ~~invention~~disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of SEQ ID NO:2, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12. Such variant is referred to as the "TM" variant (AFD.v6) in Examples herein below (see, e.g., Table 1).

[00023] In one ~~aspect~~embodiment, the anti-factor D antibody variant of the ~~invention~~disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of SEQ ID NO:2, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11, a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12 and a light chain HVR3 (HVR-L3) sequence of SEQ ID NO:13. Such variant is referred to as the "TM.D92E" variant (AFD.v7) in Examples herein below (see, e.g., Table 1).

[00024] In one ~~aspect~~embodiment, the anti-factor D antibody variant of the ~~invention~~ disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of SEQ ID NO:2, and wherein the variant comprises the following sequence modifications over the reference anti-

factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12. Such variant is referred to as the "SIESD" variant (AFD.v8) in Examples herein below (see, e.g., Table 1). In one embodiment, the "SIESD" variant (AFD.v8) comprises the light chain sequence of SEQ ID NO: 26 and the heavy chain sequence of SEQ ID NO: 27. In one embodiment, a Cys-modified version of the "SIESD" variant comprises the heavy chain sequence of SEQ ID NO: 30. In one embodiment, a Cys-Pro-Pro-Cys-modified version of the "SIESD" variant comprises the heavy chain sequence of SEQ ID NO: 31.

[00025] In one ~~aspect~~embodiment, the anti-factor D antibody variant of the ~~invention~~disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of SEQ ID NO:2, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14, a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12 and a heavy chain HVR3 (HVR-H3) sequence of SEQ ID NO:15. Such variant is referred to as the "SIESD.N103S" variant (AFD.v14) in Examples herein below (see, e.g., Table 1). In one embodiment, the "SIESD.N103S" variant (AFD.v14) comprises the light chain sequence of SEQ ID NO: 28 and the heavy chain sequence of SEQ ID NO: 29. In one embodiment, a Cys-modified version of the "SIESD.N103S" variant comprises the heavy chain sequence of SEQ ID NO: 32. In one embodiment, a Cys-Pro-Pro-Cys-modified version of the "SIESD" variant comprises the heavy chain sequence of SEQ ID NO: 33.

[00026] ~~In one aspect, the present invention relates to~~Disclosed are anti-Factor D antibody variants comprising one or more substitutions within the HVRs of a reference anti-Factor D antibody. In another aspect, there is provided an anti-Factor D antibody variant comprising substitution at one or more positions within the HVRs of a reference anti-Factor D antibody, wherein said reference anti-Factor D antibody comprises light chain HVR-1 comprising the sequence ITSTDIDDDMN (SEQ ID NO: 5), light chain HVR-2 comprising the sequence GGNTLRP (SEQ ID NO: 6), light chain HVR-3 comprising the sequence LQSDSLPYT (SEQ ID NO: 7), heavy chain HVR-1 comprising the sequence GYTFTNYGMN (SEQ ID NO: 8), heavy chain HVR-2 comprising the sequence WINTYTGETTYADDFKG (SEQ ID NO: 9), and heavy chain HVR-3 comprising the sequence EGGVNN (SEQ ID NO: 10), and wherein said substitution is one or more of the following: (a) amino acid at position 5 of SEQ ID NO: 5 is S (a, b, and c disclosed in SEQ ID NO: 22); (b) amino acid at position 7 of SEQ ID NO: 5 is E; (c) amino acid at position 8 of SEQ ID NO: 5 is S; (d) amino acid at position 13 of SEQ ID NO: 9 is E (SEQ ID NO: 23); (e) amino acid at position 4 of SEQ ID NO: 7 is E (SEQ ID NO: 24); or (f) amino acid at position 5 of SEQ ID NO: 10 is S(SEQ ID NO: 25). In one ~~aspect~~embodiment, the reference anti-Factor D antibody comprised the following HVR sequences:

HVR-L1: ITSTDIDDDMN (SEQ ID NO: 5);
HVR-L2: GGNTLRP (SEQ ID NO: 6);
HVR-L3: LQSDSLPYT (SEQ ID NO: 7);
HVR-H1: GYTFTNYGMN (SEQ ID NO: 8);
HVR-H2: WINTYTGETTYADDFKG (SEQ ID NO: 9); and
HVR-H3: EGGVNN (SEQ ID NO: 10).

And the corresponding variants comprise one or more of the following substitutions:

(a) D5S in SEQ ID NO: 5;
(b) D7E in SEQ ID NO: 5;
(c) D8S in SEQ ID NO: 5 (a, b, and c disclosed in SEQ ID NO: 22);

(d) D13E in SEQ ID NO: 9 (SEQ ID NO: 23);

(e) D4E in SEQ ID NO: 7 (SEQ ID NO: 24); or

(f) N5S in SEQ ID NO: 10 (SEQ ID NO: 25).

[00027] In one ~~aspect~~embodiment, the variant of the present disclosure~~invention~~ combines the substitutions (b)-(d) above. In another embodiment~~aspect~~, the variant combines the substitutions (b)-(e) above. In another embodiment~~aspect~~, the variant combines the substitutions (a)-(d) above. In another embodiment~~aspect~~, the variant combines the substitutions (a)-(d) and (f) above.

[00028] In ~~one~~another aspect, there is provided ~~present invention relates to~~ an anti-Factor D antibody comprising a light chain variable domain amino acid sequence of SEQ ID NO:16, 18 or 19. In another aspect, ~~the present invention relates to~~there is provided an anti-Factor D antibody comprising a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20. In another embodiment~~aspect~~, the anti-Factor D antibody comprises a light chain variable domain amino acid sequence of SEQ ID NO:16, 18 or 19 and a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20. For example, the anti-Factor D antibody can be the "TM" variant (AFD.v6) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:16 and the heavy chain variable domain amino acid sequence of SEQ ID NO:17; the "TM.D92E" variant (AFD.v7) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:18 and the heavy chain variable domain amino acid sequence of SEQ ID NO:17; the "SIESD" variant (AFD.v8) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:19 and the heavy chain variable domain amino acid sequence of SEQ ID NO:17; or the "SIESD.N103S" variant (AFD.v14) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:19 and the heavy chain variable domain amino acid sequence of SEQ ID NO:20.

[00029] In another~~one~~ aspect, there is provided ~~present invention relates to~~ an anti-Factor D antibody having a variable light chain comprising a HVR-L1 having the sequence of SEQ ID NO:11 or 14, a HVR-L2 having the sequence of SEQ ID NO:6, and a HVR-L3 having the sequence of SEQ ID NO:7 or 13; and a variable heavy chain comprising a HVR-H1 having the sequence of SEQ ID NO:8, a HVR-H2 having the sequence of SEQ ID NO:9 or 12, and a HVR-H3 having the sequence of SEQ ID NO:10 or 15. For example, the anti-Factor D antibody can be the "SIESD" variant (AFD.v8) comprising the following six HVR sequences: HVR-L1 (SEQ ID NO:14), HVR-L2 (SEQ ID NO:6), HVR-L3 (SEQ ID NO:7), HVR-H1 (SEQ ID NO:8), HVR-H2 (SEQ ID NO:12), and HVR-H3 (SEQ ID NO:10); or the "SIESD.N103S" variant (AFD.v14) comprising the following six HVR sequences: HVR-L1 (SEQ ID NO:14), HVR-L2

(SEQ ID NO:6), HVR-L3 (SEQ ID NO:7), HVR-H1 (SEQ ID NO:8), HVR-H2 (SEQ ID NO:12), and HVR-H3 (SEQ ID NO:15).

[00029a] In another aspect, there is provided an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 26 and a heavy chain having the amino acid sequence of SEQ ID NO: 27. In another aspect, there is provided an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 28 and a heavy chain having the amino acid sequence of SEQ ID NO: 29. In another aspect, there is provided an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 26 and a heavy chain having the amino acid sequence of SEQ ID NO: 30. In another aspect, there is provided an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 26 and a heavy chain having the amino acid sequence of SEQ ID NO: 31. In another aspect, there is provided an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 28 and a heavy chain having the amino acid sequence of SEQ ID NO: 32. In another aspect, there is provided an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 28 and a heavy chain having the amino acid sequence of SEQ ID NO: 33.

[00029b] In another aspect, there is provided an anti-Factor D antibody variant with no detectable Asp isomerization made by a method comprising: (a) identifying one or more Asp residues prone to Asp isomerization within HVRs of a reference anti-Factor D antibody; (b) substituting Glu for the Asp residue identified in step (a); (c) screening the resulting candidate variants for Asp isomerization; and (d) selecting those variants that have no detectable Asp isomerization.

[00030] In one embodiment~~aspect~~, the present disclosure~~invention~~ relates to anti-Factor D antibody variants with no detectable Asp isomerization made by a method for removing or reducing isomerization, comprising: (a) identifying one or more Asp residues prone to Asp isomerization within HVRs of a reference anti-Factor D antibody; (b) substituting Glu for the Asp residue identified in step (a); (c) screening the resulting candidate variants for Asp isomerization; and (d) selecting those variants that have no detectable Asp isomerization. In one embodiment~~aspect~~, the method above is combined with a method for removing or reducing deamidation, comprising (a) identifying one or more Asn residues prone to deamidation within HVRs of the reference anti-Factor D antibody; (b) substituting Ser for the Asn residue identified in step (a); (c) screening the resulting candidate variants for deamidation; and (d) selecting those variants having reduced or eliminated deamidation. In another embodiment~~aspect~~, the method for removing or reducing isomerization is combined with a method for reducing overall charge of the antibody by: (a) selecting one or more negatively charged amino acid residues D or E within HVRs of the reference anti-Factor D antibody; (b) substituting Ser for the residue selected in step (a); (c) screening the resulting candidate variants for solubility; and (d) selecting those variants having improved solubility when compared to the reference anti-Factor D antibody.

[00031] In one embodiment~~aspect~~, the anti-factor D antibody variants of the present disclosure~~invention~~ have improved stability while maintaining the factor D binding affinity when compared to the reference anti-factor D antibody. In one embodiment~~aspect~~, antibodies of the present disclosure~~invention~~ bind to Factor D with a binding affinity of at least about 10^{-9} to 10^{-12}M. In one embodiment~~aspect,~~ the antibodies of the present disclosure~~invention~~ include human, humanized or chimeric antibodies.

[00032] In one embodiment~~aspect~~, the antibodies of the present disclosure~~invention~~ are antibody fragments (e.g. antigen-binding fragments). The antibody fragments of the present disclosure~~invention~~ may, for example, be Fab, Fab', $F(ab')_2$, scFv, $(scFv)_2$, dAb, complementarity determining region (CDR) fragments, linear antibodies, single-chain antibody molecules, minibodies, diabodies, or multispecific antibodies formed from antibody fragments.

[00033] In other ~~aspects~~embodiments of the disclosure~~invention~~, the present disclosure~~invention~~ includes compositions comprising an antibody of the ~~invention~~disclosure. In another ~~aspect~~embodiment, the disclosure~~invention~~ concerns a composition of matter comprising an antibody of the ~~invention~~disclosure, as described herein, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

[00034] In another aspect, there is provided a pharmaceutical formulation comprising the antibody or antibody variant described herein. In one ~~aspect~~embodiment, the present ~~invention~~disclosure includes pharmaceutical formulations comprising the antibody or antibody variants described above, at therapeutically effective concentrations. In some ~~aspect~~embodiments, the pharmaceutical formulation comprises the antibody or antibody variant at a concentration of at least 100 mg/ml, between 100-150 mg/ml, between 100-200 mg/ml, between 100-300 mg/ml, between 100-400 mg/ml, between 100-500 mg/ml; at least 200mg/ml, at least 300 mg/ml, at least 400 mg/ml or at least 500 mg/ml. In some ~~aspect~~embodiments, the concentration of the antibody or antibody variant in the formulation is about 200, 250, 300, 350, 400, 450 or 500 mg/ml. In one ~~aspect~~embodiment, the concentration of the antibody or antibody variant in the formulation is less than 450 mg/ml.

[00034a] In another aspect, there is provided a long acting delivery device for ocular delivery comprising the pharmaceutical formulation described herein and a means for delivering the formulation intravitreally to a patient, whereby the formulation remains effective on site for a prolonged period of time.

[00034b] In another aspect, there is provided a use of the formulation or device described herein in the manufacture of a medicament for treatment of a complement-associated disorder.

[00035] Another ~~aspect~~embodiment of the present ~~invention~~disclosure is the use of the antibody of the ~~invention~~disclosure for treatment of disorders associated with excessive or uncontrolled complement activation. They include complement activation during cardiopulmonary bypass operations; complement activation due to ischemia-reperfusion following acute myocardial infarction, aneurysm, stroke, hemorrhagic shock, crush injury, multiple organ failure, hypobolemic shock, intestinal ischemia or other events causing ischemia. Complement activation has also been shown to be associated with inflammatory conditions such as severe burns, endotoxemia, septic shock, adult respiratory distress syndrome, hemodialysis; anaphylactic shock, severe asthma, angioedema, Crohn's disease, sickle cell anemia, poststreptococcal glomerulonephritis and pancreatitis. The disorder may be the result of an adverse drug reaction, drug allergy, IL-2 induced vascular leakage syndrome or radiographic contrast media allergy. It also includes autoimmune disease such as systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, Alzheimer's disease and multiple sclerosis. In another embodiment, complement activation is also associated with transplant rejection. In another embodiment, complement activation is also associated with ocular diseases (all ocular conditions and diseases the pathology of which involve complement, including the classical and the alternative pathway of complement), such as, for example, without limitation, macular degenerative disease, such as all stages of age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, diabetic retinopathy and other ischemia-related retinopathies, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization. In one example, complement-associated eye conditions include age-related macular degeneration (AMD), including non-exudative (e.g intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g. wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In a

further example, nonexudative AMD may include the presence of hard drusen, soft drusen, geographic atrophy and/or pigment clumping. In another example, complement-associated eye conditions include age-related macular degeneration (AMD), including early AMD (e.g. includes multiple small to one or more non-extensive medium sized drusen), intermediate AMD (e.g. includes extensive medium drusen to one or more large drusen) and advanced AMD (e.g. includes geographic atrophy or advanced wet AMD (CNV). In a further example, intermediate dry AMD may include large confluent drusen. In a further example, geographic atrophy may include photoreceptor and/or Retinal Pigmented Epithelial (RPE) loss. In a further example, the area of geographic atrophy may be small or large and/or may be in the macula area or in the peripheral retina. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[00036] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a kit, comprising an antibody of the ~~invention~~disclosure. In one embodiment, the ~~invention~~disclosure provides a kit, comprising an antibody of the ~~invention~~disclosure and instructions for use. In one embodiment, the ~~invention~~disclosure concerns a kit comprising an antibody of the ~~invention~~disclosure and instructions for administering said antibody, to treat a complement-associated disorder. In one embodiment, the ~~invention~~disclosure provides a kit comprising a first container comprising a composition comprising one or more one or more antibodies of the ~~invention~~disclosure; and a second container comprising a buffer. In one embodiment, the buffer is pharmaceutically acceptable. In one embodiment, a composition comprising an antibody of the ~~invention~~disclosure further comprises a carrier, which in some embodiments is pharmaceutically acceptable. In one embodiment, a kit further comprises instructions for administering the composition (.e.g the antibody, or antibody fragment thereof (e.g. antigen-binding fragment) to a subject. In one embodiment, a kit further comprises instructions for use of the kit.

[00037] In one ~~aspect~~embodiment, the ~~invention~~disclosure concerns an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of complement-associated disorders. In one embodiment, the ~~invention~~disclosure concerns an article of manufacture, comprising: (a) a container; (b) a label on the container; and (c) a composition of matter comprising an antibody of the present ~~invention~~disclosure, contained with the container, wherein the label on said container indicates that the composition can be used for treatment, prevention and/or diagnosis of complement-associated disorders.

[00038] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an anti-Factor D antibody of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disease, such as a complement-associated eye condition. In one embodiment, the complement-associated eye condition is selected from age-related macular degeneration (AMD), including non-exudative (e.g intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g. wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[00039] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an article of manufacture of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disease, such as a complement-associated eye condition. In one embodiment, the complement-associated eye condition is selected from age-related macular degeneration (AMD), including non-exudative (e.g intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g. wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[00040] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides use of a kit of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disease, such as a complement-associated eye condition. In one embodiment, the complement-associated eye condition is selected from age-related macular degeneration (AMD), including non-exudative (e.g intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g. wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[00041] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides a Factor D antagonist and a HTRA1 antagonist. In one embodiment, the Factor D antagonist is an anti-Factor D antibody. In a further embodiment, the anti-Factor D antibody is an anti-Factor D antibody variant described herein. In one embodiment the HTRA1 antagonist is an anti-HTRA1 antibody.

[00042] In one ~~aspect~~embodiment, the treatment of disorders associated with excessive or uncontrolled complement activation in a human subject with a disorder associated with excessive or uncontrolled complement activation comprises administering to the subject an effective amount of an therapeutic compound, such as a Factor D antagonist, and further comprises administering to the subject an effective amount of a second therapeutic compound, such as a HTRA1 antagonist. In one embodiment, the Factor D antagonist is an anti-Factor D antibody. In one embodiment, the anti-Factor D antibody is an anti-Factor D antibody variant described herein. In one embodiment, the HTRA1 antagonist is an anti-HTRA1 antibody. In one embodiment, the Factor D antagonist is an anti-Factor D antibody and the HTRA1 antagonist is an anti-HTRA1 antibody.

[00043] In one ~~aspect~~embodiment, the administration of the Factor D antagonist and any second therapeutic compound can be done simultaneously, e.g., as a single composition or as two or more distinct compositions using the same or different administration routes. Alternatively, or additionally the administration can be done sequentially, in any order.

Brief Description of the Figures

[00044] Figure 1 shows amino acid sequences of a reference anti-factor D antibody WT (aFD WT) and its select variants (1A: light and heavy chain sequences of WT; 1B: alignment of light and heavy chain variable domains; 1C: light and heavy chain sequences of SIESD (AFD.v8); 1D: light and heavy chain sequences of SIESD.N103S (AFD.v14)). HVRs within the variable domains are underlined. Residue substitutions in the variants are shown in bold. Cys and Cys-Pro-Pro-Cys (SEQ ID NO: 21) modifications are shown in italics in Figure 1C and 1D.

[00045] Figure 2 illustrates antigen binding capacity of various antibody Fab fragments over prolonged time under defined conditions (2A: Fab protein concentration of 10 mg/mL in pH5.5 buffer; 2B: Fab protein concentration of 100 mg/ml in PBS; 2C: Fab protein concentration of 100 mg/ml in PBS).

[00046] Figure 3 illustrates degradations of various antibody Fab fragments over time under defined conditions whereby main peak is determined by ion-exchange chromatography (IEC) (3A: Fab protein concentration of 10 mg/mL in pH5.5 buffer; 3B: Fab protein concentration of 100 mg/ml in PBS).

12. The antibody variant according to claim 11, further comprising a heavy chain HVR3 (HVR-H3) sequence of SEQ ID NO:15.

13. An anti-Factor D antibody variant comprising substitution at one or more positions within the HVRs of a reference anti-Factor D antibody, wherein said reference anti-Factor D antibody comprises light chain HVR-1 comprising the sequence ITSTDIDDDMN (SEQ ID NO: 5), light chain HVR-2 comprising the sequence GGNTLRP (SEQ ID NO: 6), light chain HVR-3 comprising the sequence LQSDSLPYT (SEQ ID NO: 7), heavy chain HVR-1 comprising the sequence GYTFTNYGMN (SEQ ID NO: 8), heavy chain HVR-2 comprising the sequence WINTYTGETTYADDFKG (SEQ ID NO: 9), and heavy chain HVR-3 comprising the sequence EGGVNN (SEQ ID NO: 10), and wherein said substitution is one or more of the following: (a) amino acid at position 5 of SEQ ID NO: 5 is S (a, b, and c disclosed in SEQ ID NO: 22); (b) amino acid at position 7 of SEQ ID NO: 5 is E; (c) amino acid at position 8 of SEQ ID NO: 5 is S; (d) amino acid at position 13 of SEQ ID NO: 9 is E (SEQ ID NO: 23); (e) amino acid at position 4 of SEQ ID NO: 7 is E (SEQ ID NO: 24); or (f) amino acid at position 5 of SEQ ID NO: 10 is S(SEQ ID NO: 25).

14. The antibody variant according to claim 13, wherein the antibody variant comprises the substitutions (b)-(d) therein.

15. The antibody variant according to claim 13, wherein the antibody variant comprises the substitutions (b)-(e) therein.

16. The antibody variant according to claim 13, wherein the antibody variant comprises the substitutions (a)-(d) therein.

17. The antibody variant according to claim 13, wherein the antibody variant comprises the substitutions (a)-(d) and (f) therein.

18. An anti-Factor D antibody comprising a light chain variable domain amino acid sequence of SEQ ID NO:16, 18 or 19.

19. An anti-Factor D antibody comprising a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20.

20. The anti-Factor D antibody according to claim 18, further comprising a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20.

21. The anti-Factor D antibody according to claim 20, wherein the light chain variable domain amino acid sequence is according to SEQ ID NO:19 and the heavy chain variable domain amino acid sequence is according to SEQ ID NO:17.

44. Use according to claim 43, wherein the ocular disease is selected from the group consisting of age-related macular degeneration (AMD), diabetic retinopathy, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

45. Use according to claim 44, wherein the ocular disease is intermediate dry form AMD or geographic atrophy (GA).

~~46. A composition comprising a Factor D antagonist and a HTRA1 antagonist.~~

~~47. The composition of claim 46 wherein the Factor D antagonist is an anti-Factor D antibody.~~

~~48. The composition of claim 46 or 47 wherein the HTRA1 antagonist is an anti-HTRA1 antibody.~~

~~49. The composition of any one of claims 46-48 wherein the anti-Factor D antibody is an anti-Factor D antibody of any one of claims 1-31.~~

~~50. Use of a composition comprising a Factor D antagonist and a HTRA1 antagonist for treatment of a complement-associated disorder.~~

~~51. Use according to claim 44, wherein the complement-associated disorder is an ocular disease.~~

~~52. A method of treating a complement-associated disorder in a human subject comprising administering to the subject an effective amount of a first therapeutic compound and an effective amount of a second therapeutic compound.~~

~~53. The method of claim 46 wherein the first and second therapeutic compounds are administered simultaneously.~~

~~54. The method of claim 52 wherein the first and second therapeutic compounds are administered as a single composition.~~

~~55. The method of claim 52 wherein the first and second therapeutic compounds are administered as distinct compositions.~~

~~56. The method of claim 52 wherein the first and second compounds are administered sequentially.~~

~~57. The method of claim 52, wherein the first therapeutic compound is a Factor D antagonist.~~

~~58. The method of claim 52 or 57, wherein the second therapeutic compound is a HTRA1 antagonist.~~