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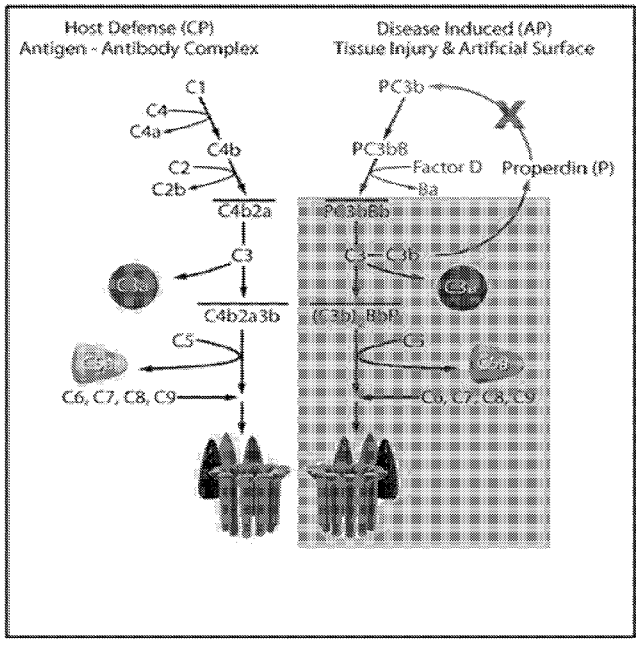

Fig. 1

(57) Abstract: A method of treating a complement mediated ocular inflammation, hemorrhaging and fibrosis, and the pathological consequences thereof, in a subject in need thereof, the method comprising of administering to the subject a therapeutically effective amount of an antibody which inhibits the alternative complement pathway, wherein the antibody administered is effective for inhibiting complement mediated ocular inflammation, hemorrhaging and fibrosis, and the pathological consequences thereof.

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COMPOSITIONS AND METHODS OF TREATING OCULAR DISEASES

RELATED APPLICATION

[0001] This application claims priority benefit of U.S. Provisional Patent Application Serial No. 61/920,541, filed on December 24, 2013, the content of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to the prevention and treatment of complement-mediated ophthalmic diseases that can be caused by or associated with complement activation and complement activation byproducts, and particularly relates to compositions and methods of using inhibitors of complement activation to treat and prevent fibrosis, hemorrhage, inflammation, neovascularization and choroidal neovascularization in ocular space.

BACKGROUND

[0003] The complement system is activated in ocular diseases. FIG. 1 provides a schematic diagram of the two primary pathways of the complement system; the classical pathway and the alternative pathway. The alternative pathway (AP) is activated by pathogens and by foreign or abnormal surfaces (such as drusen) and is capable of rapid self-amplification. Excessive and/or prolonged activation of the AP is believed to be the primary cause of many inflammatory and non-inflammatory pathologies and disorders. Age-related macular degeneration (AMD), diabetic retinopathy, uveitis, retinal fibrosis, hemorrhage, and inflammation in many ocular pathologies and disorders, are caused by AP activation and dysregulation.

[0004] The AP consists of complement Factors B, D, and P (Properdin). FIG. 2 provides a schematic diagram of the cytokines and growth factors which are produced as a result of complement system activation. Complement factors C3a and C5a activate immune system cells, and other types of cells, to produce TNF-alpha, VEGF, cytokines, growth factors, and other inflammatory mediators. Upon AP activation, C3b binds Properdin and Factor B, forming the complex PC3bB. Factor D then cleaves the Factor B within the complex. This cleavage of Factor B produces an active convertase which cleaves C3 into more C3b and C3a, thereby perpetuating the formation of additional C3 convertase. Additional molecules of C3b and Bb combine with PC3bBb to form an active C5 convertase which cleaves molecules of C5 into C5b and C5a. The C5b then associates with factors C6, C7, C8 and C9 to form the lytic macromolecule C5b-9 (also known as the Membrane Attack

Complex, or "MAC"). MAC lyses cells by penetrating cell membranes. This is one of the known processes by which RPE cells, rods and cones, in the context of AMD and other ocular disorders, become damaged as a result of complement system activation.

SUMMARY

[0005] Embodiments described herein relate to compositions and methods of treating and/or preventing ocular pathologies mediated via fibrosis, vascular hemorrhage, inflammation, and cell death in a subject in need thereof. The method can include administering to the subject a therapeutically effective amount of an alternative pathway (AP) inhibitor to the subject to inhibit fibrosis, vascular hemorrhage, inflammation, and/or cell death in a subject.

[0006] In some embodiments, the method can include treating, preventing, and/or inhibiting choroidal neovascularization, retinal atrophy, retinal fibrosis, vascular hemorrhage, and inflammation associated with ocular disorders of a subject in need thereof by administering to the subject a therapeutically effective amount of an alternative pathway inhibitor antibody or antigen binding fragment thereof that selectively blocks the alternative pathway but has no effect on the lectin or the classical pathway. For example, the method can include selective inhibition of the alternative pathway by antibodies that bind properdin with high affinity (*e.g.,* K_D of 1 pM to 1000 pM) and block the association of properdin to C3b and C5b. Such antibodies can bind to at least one of the six TSRs selected from the group consisting of TSR0, TSR1, TSR4, TSR5, and TSR6. The use of an anti-properdin antibody to inhibit retinal fibrosis and hemorrhage is novel as no complement inhibitors have shown inhibition of retinal fibrosis and retinal hemorrhage.

[0007] In other embodiments, the method can include treating, preventing, and/or inhibiting VEGF formation, C5b-9 formation and cytokine formation associated with ocular disorders of a subject in need thereof by administering to the subject a therapeutically effective amount of an alternative pathway inhibitor antibody (*i.e.,* anti-AP antibody) or antigen binding fragment thereof that selectively blocks the alternative pathway but has no effect on lectin or the classical pathway. In some embodiments, the anti-AP antibodies can include anti-properdin antibodies that bind properdin and block properdin interaction with C3b/C5b and inhibit inflammation, tissue injury, and neovascularization. The administration of the anti-AP antibodies can prevent the formation of C3a/C5a via the alternative pathway,

prevent activation of inflammatory cells including retinal epithelial cells via C3a/C5a, release of endothelial growth factors that promote neovascularization (*e.g.,* VEGF), prevent production of inflammatory mediators from activated cells (*e.g.,* cytokines), and prevent production of C5b-9 responsible for tissue injury (*e.g.,* MAC) and injury of retina epithelial cells, rods, and cones. Injured cells of the eye produce LDH which is marker of tissue death. The anti-AP antibodies can also prevent Lactate DeHydrogenase (LDH) formation and be used to inhibit ocular cell death

[0008] Both C3a/C5a generated via the alternative pathway activate ocular cells including but not limited to RPE cells, rods and cones cells, and cause subsequent release of inflammatory mediators and VEGF growth factors that promote neovascularization. Inhibition of C3a/C5a can control VEGF formation and inflammatory mediators and therefore control of inflammation. Additional molecules known to be produced via the activation of the alternative pathway are; TNF-α, IL-1, IL-6, IL-8, IL-17, VEGF, and/or PDGF. Anti-AP antibodies are cable of controlling such activation in ocular disorders.

[0009] Formation of blood vessels is critical for tissue repair, which is mediated via VEGF formation in disease. Both C3a/C5a generated via the alternative pathway, activate ocular cells including but not limited to RPE cells, rods and cones cells and cause subsequent release of VEGF and PDGF growth factors that promote neovascularization. Inhibition of C3a/C5a is therefore expected to control VEGF formation that causes pathology and not the VEGF responsible for tissue repair. In some embodiments, the anti-AP antibodies described herein can be used in a prophylactic treatment for a subject undergoing an ophthalmologic procedure who has been identified as being at risk for developing a complement mediated ocular disorder post procedure. In some embodiments, the anti-AP antibodies can inhibit fibrosis, hemorrhage and inflammation associated with the ocular procedure. In still other embodiments, the anti-AP antibodies can prevent neovascularization following the ophthalmologic procedure without inhibiting tissue repair.

[0010] In another embodiment, a process for inhibiting fibrosis and hemorrhage with normal tissue repair in a subject undergoing an ocular surgical procedure (or other physical ocular trauma) can include administering to the subject an anti-AP antibody to promote wound healing. In one embodiment, the process for treating AP mediated ocular pathologies can occur during an ocular surgical procedure wherein the subject undergoing the procedure suffers from a condition characterized by retinal hemorrhage or inflammation, which

may/may not lead to vision loss. This embodiment includes the step of administering an anti-AP antibody either immediate before, during or after the surgical procedure.

[0011] In other embodiments, an anti-AP antibody can be used to prevent fibrosis and hemorrhage secondary to a pathology of uveitis, including but not limited to; Iritis, Pars planitis, Choroiditis, Chorioretinitis, Anterior uveitis, Posterior uveitis, Scleritis, ocular neovascularization, atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, Purtscher's retinopathy, Sorsby's fundus dystrophy, Doyne Honeycomb Retinal Dystrophy, Malattia Leventinese, Familial Dominant Drusen, North Carolina macular dystrophy, Juvenile Macular degeneration, Stargardt's disease, Vitelliform Macular Dystrophy, Adult-Onset Foveomacular Vitelliform Dystrophy (AOFVD), Sorsby's fundus dystrophy, and Best's Disease.

[0012] In other embodiments, one or more of the claimed anti-AP antibodies can be used to prevent inflammation, neovascularization, cellular atrophy, tissue degradation, release of LDH, fibrosis and/or hemorrhage secondary to a pathology of uveitis, including but not limited to; Iritis, Pars planitis, Choroiditis, Chorioretinitis, Anterior uveitis, Posterior uveitis, or Scleritis, ocular neovascularization, diabetic retinopathy or other inflammatory disorder of the eye associated with diabetes, prevent hypertensive retinopathy, prevent autoimmune uveitis or uveitis secondary to an autoimmune disorder, Behçet's Disease, Eales Disease, or other autoimmune inflammatory disease of the eye, atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, Purtscher's retinopathy, AMD, Sorsby's fundus dystrophy, Doyne Honeycomb Retinal Dystrophy, Malattia Leventinese, Familial Dominant Drusen, North Carolina macular dystrophy, Juvenile Macular degeneration, Stargardt's disease, Vitelliform Macular Dystrophy, Adult-Onset Foveomacular Vitelliform Dystrophy (AOFVD), Sorsby's fundus dystrophy, or Best's Disease, vascular occlusion including, but not limited to; Central retinal vein occlusion (CRVO), occlusive peripheral arterial disease, ocular ischemic syndrome secondary to atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, or Purtscher's retinopathy, retinopathy of prematurity or familial exudative vitreoretinopathy, ocular pathology occurring in the anterior segments of the eye, and Fuchs' corneal endothelial dystrophy.

[0013] In some embodiments, an anti-AP antibody is used to prevent fibrosis and/or hemorrhage secondary to a pathology characterized by vascular occlusion. Such pathologies

associated with vascular occlusion can include: Central retinal vein occlusion (CRVO), occlusive peripheral arterial disease, ocular ischemic syndrome secondary to atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, and Purtscher's retinopathy.

[0014] In one embodiment, the anti-AP antibody is used to prevent fibrosis and hemorrhage secondary to diabetic retinopathy. In another embodiment, an anti-P, anti-C3b, or anti-Bb antibody is used to treat any or all AP mediated pathologies associated with retinal fibrosis or hemorrhage in a diabetic patient, hypertensive retinopathy, an autoimmune disorder, autoimmune uveitis or uveitis, Behçet's Disease, Eales Disease, or other autoimmune disease of the eye.

[0015] In some embodiments, the anti-AP antibody is used to prevent fibrosis and/or hemorrhage secondary to retinopathy of prematurity or familial exudative vitreoretinopathy, ocular pathology occurring in the anterior segments of the eye, Fuchs' corneal endothelial dystrophy, repeated treatment with anti-VEGF agents for prevention of neovascularization.

[0016] In some embodiments, the anti-AP antibody used to treat ocular hemorrhage and/or fibrosis is one which binds to one of the group of complement factors which includes Ba, Bb, C3b, D, C5, C6, C7 or C8. In other embodiments of the invention, the anti-AP antibody used to treat ocular hemorrhage and/or fibrosis is one which also inhibits the classical or lectin pathway.

[0017] In some embodiments, the anti-AP antibody can be an anti-properdin or anti-P antibody. The anti-properdin antibodies can be capable of inhibiting neovascularization while also inhibiting ocular inflammation, ocular edema, retinal fibrosis and hemorrhage. The present invention provides a process for preventing or treating diseases and disorders which involve AP mediated neovascularization, ocular inflammation, ocular edema, ocular tissue atrophy, vascular permeability, fibrosis, hemorrhage and other inflammatory and autoimmune driven conditions and pathologies.

[0018] In another embodiment, one or more of the anti-P antibodies described herein can be used to treat Wet AMD. One or more of the anti-P antibodies described herein may be used to treat a subject who has previously been treated with an anti-VEGF agent. One or more of the claimed anti-P antibodies described herein may be used to treat a subject requiring treatment for neovascularization wherein anti-VEGF agents are counter indicated.

In another embodiment, one or more of the anti-P antibodies can be used to prevent development of Dry AMD post treatment with an anti-VEGF agent.

[0019] Embodiments described herein also relate to a process of using an anti-P antibody for controlling and preventing ocular pathologies wherein at least one of the following are part of the disease process; inflammation, neovascularization, cellular atrophy, tissue degradation, release of LDH, fibrosis and/or hemorrhage

[0020] In another embodiment, a process for treating AP mediated ocular pathologies associated with AP activation occurring during or after an ocular surgical procedure can include administering one or more anti-P antibody to the subject either immediately prior to, during or immediately following the ocular procedure.

[0021] Another embodiment relates to the use of these anti-AP antibodies for the preparation of a medicament or composition for the treatment of disorders associated with excessive or uncontrolled complement activation. They include complement activation during ocular disorders, particularly disorders where neovascularization, tissue injury, tissue destruction, geographic atrophy characterize the disease.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. 1 is a schematic diagram of both the classical and alternative complement pathways.

[0023] FIG. 2 is a schematic diagram of how C3a and C5a produced via the AP activate cells, which produce TNF-alpha, inflammatory mediators, growth factors, such as VEGF and PDGF, and inflammatory cytokines.

[0024] FIG. 3 presents data from an experiment in which an anti-AP antibody was added to human blood during an extracorporeal model of dialysis, wherein complement activation is known to occur. After incubation at 37°C, the levels of VEGF were measured using conventional methods. The data from this experiment demonstrate that the anti-AP antibody was able to inhibit production of VEGF in human blood.

[0025] FIG. 4 presents data from an experiment in which an anti-AP antibody was added to human blood during an extracorporeal model of dialysis, wherein complement activation is known to occur. After incubation at 37°C, the levels of PDGF were measured using conventional methods. The data from this experiment demonstrate that the anti-AP antibody was able to inhibit production of PDGF in human blood.

[0026] FIG. 5 presents data from an experiment in which an anti-AP antibody was added to human blood during an extracorporeal model of dialysis, wherein complement activation is known to occur. After incubation at 37°C, the levels of TNF-alpha were measured using conventional methods. The data from this experiment demonstrate that the anti-AP antibody was able to inhibit production of TNF-alpha in human blood.

[0027] FIG. 6 presents data from an experiment in which an anti-AP antibody was added to human blood during an extracorporeal model of dialysis, wherein complement activation is known to occur. After incubation at 37°C, the levels of IL-1b were measured using conventional methods. The data from this experiment demonstrate that the anti-AP antibody was able to inhibit production of IL-1b in human blood

[0028] FIG. 7 illustrates *Ex Vivo* Inhibition of Cell Lysis - This graph is a representation of data collected from studies evaluating anti-P antibodies for their effect on MAC formation, cell lysis, and release of LDH (relative to control).

[0029] FIG. 8 illustrates images taken of rhesus monkey retinas taken from a rhesus model of CNV, wherein the reference drug was an anti-VEGF agent and the test drug was one of the invention's anti-P antibodies.

[0030] FIG. 9 illustrates a graphical representation of the data collected from quantification of CNV areas observed in week 3 of rhesus monkey model of Wet AMD and CNV – the methods used to quantify the extent of CNV in each study group is described in the specification of this application..

[0031] FIGs. 10(A-B) illustrate: A. shows the visualization of retinal hemorrhage in images taken of rhesus monkey eyes, taken from the rhesus Wet-AMD/CNV model study. Hemorrhage is seen in these images as exceptionally dark, or black, regions. For this figure, a few, but not all, of these regions have been outlined with a dotted white line. The images are provided only as examples of the visualization of hemorrhage. B provides an example, for comparison to the control, of images taken of treated retinas.

[0032] FIG. 11 illustrates the quantification of Hemorrhage observed in week 3 of rhesus monkey model of Wet AMD and CNV – the methods used to quantify the extent of hemorrhaging in each study group is described in the specification of this application.

[0033] FIG. 12 illustrates Images of Study Subject Eyes – These images are from a rhesus monkey model of Wet AMD. The images, originally in color, have been converted to grayscale for this application.

[0034] FIGs. 13(A-B) illustrate a Visualization of Fibrosis – All of the images above were taken of rhesus monkey retinas in a rhesus model of CNV study. In FIG. 13A, the areas outlined in dotted white lines are a few examples of the appearance of fibrosis, in Week3 of the study (note that there is more fibrosis in the pictures than is outlined for purposes of these examples). Observers graded each image shown in FIG. 12 using the grading key provided as FIG. 13B above.

[0035] FIG. 14 illustrates quantification of Fibrosis – The above graph presents the results of the observer grades for extent of fibrosis in each subject animal from the rhesus monkey CNV study. As can be seen from the data provided above, the anti-P antibody substantially reduced fibrosis in 2 out of the 3 animals treated.

DETAILED DESCRIPTION

Definitions

[0036] Unless specifically defined herein, all terms used in this document have the same meaning as would be understood by those of ordinary skill in the art of the present invention. The following definitions are provided for clarity, and to define their intended meaning as used in the specification and claims to describe the present invention.

Complement Pathways

[0037] "CLASSICAL PATHWAY" refers to the complement system pathway which is triggered/activated by antigen-antibody complexes.

[0038] "ALTERNATIVE PATHWAY" (abbreviated as "AP" or "the AP") refers to the complement system pathway with is triggered/activated by an artificial or dead cell surface (or cell-surface like material) which is recognized as a foreign surface.

[0039] "ALTERNATIVE PATHWAY SPECIFIC PROTEIN" refers to Factor B, Factor Bb, Factor D, Properdin, and/or AP mediated C3b which is specifically produced by AP C3 convertase.

[0040] "ANTI-AP ANTIBODIES" refers to a group of antibodies which includes all antibodies targeted to AP specific proteins, and any antibody targeted to (bind to) AP mediated C5, C6, C7, C8, and C9. AP antibodies also include antibodies which bind to any protein or molecule which regulates AP mediated production of C3, C3b, P, B, D, C5, C6, C7, C8, C9, or S protein, such as DAF, MIRL.

[0041] "ANTI-P ANTIBODIES" are antibodies which were raised against human properdin or animal properdin. Anti-P antibodies include all antibodies which bind to human or animal properdin and which inhibit the AP.

[0042] "C3a DEPENDENT CELLULAR ACTIVATION" describes the activation of neutrophils, monocytes, platelets, T lymphocytes, endothelial cells, mast cells, platelets, retinal epithelial cells, rods, cones, and other cells which occurs when C3a produced by the AP binds to C3a cell receptors.

[0043] "C5a DEPENDENT CELLULAR ACTIVATION" describes the activation of neutrophils, monocytes, platelets, T lymphocytes, endothelial cells, mast cells, platelets, retinal epithelial cells, rods, cones, and other cells which occurs when C5a produced by the AP binds to C5a cell receptors.

[0044] "C5b-9/MAC MEDIATED/DEPENDENT TISSUE INJURY / CELL DAMAGE" describes the cellular damage caused by the formation of sC5b-9 and/or C5b-9 (also known as Membrane Attack Complex, or "MAC"). Such tissue injury occurs in ocular diseases where complement mediated MAC production and deposition are a part of the disease pathology.

[0045] "AP MEDIATED INFLAMMATION" refers to a multitude of physiologic processes, cell activations, and protein productions which are mediated by the AP and which cause and/or perpetuate inflammation. AP mediated inflammation can be measured by continued or increased formation, and/or release, of AP dependent C3a, C3b, C5a, C5b, C5b-9, and/or sC5b-9, and all the anticipated consequences thereof. C3a, C5a, C5b-9 activate cells to release inflammatory mediators including but not limited to; TNF-α, IL-1, PDGF, VEGF, neutrophil elastase, and other cytokines and inflammatory mediators.

[0046] "ANTIBODY," as used herein, contains two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains; CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hyper-variability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs

and four Frameworks arranged from amino-terminus to carboxyl-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The term "antibody" encompasses whole antibodies and antibody fragments thereof, derived from any antibody-producing mammal (*e.g.,* mouse, rat, rabbit, and primate including human). Exemplary antibodies include polyclonal, monoclonal and recombinant antibodies; multi-specific antibodies (*e.g.,* bispecific antibodies); humanized antibodies; murine antibodies; chimeric, mouse-human, mouse-primate, primate-human monoclonal antibodies; and anti-idiotype antibodies, and may be any intact molecule or fragment thereof.

[0047] "ANTIGEN BINDING FRAGMENT" refers to a fragment of a whole antibody which binds to the same target as the whole antibody from which it was derived. Types of antibody fragments include nano bodies, diabodies, linear antibodies, single-chain antibody molecules and multispecific antibodies formed from antibody fragments. Examples of antibody fragments include Fab, Fab', F(ab)2, F(ab')2 and Fv fragments, or scFv fragments (and any PEGylated variations of any of the forgoing). Examples of antigen binding fragments include, but are not limited to:

"Fab" fragments (single chain variable regions with VH and VL);

"Monovalent Fragments" (antibody fragments consisting of the VL, VH, CL and CH1 domains);

"F(ab')2" fragments (bivalent fragments comprising two Fab fragments linked by a disulfide bridge at the hinge region);

"Fd" fragments (which consist of the VH and CH1 domains of an antibody);

"Fv" fragment (which consist of the VL and VH domains of a single arm of an antibody);

single domain antibody ("dAb"), which consist of a VH domain or a VL domain;

an isolated Complementarity Determining Region ("CDR," defined below).

[0048] "COMPLEMENTARITY DETERMINING REGIONS (CDRs)" are the key binding regions of the antibody. In a full-length antibody, there are typically three CDRs found within the variable regions of each of the two heavy and light chain variable regions.

[0049] "CHIMERIC ANTIBODY" is a recombinant protein that contains the variable domains and CDRs derived from an antibody from a non-human species of animal, while the remainder of the antibody molecule is derived from a human antibody.

[0050] "HUMANIZED ANTIBODY" is an antibody that consists of non-human CDRs and humanized framework regions. Humanized antibodies are typically recombinant proteins in which only the antibody complementarity-determining regions are of non-human origin.

[0051] A "FUNCTIONAL DERIVATIVE" of an antibody is any compound which is either taken from, or incorporates within itself, the functional region of the antibody. Functional derivatives of antibodies include, but are not limited to, antigen binding fragments (previously defined), CDRs, chimeric antibodies, monoclonal antibodies, recombinant antibodies, and single chain antibodies. CDRs (previously defined), as antigen binding fragments, can also be incorporated into single domain antibodies, maxi bodies, mini bodies, intrabodies, diabodies, triabodies, tetra bodies, v-NAR and bis-scFv. Antigen binding fragments of antibodies can be grafted into scaffolds based on polypeptides such as Fibronectin type III (Fn3). Antigen binding fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions.

[0052] "Fc REGION" refers to the region of the antibody that induces effector functions (defined below).

[0053] "EFFECTOR FUNCTIONS" refer to those biological activities attributable to the native Fc region of an antibody, and vary among antibody isotypes. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.,* B cell receptor); lack of activation of platelets that express Fc receptor; and B cell activation. In order to minimize or eliminate side effects of a therapeutic antibody, it may be preferable to minimize or eliminate effector functions.

[0054] "REDUCED Fc EFFECTOR FUNCTION(S)" refers to the function(s) of an antibody wherein the antibody does not act against an antigen that recognizes the Fc region of the antibody. Examples of reduced Fc effector functions can include, but are not limited to, reduced Fc binding to the antigen, lack of Fc activation against an antigen, an Fc region that contains mutations to prevent normal Fc effector functions, or prevention of the activation of platelets and other cells that have Fc receptors.

[0055] "IDENTICAL," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (i.e., 60% identity, optionally 65%, 70%, 75%,80%, 85%, 90%, 95%, or 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 50 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length. The percent identity between two amino acid sequences can also be determined using the algorithm of Meyers and Miller.

Treating Complement Mediated Ocular Inflammation, Hemorrhage and Fibrosis, and the Pathological Consequences Thereof

[0056] Embodiments described herein relate to compositions and methods for treating a subject suffering from any ocular condition associated with retinal fibrosis, hemorrhage and/or ocular inflammation by administering to the afflicted subject an effective amount of an anti-AP antibody. The administered anti-AP antibody (*e.g.,* anti-properdin antibody or anti-P antibody) may target any AP specific protein, and/or any antibody, which targets the PC3bB complex of the AP. Additionally, embodiments described herein include methods for treating complement mediated degenerative ocular disorders including (but not limited to) AMD and AMD-like conditions, by administering to the afflicted subject an effective amount of an anti-AP antibody.

Specific Mechanisms Of AP-Mediated Ocular Pathologies

AMD & Drusen

[0057] In patients with AMD and other disorders involving deposition and accumulation of lipofuscin, drusen can build up between the Bruch's membrane and the retinal pigment epithelium (RPE) of the eye. This buildup of material causes a tear in the bruch's membrane resulting in the breakage of the blood-retinal barrier. Breakage of the blood-retinal barrier leads to choroidal neovascularization (CNV), subretinal hemorrhage, serous retinal (or retinal pigment epithelium) detachments, lipid exudates, and/or

fibrovascular scar. All of these pathologies are part of one or more ocular diseases. Drusen deposits and damaged tissues are known to activate the alternative complement pathway that ultimately leads to inflammation, tissue injury, and final vision loss.

Drusen & Alternative Pathway

[0058] In the context of AMD, several inflammatory cytokines, activated microglial cells, macrophages and other inflammatory cells have been found associated with drusen. The presence of activated cells, components of activated complement pathway, and inflammatory mediators suggest activation of the alternative pathway onsite of pathology. Chronic inflammation, and the consequences thereof, can jeopardize the integrity of the retinal pigment epithelium that in turn causes photoreceptor atrophy and choroidal neovascularization (CNV). Recent findings have confirmed the role of immunologic processes in AMD pathogenesis, including the processes by which inflammatory cells and molecular mediators perpetuate inflammation in and around the Bruch's membrane. Dysregulation of complement activation results in an over production of anaphylatoxins, which activate a variety of ocular tissue cells. In the context of AMD, activated RPE cells release VEGF and recruit fibroblasts and macrophages to the site of injury, resulting in retinal fibrosis and inflammation. Chronic complement activation is the primary cause and driving force behind chronic ocular inflammation, which is the root cause of ocular disorders and pathologies.

Alternative Pathway & Inflammation

[0059] Chronic local inflammation and complement activation are inextricably involved in ocular pathologies. Our approach is to target specific molecular constituents in the complement pathway in such a way as to dampen or inhibit the eye's chronic inflammatory processes. The anti-AP antibodies described herein can be used in methods of treatment that inhibit the inflammatory processes, which cause inflammation, hemorrhage, fibrosis, and neovascularization in AMD and related ocular disorders and pathologies. The anti-AP antibodies described herein can be used to inhibit inflammation, hemorrhage, fibrosis, and neovascularization, which are associated with ocular surgery, or which are potential post-operative complications of ocular surgery.

[0060] Activation of the AP of the innate immune system produces C5a and C3a, which are potent anaphylatoxins. Dysregulation of complement activation results in an over production of C5a and C3a. C5a and C3a activate retinal and immune system cells, and thereby perpetuate a cascade of complement system activity which results in chronic ocular inflammation. C5a decreases RPE cell viability and ability to suppress immune cell proliferation, resulting in over proliferation and recruitment of fibroblasts and macrophages. At the same time, C5a also increases VEGF secretion by RPE cells, which perpetuates CNV. Immune system cells bearing C3a receptors, such as monocytes, T-lymphocytes, mast cells, basophils, and microglial cells are also activated by C3a. Activated cells release inflammatory mediators such as TNF, IL-1, IL-6, IL8, VEGF, PDGF, FGF, and several other cytokines. (see FIG. 2) In order to inhibit all of these inflammatory mediators, the agents of the present invention target the AP upstream, at the point where properdin binds C3b.

Alternative Pathway & Vascular Endothelial Growth Factor (VEGF)

[0061] As previously discussed, C5a activates RPE cells to produce VEGF. The AP also activates other cells which can mediate production of VEGF. In pathological conditions where the AP is dysregulated, production of VEGF can be excessive. Thus, AP inhibition is expected to inhibit C3a and C5a production and thereby inhibit production of VEGF. Inhibition of VEGF is important in effectively inhibiting CNV and other ocular pathologies related to vascular dysfunction. By targeting the AP upstream of complement mediated VEGF production, the anti-AP antibodies described herein can provide a treatment method, which inhibits formation of VEGF without jeopardizing tissue repair.

VEGF & Neovascularization

[0062] Under normal circumstances, production of VEGF initiates new blood vessel growth and promotes healing of injured tissue. In some pathological conditions, excessive, chronic, or otherwise uncontrolled VEGF production causes an abnormal and/or excessive growth of blood vessels. It is well known within the art that uncontrolled production of VEGF plays a key role in choroidal neovascularization (CNV). When the presence of drusen or some other source of retinal injury occurs, the inflammatory processes cause a proliferation of VEGF production. In healthy tissues, this VEGF is released to promote normal new vessel growth at the site of injury. Under pathological conditions, the

uncontrolled VEGF results in uncontrolled growth of abnormal vessels (also known as CNV). CNV exacerbates the injury and can directly cause loss of vision.

[0063] While VEGF is the primary cause of CNV, it promotes the formation of new healthy blood vessels. Normal formation of new vasculature is required for wound healing. Thus, an ideal treatment should only prevent the formation of pathological VEGF important for ocular pathologies. Unfortunately, anti-VEGF treatments completely deplete VEGF, while proven effective for preventing CNV, also prevent tissue repair. Similarly, any therapeutic, which completely inhibits all neovascularization will also inhibit tissue repair. For this reason, agents, which directly neutralize VEGF are not indicated for patients undergoing ocular surgery. Lesions formed in the normal course of the ocular procedure, along with those which are inherently associated with the disease, require VEGF for normal tissue repair. Consequently, patients undergoing ocular surgery can't be treated with anti-VEGF agents.

Neovascularization & Wet AMD

[0064] Neovascular AMD, which is also referred to as "Wet AMD" or "Exudative AMD," is associated with an inadequate regulation of the complement system. Dysregulation of VEGF causes uncontrolled growth of abnormal vasculature. In advanced cases, neovascular AMD is associated with pigment epithelial detachment and subretinal hemorrhage. Currently available drugs, which neutralize VEGF can treat CNV. These therapies include anti-VEGF agents and antibodies (PCT/US12/20855), Genentech (EP070871431), and Xoma (PCT/US08/080531). Lucentis (an anti-VEGF antibody Fab) and Eyelea (VEGF receptor) are two anti-VEGF agents of the prior art. These VEGF-targeting agents are provided to Wet AMD patients for treatment and prevention of neovascularization. While these drugs are effective for preventing CNV, they do not prevent the underlying ocular inflammation, fibrosis, and vascular leakage including hemorrhage that perpetuates disease progression even in the absence of VEGF. Agents which target VEGF directly do not inhibit the AP or AP induced inflammation or tissue injury. Consequently, such agents do not prevent complement mediated inflammation, RPE destruction via MAC formation, or any other pathological manifestations of AP dysregulation. Moreover, due to their inhibitory effect on tissue repair, recent studies have shown that such agents can ultimately cause Geographic Atrophy and permanent loss of vision. Thus agents that prevent retinal fibrosis,

vascular hemorrhage, and CNV are an unmet need. Such agents are needed to control further damage post VEGF treatment.

[0065] In two separate animal models of Wet AMD, it was found that the anti-AP antibodies described herein can prevent CNV, inflammation, fibrosis, and hemorrhage as well as wound healing. Laser induced CNV was created that is essentially a wound, which leads to inflammation, fibrosis, and hemorrhage. In the CNV model in rhesus, a anti-AP antibodies described herein (*e.g.,* an anti-properdin antibody Fab) inhibited CNV. In the same study, CNV was more completely inhibited in those monkeys treated with Lucentis (an anti-VEGF antibody Fab). However, the Lucentis treated animals experienced more hemorrhaging and more fibrosis (scarring) than did the animals treated with the anti-AP antibodies.

[0066] Other embodiments described herein relate to a combination treatment for AMD, which utilizes the efficiency of an anti-VEGF treatment in the treatment of CNV, and which also utilizes an anti-AP antibody. Short-term use of an anti-VEGF agent, followed by (or concurrent with) use of an anti-AP antibody, can provide immediate effect on CNV while also addressing inflammation, tissue atrophy, returning CNV, hemorrhaging and hemorrhaging in post CNV patients further reducing vision loss.

[0067] Activation of the alternative pathway generates multiple growth factors such as VEGF and PDGF both of which have been involved in AMD pathology. Drugs which directly target either VEGF alone or both VEGF and PDGF have shown efficacy in Wet AMD. However, treatments which target both factors are more effective. Fovista is a combination therapy with anti-VEGF and anti-PDGF both of which neutralize the existing growth factors responsible for neovascularization. In some embodiments, the anti-AP antibodies can be used to prevent the formation of multiple growth factors responsible for neovascularization, fibrosis, and inflammation. There is currently no treatment for retinal fibrosis. The anti-AP antibodies described herein can block the production of both the VEGF and PDGF.

Alternative Pathway and Tissue Injury

[0068] Complement pathway activation leads to the formation of MAC (C5b-9). As previously described, and as presented schematically in FIG. 1 and FIG. 2, once the AP is activated it will lead to inflammatory cell activation and MAC formation. MAC-mediated RPE activation, is important for vision loss in AMD and other ocular pathologies. Fragments

of destroyed RPEs have been found in drusen, along with complement system proteins, including MAC. Knockout studies, wherein study subjects are unable to form functional MAC via the AP, provide evidence of the role of the AP in tissue damage, demyelination, reduced inflammatory cell infiltrate, and improved functional recovery.

Tissue Injury & Geographic Atrophy

[0069] Geographic Atrophy (GA) is an advanced form of Dry AMD. In the course of AMD disease progression, as drusen enlarge and complement driven inflammation proliferates out of control, ocular tissues suffer from both physical and physiological damage. Drusen can put physical pressure and cause oxidative stress on these cells while complement driven MAC formation causes cell lysis and death. Further aggravating the situation, the release of inflammatory mediators causes vascular permeability, which causes edema, hemorrhaging and other vascular pathologies. The culmination and accumulation of these physical and physiological assaults on the RPE cells ultimately lead to irreversible loss of retinal epithelial tissue. The retinal pigment epithelium lies beneath the photoreceptor cells, and provides critical metabolic support for the light-sensing cells of the eye. Loss of RPE tissue results in loss of photoreceptor cells and loss of vision. Combination of these events lead to various ocular pathologies.

[0070] There is no currently available FDA approved treatment for many ocular pathologies. Lampalizumab is an anti-factor D antibody, which has shown positive data in phase II trial in GA patients. This drug is indicated only for GA and does not control CNV, retinal fibrosis, or hemorrhage. The anti-AP antibodies described herein can inhibit retinal fibrosis, vascular hemorrhage, and inflammation beyond what Lampalizumab can do despite being drugs of the same class. The anti-AP antibodies described herein prevent formation of the inactive complex of C3 convertase compared to Lampalizumab, which does not prevent the formation of the inactive C3 complex PC3bB. Thus, the invention acts at a step of the AP which is up-stream of Lampalizumab's mechanism of action.

Alternative Pathway & Retinal Fibrosis

[0071] Fibrosis is associated with old or chronic lesions within the eye. It has been shown that when subjects with Wet AMD are treated with Ranibizumab they ultimately develop fibrosis followed by unexpected vision loss that has been recently identified. CNV,

tissue atrophy, and fibrosis cause degeneration of the macula. Bevacizumab treated eyes were evaluated for fibrosis, tissue atrophy, subretinal hemorrhage, extent of CNV, and pigment epithelial detachment (PED). Size and grading of CNV leakage on fluorescein angiography were also evaluated. In a retrospective study, central retinal PED, and subretinal fluid (SRF) thickness was evaluated using optical coherence tomography. Other factors predicting a large lesion were subfoveal and bilateral lesions and the presence of hemorrhage at baseline. A large and bilateral lesion and hemorrhage at baseline were correlated with subretinal fibrosis at follow-up.

[0072] Retinal fibrosis can also result from injury and trauma to the eye tissue. The injury or trauma can result from many sources. Moreover, chronic inflammation can also cause retinal fibrosis. It has been shown that at the site of the initial tissue damage, there is often infiltration of inflammatory cells which ultimately develops into scar tissue.

[0073] One potential mechanism of fibrosis is the production of cytokines, which activate and recruit fibroblasts. Activated fibroblasts produce more cytokines and other inflammatory mediators, and assist in the recruitment and activation of immune cells, such as macrophages, which play a role in fibrosis and inflammation. Fibroblasts also mediate production of VEGF. Thus, fibrotic scars, although necrotic in nature, can also be vascularized. Fibrosis is a complex process and anti-VEGF therapy cannot control fibrosis or vascular leakage. We present a surprising discovery that anti-AP antibodies described herein can prevent the formation and persistence of fibrotic scars untreated by an anti-VEGF treatment.

Alternative Pathway and Diabetic Retinopathy

[0074] Studies have demonstrated that complement mediated inflammatory cytokines play a key role in the progression of diabetic retinopathy. In particular, VEGF has been shown to play a critical role in the breakdown of the blood-retinal barrier and the resulting macular edema. Anti-VEGF (VEGF-targeting) agents have proven effective in treating and preventing progression of diabetic retinopathy. The administration of anti-AP antibodies described herein can prevent formation of inflammatory cytokines and inhibit formation of VEGF. Accordingly, the invention will be able to effectively treat diabetic retinopathy.

Alternative Pathway and Other Ocular Diseases

[0075] Dysregulation of the AP within the eye results in a myriad of ocular pathologies, of which AMD and Diabetic Retinopathy are only two. Dysregulation of the AP in other organs and tissues also causes another range of pathologies. The leading cause of blindness in the developed world results from several disorders that have pathologic ocular inflammation and neovascularization as the common pathway leading to vision loss. These disorders include exudative age related macular degeneration (AMD), diabetic retinopathy (DR), retinopathy of prematurity (ROP), retinal vein occlusions (RVO) and ocular tumors. Dysregulation of the AP within the eye results in a myriad of ocular pathologies. Dysregulation of the AP in other organs and tissues also causes another range of pathologies in the ocular space. In the context of the eye, dysregulation of the AP can be implicated in: a) AMD-like diseases, including congenital and familial drusen; b) autoimmune uveitis and uveitis secondary to autoimmune disorder, including macular edema; c) retinal ischemia and ocular pathologies associated with or caused by retinal ischemia, including hypertensive retinopathy and retinopathy of prematurity; and, d) inflammatory pathologies of the anterior segment of the eye.

Drusen and AMD-like Diseases

[0076] Several congenital and familial disorders are characterized by the deposition of drusen and lipofuscin deposits. Such disorders include Sorsby's fundus dystrophy, Doyne Honeycomb Retinal Dystrophy, Malattia Leventinese, Familial Dominant Drusen, North Carolina macular dystrophy, Juvenile Macular degeneration, Stargardt's disease, Vitelliform Macular Dystrophy, Adult-Onset Foveomacular Vitelliform Dystrophy (AOFVD), Sorsby's fundus dystrophy, and Best's Disease. Disorders and pathologies characterized by excessive deposition of drusen result in macular degeneration and CNV in much the same way as does AMD. Drusen and lipofuscin deposits initiate an inflammatory response and put oxidative stress on ocular tissues. Inflammatory mediators and cytokines proliferate as a consequence of dysregulated AP activation. Production of VEGF causes neovascularization, edema and hemorrhaging. Formation of MAC causes tissue damage and atrophy. Recruitment of fibroblasts leads to fibrosis.

[0077] Anti-VEGF agents have proven effective against neovascularization associated with AOFVD and Malattia Leventinese (Honeycomb Retinal Dystrophy). In case reports,

anti-VEGF agents have demonstrated an ability to treat neovascularization in association with the deposition of drusen. The invention inhibits formation of inflammatory cytokines and inhibits formation of VEGF. Accordingly, the invention will be able to effectively treat neovascularization associated with deposition of drusen.

[0078] Deposition of drusen is known to cause ocular inflammation and AP activation, the release of inflammatory cytokines, and associated inflammatory pathologies. The anti-AP antibodies described herein can inhibit the AP and thereby inhibit the release of inflammatory cytokines and associated inflammatory pathologies.

Autoimmune Uveitis, and Uveitis Secondary to Autoimmune Disorder

[0079] Autoimmune uveitis is the result of dysregulated inflammation in the eye. These conditions include, but are not limited to, Iritis, Pars planitis, Choroiditis, Chorioretinitis, Anterior uveitis, Posterior uveitis, and Scleritis. Several autoimmune disorders, including several, which primarily affect other organs of the body, which are not necessarily associated with AMD, sometimes have inflammation based ocular complications include PNH, polycystic kidney disease, rheumatoid arthritis, Lupus, and others.

[0080] For example, uveitis is a common symptom in patients suffering from Behçet's Disease, an autoimmune disorder affecting small vessel vasculature. Patients with Behcet's Disease benefit from treatment with Infliximab (trademarked as Remicade), which is a TNF-alpha inhibitor. The anti-AP antibodies described herein can prevent the formation of AP-mediated TNF-alpha and can provide a similar benefit to patients with Behcet's Disease who are suffering from uveitis.

[0081] Eales disease (also known as angiopathia retinae juvenilis, periphlebitis retinae, and/or primary perivasculitis of the retina) is an idiopathic autoimmune disorder characterized by retinal vasculature occlusion and ocular inflammation. Neovascularization and recurrent retinal and vitreal hemorrhaging are hallmarks of Eale's disease. Treatment with anti-VEGF agents is effective for treating neovascularization associated with an inflammatory response to oxidative stress resulting from vascular occlusion. Accordingly, the invention will provide a benefit by inhibiting production of VEGF. Additionally, the anti-AP antibodies described herein can provide a further benefit by inhibiting production of several other inflammatory cytokines and mediators, including TNF-alpha.

Retinal Ischemia (and associated ocular pathologies)

[0082] In the case of vascular occlusion disorders, oxidative stress is caused by a lack of sufficient circulation to the retina. This oxidative stress causes alternative pathway activation, which results in uveitis, ocular edema and neovascularization. Vascular occlusion disorders, which cause inflammatory ocular pathologies include, but are not limited to Central retinal vein occlusion (CRVO), occlusive peripheral arterial disease, ocular ischemic syndrome secondary to atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, and Purtscher's retinopathy. These are all conditions where vascular pathology and/or vascular occlusion has demonstrated a potential to cause CNV and/or ocular tissue degeneration due to oxidative stress on ocular tissues and the resulting inflammatory response. Treatment with anti-VEGF agents is effective for treating neovascularization associated with an inflammatory response to oxidative stress resulting from various vascular occlusion pathologies.

[0083] Hypertensive retinopathy is caused by oxidative stress, inflammation, and neovascularization of retinal tissue caused by the pathological effects of chronic hypertension on small blood vessels of the eye. Chronic hypertension is also known to cause retinal arterial macroaneurysm. Retinal arterial macroaneurysms can also be treated with anti-VEGF treatments. The anti-AP antibodies described herein can inhibit ocular inflammation and VEGF mediated neovascularization and can be expected to provide therapeutic benefit to patients with hypertensive retinopathy and/or retinal arterial macroaneurysms associated with chronic hypertension.

[0084] Oxidative stress can also be caused by premature retinal vasculature. Retinopathy of prematurity is a condition wherein a pre-mature infant is born before the vasculature of the retina has had time to fully develop. Similarly, familial exudative vitreoretinopathy is a disorder, not associated with pre-mature birth, wherein the vasculature of the retinal has not completely matured. In both of these conditions, the lack of fully matured retinal vasculature causes oxidative stress of the retina, followed by inflammation and neovascularization similar to that see in association with AMD.

Inflammatory Pathologies of the Anterior Segment of the Eye

[0085] AP mediated inflammation has also been implicated in the pathogenesis of the anterior segments of the eye, such as anterior autoimmune uveitis. Neovascular glaucoma

and corneal neovascularization are inflammatory pathologies of the anterior eye. Anti-VEGF agents have demonstrated an ability to treat neovascular glaucoma and corneal neovascularization in the anterior regions of the eye. Accordingly, the invention will provide a benefit by inhibiting production of VEGF. Additionally, the anti-AP antibodies described herein can provide a further benefit by inhibiting ocular inflammation, inhibiting MAC formation, and inhibiting production of other inflammatory cytokines and mediators.

[0086] Fuchs' corneal endothelial dystrophy (FCED) is a degenerative disease of the corneal endothelium which ultimately leads to corneal edema and loss of vision. While the pathogenesis of FCED remains only partially understood, inflammation and edema is known to play a key role in disease progression. Moreover, recent studies support the role of complement system activation. The anti-AP antibodies described herein can treat FCED by inhibiting complement driven inflammation and edema in the cornea.

Limitations of Treatment in AMD – in light of new treatments required

[0087] Anti-VEGF treatments only control neovascularization and have no effect on the underlying inflammatory processes which cause uveitis, edema, hemorrhage and fibrosis. Due to their indiscriminate inhibition of new vessel group, anti-VEGF are contraindicated for tissue repair, and especially in cases where a patient is undergoing surgical procedure. Healthy new vessel growth is required for tissue repair. Unfortunately, anti-VEGF agents inhibit all new vessel growth, and thereby inhibit tissue repair.

Controlling AP Mediated Inflammation, Fibrosis, and Retinal Hemorrhage

[0088] Two potent anaphylatoxins are produced as a result of AP activation, C3a and C5a. Complement activation leads to the formation of both C3a and C5a. Both anaphylatoxins activate inflammatory cells too release a variety of inflammatory mediators. TNF and IL-1 are two such inflammatory mediators, both of which have been shown to be potent regulators of inflammation. VEGF and PDGF are two angiogenic molecules, which are also released from ocular cells in response to inflammation and AP activation. The C3a molecule has a high affinity for C3a receptors (C3aR). C3aRs are present on neutrophils, monocytes, platelets, mast cells, T lymphocytes, retinal epithelial cells, and other cells. Upon activation, these cells produce inflammatory mediators, growth factors, peroxides and proteases that can cause and/or exacerbate disease pathology. Similar to C3a, C5a also

causes the release of inflammatory mediators relevant to several ocular pathologies and related ocular diseases. C5a is known to activate a variety of ocular and non-ocular cells. For example, C5a is known to activate RPEs to produce/release VEGF, which has a well established role in CNV. Thus, inhibition of C3a and C5a production is essential for the treatment of any ocular pathology associated with inflammation, fibrosis, and retinal hemorrhage, wherein these inflammatory mediators have devastating consequences (such as CNV, tissue degeneration, and vision loss) for the affected ocular tissues and cells.

[0089] C5a production is concurrent with C5b production (as C5 is cleaved into C5a and C5b). C5b molecules insert into the lipid bilayer of a cell to initiate the formation of C5b-9 or sC5b-9 (MAC). C5b-9 is a complex that forms on the cell surface and causes tissue injury. Integration of C5b-9 into the cell membrane causes cell lysis, and death, resulting in tissue injury and degradation. In the context of AMD, MAC formation results in lysis of RPE cells and damage to the rods and cones of the eye. This tissue destruction, if left untreated, commonly leads to mild to severe vision loss and potentially blindness. The anti-AP antibodies described herein can prevent AP dependent cell lysis via MAC formation by inhibiting the formations of C3a, C3b, C5a, C5b, and C5b-9.

[0090] Anti-AP antibodies described herein, which prevent AP activity, can prevent C3a and C5b production, inflammation, VEGF production, and MAC formation. Thus, anti-AP antibodies, including anti-P antibodies, can be used to treat ocular pathologies associated with inflammation, fibrosis, retinal hemorrhage, CNV, and tissue degeneration.

Anti-AP Antibodies

[0091] The anti-AP antibodies can include any antibody or antigen binding fragment thereof that targets an AP specific protein or protein complex and inhibits alternative complement AP activation. In some embodiments, the anti-AP antibodies or fragments thereof can inhibit alternate complement pathway activation without inhibiting or affecting classical pathway complement activation. The anti-AP antibodies described herein can be used for the treatment of ocular Inflammation, Fibrosis, retinal hemorrhage, CNV, and tissue degeneration.

Anti-C3b Antibodies

[0092] In one embodiment, the anti-AP antibody described herein can be an anti-C3b antibody or antigen binding fragment thereof. C3b is a large protein and therefore multiple antibodies can be produced against various segments of this protein. There exist multiple sites where-on an antibody might bind and inhibit the protein's activity in any variety of ways. Depending on how and where an antibody binds to C3b, the effect of that antibody could range from inconsequential to complete inhibition.

[0093] The anti-C3b antibodies can include those that bind to C3b in such a way as to prevent the interaction of C3b with Factor B. The effect of these antibodies is necessarily isolated to the alternative pathway since no such interaction exists within the classical pathway. These antibodies prevent the formation of C3a/C3b, C5a/C5b, and C5b-9/sC5b-9 critical for pathological outcome causing disease initiation and progression. Inhibition of the formation of each of these molecules, by the alternative pathway, has significant physiological consequences. Inhibition of alternative pathway produced C3b (herein referred to as "aC3b") impacts extravascular hemolysis of erythrocytes. The C3b produced by the classical pathway is not inhibited by these antibodies and therefore is required for opsonization of foreign particles/bacteria that are coated with CP produced C3b (herein referred to as "cC3b"). The inhibition of C3a formation has direct effect on monocytes activation and production of TNF-α which is a validated marker of inflammation.

Anti-properdin antibodies

[0094] In another embodiment, the anti-AP antibody described herein can be an anti-properdin antibody or antigen binding fragment thereof. As is the case with C3b, properdin is a large protein with many potential sites where antibodies can bind. Different antibodies binding in different ways and/or on different sites of the Properdin protein, will inhibit either amplification loop of the classical pathway or alternative pathway. Properdin is known to be part of the amplification loop of the classical pathway. Thus, classical pathway activation can be dampened by the use of specific anti-properdin antibodies that inhibit the amplification loop (*e.g.,* U.S. Patent No. 6,333,034). Some antibodies can inhibit the classical pathway activation where interactions of properdin to C3b, within the classical pathway, become important for classical pathway amplification.

[0095] Properdin binds to itself and generates aggregates. Depending upon the configuration of the aggregate, antibodies binding properdin can bind mono, di-, tri- and tetramer, with each generating different responses. Thus antibody-to-properdin ratio can be 1:1, 1:2, 1:3, and 1:4. This means that an antibody can bind in any configuration.

[0096] Properdin is involved directly in the AP activation but indirectly in classical pathway activation via the amplification loop *in vivo*. Also, properdin binds both C3b and C5b. An antibody which disrupts properdin's interaction with C3b may or may not interrupt properdin's interaction with C5b (and vice versa). Antibodies that prevent one or both may be of distinguishable clinical significance.

[0097] Thus, some antibodies targeting properdin a) inhibit both the classical pathway and alternative pathway, or b) inhibit the alternative pathway alone.

[0098] In some embodiments, the anti-AP antibody can be an anti-properdin antibody that is directed to or specifically binds to domains on properdin that are involved in controlling properdin function. The anti-properdin antibodies or fragments thereof can inhibit alternate complement pathway activation without inhibiting or effecting classical complement activation as well as inhibit binding of properdin (oligomer/monomer) to C3b, inhibit binding of properdin to factor B, inhibit properdin binding to C3bB complex, inhibit factor D cleavage of factor B, reduce half life of the C3 convertase, prevent oligomerization of properdin monomers by blocking the N terminus of properdin, which associates with TSR6 to generate oligomers, inhibit the binding of properdin to C5 or C5b, reduce the formation of membrane attack complex C5b-9, reduce the formation of anaphylatoxins, for example C3a and/or C5a, reduce the formation of C3b, reduce the activation of neutrophils, monocytes and platelets, and/or reduce leukocyte aggregate formation.

[0099] The amino acid sequences of mammalian properdin are known. For example, the amino acid sequence of human properdin is disclosed in the GenBank database under Accession No. AAA36489. Human properdin is a 469 amino acid protein that includes a signal peptide (amino acids 1-28), and six, non-identical thrombo spondin type 1 repeats (TSR) of about 60 amino acids each, as follows: amino acids 80-134 (TSR1), amino acids 139-191 (TSR2), amino acids 196-255 (TSR3), amino acids 260-313 (TSR4), amino acids 318-377 (TSR5), and amino acids 382-462 (TSR6).

[00100] In some embodiments, the anti-properdin antibodies can bind to a specific epitope located on properdin to inhibit AP activation. In one example, the anti-properdin

agent can bind to the N-terminal domain of properdin to inhibit the binding of properdin to C3b. In other embodiments, the anti-properdin antibodies can bind to the N-terminal segment spanning into the TSR1 of properdin.

[00101] The anti-properdin antibody can also inhibit the level of functional properdin in a mammalian host. Functional properdin means properdin molecules capable of activating the alternative pathway.

[00102] In another aspect, the anti-properdin antibody can bind properdin with high affinity, inhibit oligomerization of properdin, inhibit factor D mediated cleavage of factor B in a C3bB complex, not inhibit the classical complement pathway, prevent alternative complement pathway activation, inhibit C3a, C5a, and C5b-9 formation, Inhibit neutrophil, monocyte and platelet activation. Inhibit leukocyte platelet conjugate formation.

Anti-Ba antibodies

[00103] In other embodiments, the anti-AP antibody described herein can be an anti-Ba antibody or antigen binding fragment thereof. The protein Ba (cleaved from Factor B) is a large protein with a molecular weight of approximately 33,000. Thus, like Properdin and C3b, any of a multitude of antibodies can be produced against various protein motifs of, and locations on, the protein. With this protein, as with the other proteins of the AP, the anti-Ba antibodies bind to the protein in such a way so as to inhibit the formation of C3a, C3b, C5a, C5b, and C5b-9.

Anti-Bb Antibodies

[00104] In still other embodiments, the anti-AP antibody described herein can be an anti-Bb antibody or antigen binding fragment thereof. The protein Bb (cleaved product of Factor B) is a large protein with a molecular weight of approximately 64,000. Anti-Bb antibodies bind Bb and factor B, but not Ba as the target antigen. In some embodiments, the anti-factor Bb antibody binds the Bb fragments, does not bind Ba fragment, does not inhibit the factor B binding to C3b, inhibits C3b production, inhibits C3a, C5a, and C5b-9 formation and inhibits lysis of rabbit erythrocytes. The anti-Bb antibodies can prevent the formation of C3a, C3b, C5a, C5b, and C5b-9 by the alternative pathway at a juncture not shared with the classical pathway. Inhibition of formation of each of these molecules has physiologic consequences. The anti-Bb antibody can also inhibit oligomerization of C3b. The molecular weight of

native C3 is in the order of 190kDa, upon cleavage by the convertase, C3 is converted into a C3a (10kDa) and C3b (180kDa). This C3b molecule has high affinity for properdin oligomers, as a result forms a complex containing 3 C3b molecules attached to a properdin trimer. Anti-Bb antibodies described herein can prevent formation of additional molecules of C3b and therefore result in a complex where C3b oligomer will not form. If C3b formation is completely prevented, properdin will float alone without any C3b attached. Properdin does not bind C3 or the isoforms of C3b.

[00105] Inhibition of C3b (aC3b) will impact extravascular hemolysis. Inhibition of C3a and C5a will impact cellular activation and subsequent release of inflammatory mediators. Inflammatory mediators, when over-produced, can cause any number of disease pathologies in humans. In so doing, these antibodies also prevent the formation of well known markers of inflammation, such as TNF-α and IL-1.

[00106] In some embodiments, the anti-Bb antibody can bind to the serine protease domain and particularly the catalytic triad of serine protease of the Bb region. The serine protease domain forms the third and the last domain of intact factor B. The serine protease domain carries the catalytic site, which is solely responsible for C3 cleavage. While the catalytic site is exposed in both intact factor B and the Bb fragment, it becomes active only after the Ba is cleaved off by factor D. In other embodiments, the anti-factor Bb antibody can bind the catalytic triad and prevent its activity by either locking the inactive conformation in place or by binding to the region where factor D cleaves the factor B.

[00107] Table 1 and Table 2 lists the amino acid sequences of the heavy and light chain variable domains or regions of anti-C3b, anti-P, ant-Ba, and anti-Bb antibodies that can be used as anti-AP antibodies in the methods described herein. The Tables identify the heavy chain and light chain CDR1s, CDR2s and CDR3s of the antibodies as well as the framework regions. Accordingly, aspects of the application described herein, relate to an isolated monoclonal antibody, or antigen binding portion thereof comprising: (a) a heavy chain variable region comprising CDR1, CDR2, and CDR3, of the respective antibodies; and (b) a light chain variable region comprising CDR1, CDR2, and CDR3 of the respective antibodies.

[00108] Table 3 lists examples of complete amino acid sequences of the heavy and light chains of anti-C3b, anti-P, and anti-Bb antibodies that can be used in the methods described herein. The heavy and light chains include the CDRs of the heavy and light chain variable regions listed in Tables 1 and 2.

TABLE 1

	TARGET	SPECIES	SEQUENCE	FW1	CDR1	FW2	CDR2	FW3	CDR3	FW4
L-1	Bb	Rabbit	1	AVVLT	QASENI	WYQQ	YASDLA	GVPSRFG	HSYY	FGGG
				QTASP	YSRLA	KPGQP	S	GSGSGTD	WNSA	TEVV
				VSGVV		PRVLI		YTLTISDL	YSDNT	VEG
				GGTVT		Y		ECADAAT		
				INC				YYC		
L-2	P	Rabbit	2	AYDLT	QASDNI	WYQQ	RASTLA	GVPSRFK	QQHY	FGGG
				QTPAS	YSLLA	KPGQP	S	GSGSGTQ	DYNYL	TEVV
				VEAAV		PKLLIY		FTLTISGV	DVA	VKG
				GGTVT				ECADAAT		
				INC				YYC		
L-3	P	Rabbit	3	AYDLT	QASDNI	WYQQ	RASTLA	GVPSRFK	QQHY	FGGG
				QTPAS	YSLLA	KPGQP	S	GSGSGTQ	DYNYL	TEVV
				VEAAV		PKLLIY		FTLTISGV	DVA	VKG
				GGTVT				ECADAAT		
				INC				YYC		
L-4	P	Rabbit	4	AYDM	QASQNI	WYQQ	RASTLA	GVPSRFSG	QQHW	FGGG
				TQTPF	YSNLA	KPGQR	S	SRSGTQFT	DYDYI	TEVV
				SVSAA		PKLLIY		LTISGVEC	DVA	VKG

			VGGTV TINC				ADAATYY C		
L-5	Bb	Rabbit	DVVM TQTPS SVEAA VGGTV TIKC	QASENI YSYLA	WYQQ KPGQP PKLLIY	KASYLA S	GVSSRFK GSGSGTEF TLTISDLE CADAATY YC	LSTIAS ASNFD A	FGGG TEVV VKG
			5						
L-6	Bb	Rabbit	DPVLT QTASS VSAPV GGTVT ISC	QSSQSV YRSNN VA	WYQQ KPGKP PKLLIY	EASSLAS	GVPSRFT GSGSGTQ FTLTISGV QCDDAAT YYC	AGGYS SSVDF FFA	FGGG TEVV VKG
			6						
L-7	P	Mouse	DIVMT QSHKF MSTSV GDRVS ISC	KASQD VSDAV A	WFQQ KPGQS PKLLIY	SPSYRY T	GVPDRFT GSGSGTD FTFTISSV QAEDLAV YYC	QQHYS TPWT	FGGG TKLEI KR
			7						
L-8	P	Humanized	DIQMT QSHKF	KASQD VSDAV	WFQQ KPGKS	SPSYRY T	GVPSRFT GSGSGTD	QQHYS TPWT	FGQG TKLEI
			8						

			MSTSV GDRVT ITC	A	PKLLIY		FTFTISSV QAEDLAV YYC		K
L-9	P	Humanized	DIQMT QSHKF MSTSV GDRVS ISC	KASQD VSDAV A	WFQQ KPGKS PKLLIY	SPSYRY T	GVPSRFT GSGSGTD FTFTISSV QAEDLAV YYC	QQHYS TPWT	FGQG TKLEI K
L-10	P	Humanized	DIQMT QSPSSL STSVG DRVTI TC	KASQD VSDAV A	WFQQ KPGKA PKLLIY	SPSYRY T	GVPSRFT GSGSGTD FTFTISSV QAEDLAV YYC	QQHYS TPWT	FGQG TKLEI K
L-11	P	Humanized	DIQMT QSPSSL SASVG DRVTI TC	QASQDI SNYLN	WYQQ KPGKA PKLLIY	DASTLE T	GVPSRFSG SGSGTDFT FTISSLQP EDIATYY C	QNYD NLPLT	FGGG TKVEI KR
L-12	P	Humanized	DIQMT	RASQNI	WYQQ	ATSRLQ	GVPSRISG	QQSYS	FGGG

			QSPSSL SASVG DRVTI TC	SSFLN	KSGKA PKLLIF	S	SGSGTDFT LTISGLQP EDFATFY C	IPLT	TKVDI KR
L-13	P	Humanized	DIQMT QSPSSL SASVG DRVTI TC	RASQGI SNYLA	WYQQ KPGKV PKLLIY	AASTLQ S	GVPSRFSG SGSGTDFT LTISSLQP EDVATYY C	QKYDS APWT	FGQG TKVEI KR
L-14	P	Humanized	DIQMT QSPSSL SASVG DRVTI TC	RASQDI SFFLN	WYLQ KPGQS PQLLIY	YTSRYH S	GVPSRFSG SGSGTEFT LTISSLQP DDFATYY C	QHGNT LPWT	FGQG
L-15	P	Humanized	DIQMT QSPSSL SASVG DRVTI TC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GVPSRFSG SGSGTEFT LTISSLQS EDFAVYY C	QHGNT LPWT	FGQG

L-16	P	Humanized	16	EIVMT QSPAT LSVSP GERAT LSC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GVPSRFSG SGSGTDFT FTISSLQP EDIATYY C	QHGNT LPWT	FGQG
L-17	P	Humanized	17	EIVLT QSPAT LSLSP GERAT LSC	RASQDI SFFLN	WFQQ RPGQS PRRLIY	YTSRYH S	GIPPRFSG SGYGTDF TLTINNIE SEDAAYY FC	QHGNT LPWT	FGQG
L-18	P	Humanized	18	EIVMT QSPAT LSVSP GERAT LSC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GVPSRFSG SGSGTDFT FTISSLQP EDIATYY C	QHGNT LPWT	FGQG
L-19	P	Humanized	19	DIQMT QSPSSL SASVG DRVTI	RASQDI SFFLN	WYLQ KPGQS PQLLIY	YTSRYH S	GVPSRFSG SGSGTEFT LTISSLQP DDFATYY	QHGNT LPWT	FGQG

				TC				C		
L-20	P	Humanized	20	DIQMT QSPSSL SASVG DRVTI TC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GVPSRFSG SGSGTEFT LTISSLQS EDFAVYY C	QHGNT LPWT	FGQG
L-21	P	Humanized	21	DIQMT QSPSSL SASVG DRVTI TC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GVPSRFSG SGSGTEFT LTISSLQS EDFAVYY C	QHGNT LPWT	FGQG
L-22	P	Humanized	22	DIQMT QSPSSL SASVG DRVTI TC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GVPSRFSG SGSGTEFT LTISSLQS EDFAVYY C	QHGNT LPWT	FGQG
L-23	P	Humanized	23	DIQMT QSPSSL SASVG	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GIPPRFSG SGYGTEF TFTISSLE	QHGNT LPWT	FGQG

L-24	P	Humanized	24	DRVTI TC EIVMT QSPAT LSVSP GERAT LSC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	AEDAATY YC GVPSRFSG SGSGTDFT FTISSLQP EDIATYY C	QHGNT LPWT	FGQG
L-25	P	Humanized	25	DIQMT QSPSSL SASVG DRVTI TC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GVPSRFSG SGSGTEFT LTISSLQS EDFAVYY C	QHGNT LPWT	FGQG
L-26	P	Mouse	26	DIQMT QTTSS LSASL GDRVT ISC	RASQDI SFFLN	WYQQ KPDGT VKLLI Y	YTSRYH S	GVPSRFSG SGSGTDFS LTINNLEQ EDFATYF C	QHGNT LPWT	FGGG TKLEI KR
L-27	P	Humanized	27	DIQMT QSPSSL	RASQDI SFFLN	WYQQ KPGKA	YTSRYH S	GVPSRFSG SGSGTEFT	QHGNT LPWT	FGQG

			SASVG DRVTI TC		PKLLIY		LTISSLQS EDFAVYY C		
L-28	P	Humanized	DIQMT QSPSSL SASVG DRVTI TC	RASQDI SFFLN	WYLQ KPGQS PQLLIY	YTSRYH S	GVPSRFSG SGSGTEFT LTISSLQP DDFATYY C	QHGNT LPWT	FGQG
L-29	P	Humanized	EIVMT QSPAT LSVSP GERAT LSC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GVPSRFSG SGSGTDFT FTISSLQP EDIATYY C	QHGNT LPWT	FGQG
L-30	P	Humanized	DIQMT QSPSSL SASVG DRVTI TC	RASQDI SFFLN	WYQQ KPGKA PKLLIY	YTSRYH S	GIPPRFSG SGYGTEF TFTISSLE AEDAATY YC	QHGNT LPWT	FGQG
L-31	P	Humanized	DIQMT	RASQDI	WYQQ	YTSRYH	GVPSRFSG	QHGNT	FGQG

			QSPSSL SASLG DRVTI TC	SFFLN	KPDGT VKLLI Y	S	SGSGTDFT LTISSLQP EDFATYF C	LPWT	TKLEI KR
L-32	P	Humanized	DIQMT QSPSSL SASLG DRVTI TC	RASQDI SFFLN	WYQQ KPDGT VKLLI Y	YTSRYH S	GVPSRFSG SGSGTDFT LTISSLQP EDFATYF C	QHGNT LPWT	FGQG TKLEI KR
			32						
L-33	P	Mouse	KEIHQ AGKGI KMKS QTQVF VFLLL CVSGA HGSIV MTQTP KFLLV SAGDR	KASQS VNNDV A	WYQQ KPGQS PKLLIY	YASNRY T	GVPDRFT GSGYGTD FTFTITTV KAEDLAV YFC	QQDYS SPLT	FGAG TKLEL KRAD AAPT VSAC TKGEF AA
			33						

			ITITC						
L-34	P	Mouse	DIQMT QTTSS LSASL GDRVT ISC	RASQDI SFFLN	WYQQ KPDGT VKLLI Y	YTSRYH S	GVPSRFSG SGSGTDFS LTINNLEQ EDFATYF C	QHGNT LPWT	FGGG
				34					
L-35	Bb	Mouse	DVQIT QSPSY LAASP GETTTI NC	RASKSI SKYLA	WYQD KPGKT NKLLI Y	SGSTLQS	GIPSRFSG SGSGTDFT LTISSLEPE DFAMYYC	QQHDE YPWT	FGGG TKLEI KR
				35					
L-36	Bb	Humanized	DVQIT QSPST LSASP GDRITI TC	RASKSI SKYLA	WYQD KPGKT NKLLI Y	SGSTLQS	GIPSRFSG SGSGTEFT LTISSLQP DDFAMYY C	QQHDE YPWT	FGQG TKLEI KR
				36					
L-37	Bb	Humanized	DVQIT QSPSY LSASP	RASKSI SKYLA	WYQD KPGKT NKLLI	SGSTLQS	GIPSRFSG SGSGTEFT LTISSLQP	QQHDE YPWT	FGQG TKLEI KR
				37					

L-38	C3b	Mouse	38	QIVLT QSPAIL SASPG EKVTM TC	SATSSIT YIH	WYQQ KSGTS PKRWI Y	DTSRLA S	DDFAMYY C GVPTRFS GSGSGTS YSLTISTM EAEDAAT YYC	QQWSS NPPT	FGGG TKLEI KR
L-39	C3b	Humanized	39	EIVLT QSPAT LSASP GEKVT MTC	SATSSIT YIH	WYQQ KSGQS PKRWI Y	DTSRLA S	GVPSRFSG SGSGTSYS LTISTMEA EDAATYY C	QQWSS NPPT	FGGG TKLEI K
L-40	C3b	Humanized	40	EIVLT QSPAT LSASP GEKVT MTC	SATSSIT YIH	WYQQ KSGTS PKRWI Y	DTSRLA S	GVPARFS GSGSGTS YSLTISTM EAEDAAT YYC	QQWSS NPPT	FGGG TKLEI K
L-41	C3b	Humanized	41	EIVLT QSPAT	SATSSIT YIH	WYQQ KPGQA	DTSRLA S	GVPARFS GSGSGTS	QQWSS NPPT	FGGG TKLEI

			LSASP GEKVT MTC		PKRWI Y		YSLTISTM EpEDFATY YC		K
L-42	P	Humanized	DIQMT QSPSSL SASVG DRVTS TC	RASQDI SNYLA	WYQQ KPGKV PKLLIY	AASTLQ S	GVPSRFSG SGSGTDFT LTISSLQP EDVATYY C	QKYNS APWT	FGQG TKVEI KR
L-43	P	Humanized	DIQMT QSPSS VSASV GDRVT ITC	RASQGI SSWLA	WYQQ KPGKA PKLLIY	VASSLQ S	GVPSRFSG SGSGTDFT LTISSLQP EDIATYY C	QQADS FPRT	FGQG TKVEI KR

42

43

Table 2

	TARGET	SPECIES	SEQUENCE	FW1	CDR1	FW2	CDR2	FW3	CDR3	FW4
H-1	Bb	Rabbit	44	QSLEESGGRLVTPGTPLTLTCTVS	GFDLSTYAMS	WVRQAPGKGLEWIG	AVSATTGNTYYATWAKG	RFTMSKASTTVDLKITSPTTEDTATYFCVR	YASSGVGTYFDL	WGQGTLVTVSS
H-2	P	Rabbit	45	QSLEESGGGLVKPGASLTLTCTAS	GFSFSSGYWIF	WVRQAPGKGLELVG	GIYSGSSGTTYYANWAKG	RFTISKTSSTTVTLQMTSLTAADTATYFCAR	SVDGIDSYDAAFNL	WGPGTLVTVSS
H-3	P	Rabbit	46	QSLEESGGGLVKPGASLTLTCTAS	GFSFSSGYWIF	WVRQAPGKGLELVG	GIYSGSSGTTYYANWAKG	RFTISKTSSTTVTLQMTSLTAADTATYFC	SVDGIDSYDAAFNL	WGPGTLVTVSS

H-4	P	Rabbit	47	QSLEESG GDLAKP GASLTIT CTAS	GFSFSS SYWIF	WVRQA PGKGLE LIG	GIYSSSG RMYYAS WAKG	RFTISK TSSTTM TLQMT SLTAAD TATYFC AR	SADG SDSY DAYF TL	WGP GTL VTV SS
H-5	Bb	Rabbit	48	QSLEESG GRLVTPG GSLTLTC TVS	GFSLSN YHLG	WVRRA PGKGLE WIG	VITYGG STYYAS WVKG	RFTISK TSTTVD LKMTS LTTEDT ATYFC AR	RDSG GYHL DL	WGQ GTL VTIS S
H-6	Bb	Rabbit	49	QSVEESG GRLVTPG GSLTLTC TVS	GFSLSS NAIN	WVRQA PGEGLD WIG	TIHTNTK TYYATW ARG	RFTISR TSSTTV DLKVTS LTAAD TATYFC GR	ADL	WGQ GTL VTV SS

H-7	P	Mouse	50	QVTLKES GPGILQP SQTLSLT CSFS	GFSLST SGMGV G	WIRQPS GKGLE WLA	HIWWD DVKSYN PALKS	RLTISK DTSSSQ VFLRIA SVDTA DTATY YCAR	IGDGY YSFD Y	WGQ GTT LTV SS
H-8	P	Humanized	51	QVTLKES GPTILQPT QTLTLTC TFS	GFSLST SGMGV G	WIRQPS GKALE WIA	HIWWD DVKSYN PALKS	RLTITK DTSKSQ VVLRIA SVDPV DTATY YCAR	IGDGY YSFD Y	WGQ GTT LTV SS
H-9	P	Humanized	52	QVTLKES GPTILQPT QTLTLTC TFS	GFSLST SGMGV G	WIRQPS GKGLE WIA	HIWWD DVKSYN PALKS	RLTITK DTSKSQ VVLRIA SVDTA DTATY YCAR	IGDGY YSFD Y	WGQ GTT LTV SS
H-10	P	Humanized	53	QVTLKES	GFSLST	WIRQPP	HIWWD	RLTITK	IGDGY	WGQ

			GPTLVKP TQTLTLT CTFS	SGMGV G	GKALE WIA	DVKSYN PALKS	DTSKN QVVLRI ASVDP VDTAT YYCAR	YSFD Y	GTT LTV SS
H-11	P	Humanized	QVQLVES GGGVVQ PGRSLRL SCAAS	GFTFSC YGMH	WVRQA PGKGLE WVA	VIWYDG SNKYYA DSVKG	RFTISR DNSKN TLYLQ MNSLR AEDTA VYYC	AGGA TAMD V	WGQ GTT VTV SS
H-12	P	Humanized	QEQSGG GVVQPG RSLRLSC AAS	GFTFSN YGIH	WVRQA PGKGLE WVA	VIWYDG NNKYYA DSVKG	RFTISR DNSKN TLYLQ MNSLR AEDTA VYYCA R	GGYY DSRG YYTP YYYY GMDV	WGQ GTT VTV SS
H-13	P	Humanized	QVQLQES	GGSISIY	WIRQPP	YIYYSGS	RVTISV	WNYG	WGQ

54 55 56

			GPGLVKP SETLSLT CTVS	YWS	GKGLE WIG	TNYNPS LKS	DTSKN QFSLKL SSVTAA DTAVY YCAV	DAFDI	GTM VTV SS
H-14	P	Humanized	EVQLVQS GAEVKK PGATVKI SCKVS	GYIFTN YPIH	WVRQA PGKGLE WVS	FIDPGGG YDEPDE RFRD	RFTISR DNAKN SLYLQ MNSLR AEDTA VYYCA R	RGGG YYLD Y	WGQ G
			57						
H-15	P	Humanized	EVQLVQS GAEVKK PGATVKI SCKVS	GYIFTN YPIH	WVRQA PGKGLE WVS	FIDPGGG YDEPDE RFRD	RFTISR DNAKN SLYLQ MNSLR AEDTA VYYCA R	RGGG YYLD Y	WGQ G
			58						

H-16	P	Humanized	59	EVQLVQS GAEVKK PGATVKI SCKVS	GYIFTN YPIH	WVRQA PGKGLE WVS	FIDPGGG YDEPDE RFRD	RFTISR DNAKN SLYLQ MNSLR AEDTA VYYCA R	RGGG YYLD Y	WGQ G
H-17	P	Humanized	60	EVQLVQS GAEVKK PGESLRIS CKGS	GYIFTN YPIH	WIRQPP GKGLE WIG	FIDPGGG YDEPDE RFRD	RFVFSL DTSVST AYLQIC SLKAED TAVYY CAR	RGGG YYLD Y	WGQ G
H-18	P	Humanized	61	EVQLVQS GAEVKK PGESLRIS CKGS	GYIFTN YPIH	WIRQPP GKGLE WIG	FIDPGGG YDEPDE RFRD	RFVFSL DTSVST AYLQIC SLKAED TAVYY CAR	RGGG YYLD Y	WGQ G

H-19	P	Humanized	62	EVQLVQS GAEVKK PGESLRIS CKGS	GYIFTN YPIH	WIRQPP GKGLE WIG	FIDPGGG YDEPDE RFRD	RFVFSL DTSVST AYLQIC SLKAED TAVYY CAR	RGGG YYLD Y	WGQ G
H-20	P	Humanized	63	EVQLVQS GAEVKK PGESLRIS CKGS	GYIFTN YPIH	WIRQPP GKGLE WIG	FIDPGGG YDEPDE RFRD	RFVFSL DTSVST AYLQIC SLKAED TAVYY CAR	RGGG YYLD Y	WGQ G
H-21	P	Humanized	64	EVQLVQS GAEVKK PGESLRIS CKGS	GYIFTN YPIH	WIRQSP SRGLE WLG	FIDPGGG YDEPDE RFRD	RVTISA DKSIST AYLQW SSLKAS DTAMY YCAR	RGGG YYLD Y	WGQ G
H-22	P	Humanized	65	EVQLVQS	GYIFTN	WVRQA	FIDPGGG	RLTISK	RGGG	WGQ

			GAEVKK PGESLRIS CKGS	YPIH	PGKGLE WVS	YDEPDE RFRD	DTSKN QVVLT MTNMD PVDTAT YYCAR	YYLD Y	G
H-23	P	Humanized	EVQLVQS GAEVKK PGESLRIS CKGS	GYIFTN YPIH	WVRQA PGKGLE WVS	FIDPGGG YDEPDE RFRD	RVTISV DTSKN QFSLKL SSVTAA DTAVY YCAR	RGGG YYLD Y	WGQ G
			66						
H-24	P	Humanized	EVQLVQS GAEVKK PGESLRIS CKGS	GYIFTN YPIH	WVRQA PGQGLE WMG	FIDPGGG YDEPDE RFRD	RFVFSL DTSVST AYLQIC SLKAED TAVYY CAR	RGGG YYLD Y	WGQ G
			67						
H-25	P	Humanized	EVQLVQS GAEVKK	GYIFTN YPIH	WVRQA TGQGL	FIDPGGG YDEPDE	RFTISR DDSKN	RGGG YYLD	WGQ G
			68						

H-26	P	Mouse	69	PGESLRIS CKGS	GYIFTN YPIH	EWMG	RFRD	TAYLQ MNSLK TEDTA VYYCT R	Y	WGQ GTT LTV SS
				QVLLQQS APELARP GASVKM SCTAS		WVKQR PGQGLE WIG	FIDPGGG YDEPDE RFRD	RATLTA DKSSST AYMQL SSLTSE DSAIYY CAR	RGGG YYLD Y	
H-27	P	Humanized	70	QVQLQES GPGLVKP SQTLSLT CTVS	GYIFTN YPIH	WVRQA PGKGLE WVS	FIDPGGG YDEPDE RFRD	RVTISV DTSKN QFSLKL SSVTAA DTAVY YCAR	RGGG YYLD Y	WGQ G
H-28	P	Humanized	71	QVQLQES GPGLVKP	GYIFTN YPIH	WVRQA PGKGLE	FIDPGGG YDEPDE	RVTISV DTSKN	RGGG YYLD	WGQ G

			SQTLSLT CTVS	GYIFTN YPIH	WVS	RFRD	QFSLKL SSVTAA DTAVY YCAR	Y	
H-29	P	Humanized	QVQLQES GPGLVKP SQTLSLT CTVS	GYIFTN YPIH	WVRQA PGKGLE WVS	FIDPGGG YDEPDE RFRD	RVTISV DTSKN QFSLKL SSVTAA DTAVY YCAR	RGGG YYLD Y	WGQ G
			72						
H-30	P	Humanized	QVQLQES GPGLVKP SQTLSLT CTVS	GYIFTN YPIH	WVRQA TGQGL EWMG	FIDPGGG YDEPDE RFRD	RVTITA DKSTST AYMEL SSLRSE DTAVY YCAR	RGGG YYLD Y	WGQ G
			73						
H-31	P	Humanized	QVQLVQ SAPEVAK PGTSVK	GYIFTN YPIH	WVKQA PGQGLE WIG	FIDPGGG YDEPDE RFRD	RATLTA DKSTST AYMEL	RGGG YYLD Y	WGQ GTL VTV
			74						

H-32	P	Humanized	75	QVQLVQ SGPEVAK PGSSVKV SCKAS	GYIFTN YPIH	WVRQA PGQGLE WIG	FIDPGGG YDEPDE RFRD	SSLRSE DTAIYY CAR	SS
								RATITA DKSTST AYMEL SSLRSE DTAVY YCAR	RGGG YYLD Y	WGQ GTL VTV SS
H-33	P	Mouse	76	LNMERH WIFLFLL SVTAGV HSQVLLQ QSAPELA RPGASVK MSCTAS	GYIFTN YPIH	WVKQR PGQGLE WIGFID PGGGY DEPDER FRDRAT LTADKS SSTAY MQLSSL TSEDSA	FIDPGGG YDEPDE RFRD	RATLTA DKSSST AYMQL SSLTSE DSAIYY CARRG GGYYL DYWGQ DTTLTV SAASTT		

H-34	P	Mouse	77	EVQLQQS VPELARP GASVKM SCTAS	GYIFTT YPIH	IYYCAR RGGGY YLDYW GQDTT LTVSAA STTPPS VKGEF	FIDPGGG YDEPDD KFRD	PPSVKG EF	RATLTADKSSTTAYMQL SSLTSEDSAVYYCAR	
H-35	Bb	Mouse	78	QVQLQQ SGAELAK PGASVR MSCKAS	GYTFTN YWIH	WVKQR PGQGLE WIG	YINPNT GYNDYN QKFKD	KATLT ADKSSS TVYMQ LSSLTS EDSAV YYCAR	GGQL GLRR AMDY	WGQ GTS VTV SS
H-36	Bb	Humanized	79	QVQLVQ SGAEVK	GYTFTN YWIH	WVRQA PGQGLE	YINPNT GYNDYN	RATLTA DKSSST	GGQL GLRR	WGQ GTL

			KPGASVK		WIG	QKFKD	VYMQL	AMDY	VTV
			MSCKAS				SSLRSE		SS
							DTAVY		
							YCAR		
H-37	Bb	Humanized	QVQLVQ	GYTFTN	WVKQR	YINPNT	KATLT	GGQL	WGQ
			SGAEVA	YWIH	PGQGLE	GYNDYN	ADKSSS	GLRR	GTL
			KPGASVK		WIG	QKFKD	TVYMQ	AMDY	VTV
			MSCKAS				LSSLTS		SS
							EDTAV		
							YYCAR		
H-38	C3b	Mouse	QVQLQQ	GYTFTS	WVKQR	DIYPVR	KAKMIP	GNFG	WGQ
			SGAEIVK	YWIN	PGQGLE	GITNYSE	DTSSST	NFDA	GTS
			PGASVK		WIG	KFKN	VYMQL	MDY	VTV
			MSCKAS				SSLTSE		SS
							DSAVY		
							YCSR		
H-39	C3b	Humanized	QVQLVQ	GYTFTS	WVKQA	DIYPVR	KATMIP	GNFG	WGQ
			SGAEIVK	YWIN	PGQGLE	GITNYSE	DTSTST	NFDA	GTM
			PGASVK		WIG	KFKN	VYMEL	MDY	VTV

80 81 82

H-40	C3b	Humanized	83	QVQLVQ SGAEIVK PGASVK MSCKAS	GYTFTS YWIN	WVKQR PGQGLE WIG	DIYPVR GITNYSE KFKN	SSLRSE DTAVY YCSR	GNFG NFDA MDY	SS WGQ GTM VTV SS
H-41	C3b	Humanized	84	QVQLVQ SGAEVK KPGASVK MSCKAS	GYTFTS YWIN	WVRQA PGQGLE WIG	DIYPVR GITNYSE KFKN	KATMIP DTSTST VYMEL SSLRSE DTAVY YCSR	GNFG NFDA MDY	WGQ GTM VTV SS
H-42	P	Humanized	85	QVQLVQ SGAEVK KPGASVK VSVKVS	GYTLTE LSMH	WVRQA PGKGLE WMG	GFDPED GETIYA QMFQG	RVTMT EDTSTD TAYMD LSSLRS	GTYY DILTG PSYY YYGL	WGQ GTT VTV SS

H-43	P	Humanized	86	QVQLEQS GPGLVKP SQTLSLT CTVS	GDSISS GGHYW S	WIRQHP GKGLE WIG	YIYYSGS SYYNPS LKS	EDTAV YYCAT	GV	WGL GTL VTV SS
								RFTISV DTSKN QFSLKL TSVTAA DTAVY YCAR	TGDY FDY	

TABLE 3

Target	HEAVY	SEQUENCE	LIGHT	SEQUENCE
P	EVQLVQSGAEVKKPGESLRISCK GSGYIFTNYPIHWIRQSPSRGLEW LGFIDPGGGYDEPDERFRDRVTIS ADKSISTAYLQWSSLKASDTAMY YCARRGGGYYLDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTP	87	DIQMTQSPSSLSASVGDRV TITCRASQDISFFLNWYQQ KPGKAPKLLIYYTSRYHSG VPSRFSGSGSGTEFTLTISS LQSEDFAVYYCQHGNTLP WTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPV TKSFNRGEC	88

	PVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKS LSLSPGK			
P	QVQLQESGPGLVKPSQTLSLTCTV SGYIFTNYPIHWVRQATGQGLEW MGFIDPGGGYDEPDERFRDRVTIT ADKSTSTAYMELSSLRSEDTAVY YCARRGGGYYLDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGF	89	DIQMTQSPSSLSASVGDRV TITCRASQDISFFLNWYQQ KPGKAPKLLIYYTSRYHSG IPPRFSGSGYGTEFTFTISSL EAEDAATYYCQHGNTLP WTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPV TKSFNRGEC	90

	YPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKS LSLSPGK			
P	QVQLVQSAPEVAKPGTSVKMSCK ASGYIFTNYPIHWVKQAPGQGLE WIGFIDPGGGYDEPDERFRDRATL TADKSTSTAYMELSSLRSEDTAIY YCARRGGGYYLDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQV	91	DIQMTQSPSSLSASLGDRV TITCRASQDISFFLNWYQQ KPDGTVKLLIYYTSRYHSG VPSRFSGSGSGTDFTLTISS LQPEDFATYFCQHGNTLP WTFGQGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPV TKSFNRGEC	92

	YTLPPSRDELTKNQVSLTCLVKGF			
	YPSDIAVEWESNGQPENNYKTTP			
	PVLDSDGSFFLYSKLTVDKSRWQ			
	QGNVFSCSVMHEALHNHYTQKS			
	LSLSPGK			
P	QVQLVQSGPEVAKPGSSVKVSCK		DIQMTQSPSSLSASLGDRV	
	ASGYIFTNYPIHWVRQAPGQGLE		TITCRASQDISFFLNWYQQ	
	WIGFIDPGGGYDEPDERFRDRATI		KPDGTVKLLIYYTSRYHSG	
	TADKSTSTAYMELSSLRSEDTAV		VPSRFSGSGSGTDFTLTISS	
	YYCARRGGGYYLDYWGQGTLVT		LQPEDFATYFCQHGNTLP	
	VSSASTKGPSVFPLAPSSKSTSGG		WTFGQGTKLEIKRTVAAP	
	TAALGCLVKDYFPEPVTVSWNSG	93	SVFIFPPSDEQLKSGTASVV	94
	ALTSGVHTFPAVLQSSGLYSLSSV		CLLNNFYPREAKVQWKV	
	VTVPSSSLGTQTYICNVNHKPSNT		DNALQSGNSQESVTEQDS	
	KVDKKVEPKSCDKTHTCPPCPAP		KDSTYSLSSTLTLSKADYE	
	ELLGGPSVFLFPPKPKDTLMISRTP		KHKVYACEVTHQGLSSPV	
	EVTCVVVDVSHEDPEVKFNWYV		TKSFNRGEC	
	DGVEVHNAKTKPREEQYASTYR			
	VVSVLTVLHQDWLNGKEYKCKV			

	SNKALPAPIEKTISKAKGQPREPQ			
	VYTLPPSRDELTKNQVSLTCLVK			
	GFYPSDIAVEWESNGQPENNYKT			
	TPPVLDSDGSFFLYSKLTVDKSR			
	WQQGNVFSCSVMHEALHNHYTQ			
	KSLSLSPGK			
P	EVQLVQSGAEVKKPGASVKMSC		DIQMTQSPSSLSASLGDRV	
	KASGYIFTNYPIHWVRQAPGQGL		TITCRASQDISFFLNWYQQ	
	EWIGFIDPGGGYDEPDERFRDRAT		KPGKAPKLLIYYTSRYHSG	
	LTADKSSSTAYMQLSSLTSEDSAI		VPSRFSGSGSGTDFTLTISS	
	YYCARRGGGYYLDYWGQGTLVT		LQPEDFATYFCQHGNTLP	
	VSSASTKGPSVFPLAPSSKSTSGG		WTFGGGTKVEIKRTVAAP	
	TAALGCLVKDYFPEPVTVSWNSG	95	SVFIFPPSDEQLKSGTASVV	96
	ALTSGVHTFPAVLQSSGLYSLSSV		CLLNNFYPREAKVQWKV	
	VTVPSSSLGTQTYICNVNHKPSNT		DNALQSGNSQESVTEQDS	
	KVDKKVEPKSCDKTHTCPPCPAP		KDSTYSLSSTLTLSKADYE	
	ELLGGPSVFLFPPKPKDTLMISRTP		KHKVYACEVTHQGLSSPV	
	EVTCVVVDVSHEDPEVKFNWYV		TKSFNRGEC	
	DGVEVHNAKTKPREEQYASTYR			

VVSVLTVLHQDWLNGKEYKCKV			
SNKALPAPIEKTISKAKGQPREPQ			
VYTLPPSRDELTKNQVSLTCLVK			
GFYPSDIAVEWESNGQPENNYKT			
TPPVLDSDGSFFLYSKLTVDKSR			
WQQGNVFSCSVMHEALHNHYTQ			
KSLSLSPGK			
P			DIQMTQSTSSLSASLGDRV
			TITCRASQDISFFLNWYQQ
			KPGKAPKLLIYYTSRYHSG
			VPSRFSGSGSGTDFTLTISN
			LQPEDFATYFCQHGNTLP
			WTFGGGTKVEIKRTVAAP
		98	SVFIFPPSDEQLKSGTASVV
			CLLNNFYPREAKVQWKV
			DNALQSGNSQESVTEQDS
			KDSTYSLSSTLTLSKADYE
			KHKVYACEVTHQGLSSPV
			TKSFNRGEC
	97		

	DGVEVHNAKTKPREEQYASTYR			
	VVSVLTVLHQDWLNGKEYKCKV			
	SNKALPAPIEKTISKAKGQPREPQ			
	VYTLPPSRDELTKNQVSLTCLVK			
	GFYPSDIAVEWESNGQPENNYKT			
	TPPVLDSDGSFFLYSKLTVDKSR			
	WQQGNVFSCSVMHEALHNHYTQ			
	KSLSLSPGK			
P	QVTLKESGPTILQPTQTLTLTCTFS	99	DIQMTQSHKFMSTSVGDR	100
	GFSLSTSGMGVGWIRQPSGKALE		VTITCKASQDVSDAVAWF	
	WIAHIWWDDVKSYNPALKSRLTI		QQKPGKSPKLLIYSPSYRY	
	TKDTSKSQVVLRIASVDPVDTAT		TGVPSRFTGSGSGTDFTFTI	
	YYCARIGDGYYSFDYWGQGTTLT		SSVQAEDLAVYYCQQHYS	
	VSSASTKGPSVFPLAPSSKSTSGG		TPWTFGQGTKLEIKRTVA	
	TAALGCLVKDYFPEPVTVSWNSG		APSVFIFPPSDEQLKSGTAS	
	ALTSGVHTFPAVLQSSGLYSLSSV		VVCLLNNFYPREAKVQW	
	VTVPSSSLGTQTYICNVNHKPSNT		KVDNALQSGNSQESVTEQ	
	KVDKKVEPKSCDKTHTCPPCPAP		DSKDSTYSLSSTLTLSKAD	
	ELLGGPSVFLFPPKPKDTLMISRTP		YEKHKVYACEVTHQGLSS	

EVTCVVVDVSHEDPEVKFNWYV		PVTKSFNRGEC	
DGVEVHNAKTKPREEQYASTYR			
VVSVLTVLHQDWLNGKEYKCKV			
SNKALPAPIEKTISKAKGQPREPQ			
VYTLPPSRDELTKNQVSLTCLVK			
GFYPSDIAVEWESNGQPENNYKT			
TPPVLDSDGSFFLYSKLTVDKSR			
WQQGNVFSCSVMHEALHNHYTQ			
KSLSLSPGK			
P	QVTLKESGPTLVKPTQTLTLTCTF	DIQMTQSPSSLSTSVGDRV	102
	SGFSLSTSGMGVGWIRQPPGKAL	TITCKASQDVSDAVAWFQ	
	EWIAHIWWDDVKSYNPALKSRLT	QKPGKAPKLLIYSPSYRYT	
	ITKDTSKNQVVLRIASVDPVDTAT	GVPSRFTGSGSGTDFTFTIS	
	YYCARIGDGYYSFDYWGQGTTLT	SVQAEDLAVYYCQQHYST	
	VSSASTKGPSVFPLAPSSKSTSGG	PWTFGQGTKLEIKRTVAA	
	TAALGCLVKDYFPEPVTVSWNSG	PSVFIFPPSDEQLKSGTASV	
	ALTSGVHTFPAVLQSSGLYSLSSV	VCLLNNFYPREAKVQWK	
	VTVPSSSLGTQTYICNVNHKPSNT	VDNALQSGNSQESVTEQD	
	KVDKKVEPKSCDKTHTCPPCPAP	SKDSTYSLSSTLTLSKADY	
	101		

	ELLGGPSVFLFPPKPKDTLMISRTP		EKHKVYACEVTHQGLSSP
	EVTCVVVDVSHEDPEVKFNWYV		VTKSFNRGEC
	DGVEVHNAKTKPREEQYASTYR		
	VVSVLTVLHQDWLNGKEYKCKV		
	SNKALPAPIEKTISKAKGQPREPQ		
	VYTLPPSRDELTKNQVSLTCLVK		
	GFYPSDIAVEWESNGQPENNYKT		
	TPPVLDSDGSFFLYSKLTVDKSR		
	WQQGNVFSCSVMHEALHNHYTQ		
	KSLSLSPGK		
P	QSLEESGGGLVKPGASLTLTCTAS		AYDLTQTPASVEAAVGGT
	GFSFSSGYWIFWVRQAPGKGLEL		VTINCQASDNIYSLLAWY
	VGGIYSGSSGTTYYANWAKGRFT		QQKPGQPPKLLIYRASTLA
	ISKTSSTTVTLQMTSLTAADTATY		SGVPSRFKGSGSGTQFTLTI
	FCARSVDGIDSYDAAFNLWGPGT	103	SGVECADAATYYCQQHY 104
	LVTVSSASTKGPSVFPLAPSSKSTS		DYNYLDVAFGGGTEVVV
	GGTAALGCLVKDYFPEPVTVSWN		KGTVAAPSVFIFPPSDEQL
	SGALTSGVHTFPAVLQSSGLYSLS		KSGTASVVCLLNNFYPRE
	SVVTVPSSSLGTQTYICNVNHKPS		AKVQWKVDNALQSGNSQ

	NTKVDKKVEPKSCDKTH		ESVTEQDSKDSTYSLSSTL	
			TLSKADYEKHKVYACEVT	
			HQGLSSPVTKSFNRGEC	
P	QVQLVQSAPEVAKPGTSVKMSCK			
	ASGYIFTNYPIHWVKQAPGQGLE		DIQMTQSPSSLSASLGDRV	
	WIGFIDPGGGYDEPDERFRDRATL		TITCRASQDISFFLNWYQQ	
	TADKSTSTAYMELSSLRSEDTAIY		KPDGTVKLLIYYTSRYHSG	
	YCARRGGGYYLDYWGQGTLVTV		VPSRFSGSGSGTDFTLTISS	
	SSASTKGPSVFPLAPSSKSTSGGT		LQPEDFATYFCQHGNTLP	
	AALGCLVKDYFPEPVTVSWNSGA		WTFGQGTKLEIKRTVAAP	106
	LTSGVHTFPAVLQSSGLYSLSSVV	105	SVFIFPPSDEQLKSGTASVV	
	TVPSSSLGTQTYICNVNHKPSNTK		CLLNNFYPREAKVQWKV	
	VDKKVEPKSCDKTHTCPPCPAPE		DNALQSGNSQESVTEQDS	
	LLGGPSVFLFPPKPKDTLMISRTPE		KDSTYSLSSTLTLSKADYE	
	VTCVVVDVSHEDPEVKFNWYVD		KHKVYACEVTHQGLSSPV	
	GVEVHNAKTKPREEQYNSTYRV		TKSFNRGEC	
	VSVLTVLHQDWLNGKEYKCKVS			
	NKALPAPIEKTISKAKGQPREPQV			
	YTLPPSRDELTKNQVSLTCLVKGF			

	YPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKS LSLSPGK			
P	QVQLVQSAPEVAKPGTSVKMSCK ASGYIFTNYPIHWVKQAPGQGLE WIGFIDPGGGYDEPDERFRDRATL TADKSTSTAYMELSSLRSEDTAIY YCARRGGGYYLDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTH	107	DIQMTQSPSSLSASLGDRV TITCRASQDISFFLNWYQQ KPDGTVKLLIYYTSRYHSG VPSRFSGSGSGTDFTLTISS LQPEDFATYFCQHGNTLP WTFGQGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPV TKSFNRGEC	108
P	QVQLVQSAPEVAKPGTSVKMSCK ASGYIFTNYPIHWVKQAPGQGLE WIGFIDPGGGYDEPDERFRDRATL	109	DIQMTQSPSSLSASLGDRV TITCRASQDISFFLNWYQQ KPDGTVKLLIYYTSRYHSG	110

TADKSTSTAYMELSSLRSEDTAIY		VPSRFSGSGSGTDFTLTISS	
YCARRGGGYYLDYWGQGTLVTV		LQPEDFATYFCQHGNTLP	
SSASTKGPSVFPLAPSSKSTSGGT		WTFGQGTKLEIKRTVAAP	
AALGCLVKDYFPEPVTVSWNSGA		SVFIFPPSDEQLKSGTASVV	
LTSGVHTFPAVLQSSGLYSLSSVV		CLLNNFYPREAKVQWKV	
TVPSSSLGTQTYICNVNHKPSNTK		DNALQSGNSQESVTEQDS	
VGGPGSGGGGSGGGSPSCPAPE		KDSTYSLSSTLTLSKADYE	
FLGGPSVFLFPPKPKDTLMISRTPE		KHKVYACEVTHQGLSSPV	
VTCVVVDVSQEDPEVQFNWYVD		TKSFNRGECGGGGSGGGG	
GVEVHNAKTKPREEQFNSTYRVV		SGGGGSPSCPAPEFLGGPS	
SVLTVLHQDWLNGKEYKCKVSN		VFLFPPKPKDTLMISRTPE	
KGLPSSIEKTISKAKGQPREPQVY		VTCVVVDVSQEDPEVQFN	
TLPPSQEEMTKNQVSLTCLVKGF		WYVDGVEVHNAKTKPRE	
YPSDIAVEWESNGQPENNYKTTP		EQFNSTYRVVSVLTVLHQ	
PVLDSDGSFFLYSRLTVDKSRWQ		DWLNGKEYKCKVSNKGL	
EGNVFSCSVMHEALHNHYTQKSL		PSSIEKTISKAKGQPREPQV	
SLSLGK		YTLPPSQEEMTKNQVSLTC	
		LVKGFYPSDIAVEWESNG	
		QPENNYKTTPPVLDSDGSF	

			FLYSRLTVDKSRWQEGNV	
			FSCSVMHEALHNHYTQKS	
			LSLSLGK	
P	EVQLVQSGAEVKKPGASVKMSC		DIQMTQSPSSLSASLGDRV	
	KASGYIFTNYPIHWVRQAPGQGL		TITCRASQDISFFLNWYQQ	
	EWIGFIDPGGGYDEPDERFRDRAT		KPGKAPKLLIYYTSRYHSG	
	LTADKSSSTAYMQLSSLTSEDSAI		VPSRFSGSGSGTDFTLTISS	
	YYCARRGGGYYLDYWGQGTLVT		LQPEDFATYFCQHGNTLP	
	VSSASTKGPSVFPLAPSSKSTSGG		WTFGGGTKVEIKRTVAAP	
	TAALGCLVKDYFPEPVTVSWNSG		SVFIFPPSDEQLKSGTASVV	
	ALTSGVHTFPAVLQSSGLYSLSSV	111	CLLNNFYPREAKVQWKV	112
	VTVPSSSLGTQTYICNVNHKPSNT		DNALQSGNSQESVTEQDS	
	KVGGGGSGGGGSGGGSPPCPAP		KDSTYSLSSTLTLSKADYE	
	ELLGGPSVFLFPPKPKDTLMISRTP		KHKVYACEVTHQGLSSPV	
	EVTCVVVDVSHEDPEVKFNWYV		TKSFNRGECGGGGSGGGG	
	DGVEVHNAKTKPREEQYASTYR		SGGGGSPPCPAPELLGGPS	
	VVSVLTVLHQDWLNGKEYKCKV		VFLFPPKPKDTLMISRTPE	
	SNKALPAPIEKTISKAKGQPREPQ		VTCVVVDVSHEDPEVKFN	
	VYTLPPSRDELTKNQVSLTCLVK		WYVDGVEVHNAKTKPRE	

	GFYPSDIAVEWESNGQPENNYKT		EQYASTYRVVSVLTVLHQ	
	TPPVLDSDGSFFLYSKLTVDKSR		DWLNGKEYKCKVSNKAL	
	WQQGNVFSCSVMHEALHNHYTQ		PAPIEKTISKAKGQPREPQ	
	KSLSLSPGK		VYTLPPSRDELTKNQVSLT	
			CLVKGFYPSDIAVEWESN	
			GQPENNYKTTPPVLDSDG	
			SFFLYSKLTVDKSRWQQG	
			NVFSCSVMHEALHNHYTQ	
			KSLSLSPGK	
P	QVTLKESGPTLVKPTQTLTLTCTF		DIQMTQSPSSLSTSVGDRV	
	SGFSLSTSGMGVGWIRQPPGKAL		TITCKASQDVSDAVAWFQ	
	EWIAHIWWDDVKSYNPALKSRLT		QKPGKAPKLLIYSPSYRYT	
	ITKDTSKNQVVLRIASVDPVDTAT		GVPSRFTGSGSGTDFTFTIS	
	YYCARIGDGYYSFDYWGQGTTLT	113	SVQAEDLAVYYCQQHYST	114
	VSSASTKGPSVFPLAPSSKSTSGG		PWTFGQGTKLEIKRTVAA	
	TAALGCLVKDYFPEPVTVSWNSG		PSVFIFPPSDEQLKSGTASV	
	ALTSGVHTFPAVLQSSGLYSLSSV		VCLLNNFYPREAKVQWK	
	VTVPSSSLGTQTYICNVNHKPSNT		VDNALQSGNSQESVTEQD	
	KVGGGGSGGGGSGGGGSPPCPAP		SKDSTYSLSSTLTLSKADY	

	ELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYASTYR VVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK		EKHKVYACEVTHQGLSSP VTKSFNRGECGGGGSGGG GSGGGGSPPCPAPELLGGP SVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPRE EQYASTYRVVSVLTVLHQ DWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQ KSLSLSPGK	
C3B	qvqlqqsgaeivkpgasvkmsckasgytftsywi nwvkqrpgqglewigdiypvrgitnysekfknka kmipdtsstvymqlssltsedsavyycsrgnfgn fdamdywgqgtsvtvssASTKGPSVFPL	115	qivltqspailsaspgekvtmtcsatssit yihwyqqksgtspkrwiydtsrlasgv ptrfsggsgtsyslistmeaedaatyyc qqwssnpptfgggtkleikRTVAAP	116

	APSSKSTSGGTAALGCLVKDYFPE		SVFIFPPSDEQLKSGTASVV	
	PVTVSWNSGALTSGVHTFPAVLQ		CLLNNFYPREAKVQWKV	
	SSGLYSLSSVVTVPSSSLGTQTYIC		DNALQSGNSQESVTEQDS	
	NVNHKPSNTKVDKKVEPKSCDKT		KDSTYSLSSTLTLSKADYE	
	HTCPPCPAPELLGGPSVFLFPPKPK		KHKVYACEVTHQGLSSPV	
	DTLMISRTPEVTCVVVDVSHEDPE		TKSFNRGEC	
	VKFNWYVDGVEVHNAKTKPREE			
	QYASTYRVVSVLTVLHQDWLNG			
	KEYKCKVSNKALPAPIEKTISKAK			
	GQPREPQVYTLPPSRDELTKNQVS			
	LTCLVKGFYPSDIAVEWESNGQP			
	ENNYKTTPPVLDSDGSFFLYSKLT			
	VDKSRWQQGNVFSCSVMHEALH			
	NHYTQKSLSLSPGK			
C3b	QVQLvQSGAEVKKPGASVKMSC		EIVLTQSPATLSASPGEKV	
	KASGYTFTSYWINWVRQAPGQG		TMTCSATSSITYIHWYQQK	
	LEWIGDIYPVRGTTNYSEKFKNKA	117	pGQAPKRWIYDTSRLASG	118
	TMIPDTSTSTVYMELSSLRSEDTA		VPARFSGSGSGTSYSLTIST	
	VYYCSRGNFGNFDAMDYWGQGT		MEpEDFATYYCQQWSSNP	

	mVTVSSASTKGPSVFPLAPSSKST		PTFGGGTKLEIKRTVAAPS	
	SGGTAALGCLVKDYFPEPVTVSW		VFIFPPSDEQLKSGTASVV	
	NSGALTSGVHTFPAVLQSSGLYSL		CLLNNFYPREAKVQWKV	
	SSVVTVPSSSLGTQTYICNVNHKP		DNALQSGNSQESVTEQDS	
	SNTKVDKKVEPKSCDKTHTCPPC		KDSTYSLSSTLTLSKADYE	
	PAPELLGGPSVFLFPPKPKDTLMIS		KHKVYACEVTHQGLSSPV	
	RTPEVTCVVVDVSHEDPEVKFNW		TKSFNRGEC	
	YVDGVEVHNAKTKPREEQYAST			
	YRVVSVLTVLHQDWLNGKEYKC			
	KVSNKALPAPIEKTISKAKGQPRE			
	PQVYTLPPSRDELTKNQVSLTCLV			
	KGFYPSDIAVEWESNGQPENNYK			
	TTPPVLDSDGSFFLYSKLTVDKSR			
	WQQGNVFSCSVMHEALHNHYTQ			
	KSLSLSPGK			
C3b	QVQLVQSGAEVAKPGASVKMSC		DVQITQSPSYLSASPGDTIT	
	KASGYTFTNYWIHWVKQRPGQG	119	ITCRASKSISKYLAWYQDK	120
	LEWIGYINPNTGYNDYNQKFKDK		PGKTNKLLIYSGSTLQSGIP	
	ATLTADKSSSTVYMQLSSLTSEDT		SRFSGSGSGTEFTLTISSLQ	

AVYYCARGGQLGLRRAMDYWG		PDDFAMYYCQQHDEYPW	
QGTLVTVSSASTKGPSVFPLAPSS		TFGQGTKLEIKRTVAAPSV	
KSTSGGTAALGCLVKDYFPEPVT		FIFPPSDEQLKSGTASVVCL	
VSWNSGALTSGVHTFPAVLQSSG		LNNFYPREAKVQWKVDN	
LYSLSSVVTVPSSSLGTQTYICNV		ALQSGNSQESVTEQDSKD	
NHKPSNTKVDKKVEPKSCDKTHT		STYSLSSTLTLSKADYEKH	
CPPCPAPELLGGPSVFLFPPKPKDT		KVYACEVTHQGLSSPVTK	
LMISRTPEVTCVVVDVSHEDPEV		SFNRGEC	
KFNWYVDGVEVHNAKTKPREEQ			
YASTYRVVSVLTVLHQDWLNGK			
EYKCKVSNKALPAPIEKTISKAKG			
QPREPQVYTLPPSRDELTKNQVSL			
TCLVKGFYPSDIAVEWESNGQPE			
NNYKTTPPVLDSDGSFFLYSKLTV			
DKSRWQQGNVFSCSVMHEALHN			
HYTQKSLSLSPGK			

[00109] In some embodiments, an anti-AP antibody described herein can comprise heavy and light chain variable regions comprising amino acid sequences that are substantially homologous or identical to the CDRs of the heavy chain and light chain variable regions of the amino acid sequences of the antibodies described herein, and wherein the antibodies retain the desired functional properties. For example, the invention provides an isolated monoclonal antibody, or antigen binding portion thereof, comprising the CDRs of a heavy chain variable region and a light chain variable region, wherein: (a) the heavy chain variable region comprises at least one, two, or three CDRs at least 80%, 85%, 90%, 95%, 99%, or 100% homologous or identical to the CDRs of a heavy chain variable region listed in Table 2 for a respective antibody; (b) the light chain variable region comprises at least one, two, or three CDRs that is at least 80%, 85%, 90%, 95%, 99%, or 100% homologous or identical to the amino acid sequence of a light chain variable region listed in Table 1 for the respective antibody; and (c) the antibody specifically binds to respective protein, C3b, P, Ba, or Bb.

[00110] In various aspects, the antibody can be, for example, a human antibody, a humanized antibody or a chimeric antibody. In other aspects, the V_H and/or V_L amino acid sequences may be 85%, 90%, 95%, 96%, 97%, 98% or 99% homologous to the sequences set forth above. An antibody having V_H and V_L regions having high (*i.e.,* 80% or greater) homology to the V_H and V_L regions of the sequences set forth above, can be obtained by mutagenesis (*e.g.,* site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding the amino acid sequences, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

[00111] As used herein, the percent homology between two amino acid sequences is equivalent to the percent identity between the two sequences. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.,* % homology=# of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

[00112] In certain aspects, an anti-AP antibody of the invention can include a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences and a light chain variable region comprising CDR1, CDR2 and CDR3 sequences, wherein one or more of these CDR sequences comprise specified amino acid sequences based on the preferred antibodies described herein, or conservative modifications thereof, and wherein the antibodies retain the desired functional properties. Accordingly, the invention provides an isolated monoclonal antibody, or antigen binding portion thereof, comprising a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences.

[00113] As used herein, the term "conservative sequence modifications" is intended to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.,* lysine, arginine, histidine), acidic side chains (*e.g.,* aspartic acid, glutamic acid), uncharged polar side chains (*e.g.,* glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.,* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.,* threonine, valine, isoleucine) and aromatic side chains (*e.g.,* tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within the CDR regions of an antibody can be replaced with other amino acid residues from the same side chain family and the altered antibody can be tested for retained function (*i.e.,* the functions set forth in (c) through (j) above) using the functional assays described herein.

[00114] An anti-AP antibody described herein can be prepared using an antibody having one or more of the V_H and/or V_L sequences disclosed herein as starting material to engineer a modified antibody, which modified antibody may have altered properties from the starting

antibody. An antibody can be engineered by modifying one or more residues within one or both variable regions (*i.e.*, V_H and/or V_L), for example within one or more CDR regions and/or within one or more framework regions. Additionally or alternatively, an antibody can be engineered by modifying residues within the constant region(s), for example to alter the effector function(s) of the antibody.

[00115] One type of variable region engineering that can be performed is CDR grafting. Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties. Thus, such antibodies contain the V_H and V_L CDR sequences described in the Tables yet may contain different framework sequences from these antibodies.

[00116] Another type of variable region modification is to mutate amino acid residues within the V_H and/or V_K CDR1, CDR2 and/or CDR3 regions to thereby improve one or more binding properties (*e.g.,* affinity) of the antibody of interest. Site-directed mutagenesis or PCR-mediated mutagenesis can be performed to introduce the mutation(s) and the effect on antibody binding, or other functional property of interest, can be evaluated in *in vitro* or *in vivo* assays as described herein and provided in the Examples. Conservative modifications (as discussed above) are introduced. The mutations may be amino acid substitutions, additions or deletions, but are preferably substitutions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are altered.

[00117] In general, therapeutic antibodies, once selected, can be manipulated, altered and engineered in a variety of ways for various different reasons. For example, the inactive (non-binding) parts of an selected antibody may be changed and manipulated in countless ways which do not at all change the defining functions of the antibody. In fact, the functional (protein

binging part) of the antibody might be entirely severed from the rest of the antibody. These alterations may have utility for making the antibody easier or less costly to produce. Or, such alterations may make the antibody more chemically stable in human subjects. These manipulations and derivations of the selected antibodies are not new or separate inventions. Accordingly, any such manipulations, alternations and derivations of the selected genus of antibodies which utilize the same defining characteristics of the genus itself are within the scope of the invention.

[00118] The invention includes compounds which constitute the functional (target protein binding) components of any one or several of the selected genus of antibodies, as well as the therapeutic use of such compounds. These compounds include, but are not limited to, whole antibodies of the selected genus, antigen-binding fragments of antibodies of the selected genus, and chimeric or humanized manifestations of any antibody or antibody fragment derived from the selected genus of antibodies. Such derivations of the inventions may include, but are not limited to, truncated, linear, single-chained, an IgG fragment, a F(ab) fragment, a F(ab') fragment, a F(ab)2 fragment, a F(ab')2 fragment, an Fv fragment or an scFv fragment which may be manifested from any antibody of the selected genus.

[00119] The invention includes the result of any member of the antibody genus having its Fc region mutated at the 297 position to generate an aglycosylated antibody. The invention includes the results of any antibody of the selected genus being engineered to elicit reduced Fc-mediated effector functions. Methods of engineering may include, without limitation, amino acid mutations, amino acid additions or deletions, glycan modification or removal, pegylation, and/or truncation.

[00120] In some embodiments, the anti-AP antibody or antigen binding fragment thereof that specifically binds to properdin and inhibits alternative complement pathway activation. The anti-AP antibody comprises a heavy chain having at least one, two, or three CDR(s) having at least 80%, at least 90%, or 100% sequence identity to the CDRs of the heavy chain variable domains of SEQ ID NOs: 44, 46-48, 51-78 or 86, or (ii) competitively inhibits binding of an isolated anti-properdin antibody or antigen binding fragment thereof, a heavy chain variable region having at least one, two, three CDR(s) having at least 80%, at least 90%, or 100%

sequence identity to the CDRs of the heavy chain variable domains of SEQ ID NOs: 44, 46-48, 51-78 or 86, to properdin.

[00121] In some embodiments, the anti-properdin antibody or antigen binding fragment thereof that specifically binds to properdin and inhibits alternative complement pathway activation comprises a light chain having at least one, two, or three CDR(s) having at least 80%, at least 90%, or 100% sequence identity to the CDRs of the light chain variable domains of SEQ ID NOs: 2, 3, 4, 7-33, 41, 42, or 43, or (ii) competitively inhibits binding of an isolated anti-properdin antibody or antigen binding fragment thereof, a heavy chain variable region having at least one, two, three CDR(s) having at least 80%, at least 90%, or 100% sequence identity to the CDRs of the light chain variable domains of SEQ ID NOs: 2, 3, 4, 7-33, 41, 42, or 43, to properdin.

[00122] In other embodiments, the anti-properdin antibody or antigen binding fragment thereof that specifically binds to properdin and inhibits alternative complement pathway activation comprises a heavy chain including three CDRs of heavy chain variable domains selected from the group consisting of SEQ ID NOs: 44, 46-48, 51-78 and 86, or (ii) competitively inhibits binding of an isolated anti-properdin antibody or antigen binding fragment thereof, which comprises a heavy chain including three CDRs of heavy chain variable domains selected from the group consisting of SEQ ID NOs: SEQ ID NOs: 44, 46-48, 51-78 and 86, to properdin.

[00123] In other embodiments, the anti-properdin antibody or antigen binding fragment thereof that specifically binds to properdin and inhibits alternative complement pathway activation comprises a light chain including three CDRs of light chain variable domains selected from the group consisting of SEQ ID NOs: 2, 3, 4, 7-33, 41, 42, and 43, or (ii) competitively inhibits binding of an isolated anti-properdin antibody or antigen binding fragment thereof, which comprises a light chain including three CDRs of light chain variable domains selected from the group consisting of SEQ ID NOs: 2, 3, 4, 7-33, 41, 42, and 43, to properdin.

[00124] It will be appreciated that any anti-AP antibody or antigen binding fragment thereof can be used to treat ocular hemorrhage and/or fibrosis. These anti-AP antibodies can include anti-AP disclosed in, for example, patent application numbers US2012/501,165 (Bansal),

PCT/US2012/675,220 (Bansal), PCT/US2013/034,982 (Bansal), PCT/2011/026,841 (Bansal), PCT/US2013/583,879 (Bansal), US2013/646,286 (Bansal), US 09/138,723 (Bansal, Gliatech), PCT/US2012/044974 (Song), PCT/US2008/007270 (Song), US 14/183,213 (Holers, et al.), US 11/057,047 (Holers, et al.), US 13/482,328 (Fung, et al., Genentech), US 13/135,907 (Campagne, Genentech), PCT/US2008/065771 (Champagne, Genentech), PCT/EP2003/007487 (Tedesco), PCT/IB2012/057394 (Brannetti, Novartis), PCT/EP2009/060052 (Diefenbach-Streiber, Novartis), US 13/716,526 (Johnson et al., Novartis), PCT/EP2010/056129 (Etemad-Gilbertson, et al., Novartis), PCT/US2006/043103 (Fung et al.), PCT/US2003/027808 (Wang, Alexion), US 11/050,543 (Bell), and issued patent numbers 8,435,512 (Bansal).

Treatment Methods

[00125] The methods of the present invention can generally involve the steps of: administering to a mammalian subject in need thereof an effective amount or therapeutically effective amount of an anti-AP antibody to treat retinal fibrosis, hemorrhage and/or ocular inflammation.

[00126] An "effective amount" or "therapeutically effective amount" of a subject antibody is an amount that is effective to reduce the production and/or level of a polypeptide generated following activation of the alternative complement pathway by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or more.

[00127] The anti-properdin antibody can be administered to an individual in a formulation with a pharmaceutically acceptable excipient(s). A wide variety of pharmaceutically acceptable excipients as known in the art and need not be discussed in detail herein.

[00128] In the methods described herein, a subject antibody can be administered to the host using any convenient means capable of resulting in the desired therapeutic effect. Thus, the antibody can be incorporated into a variety of formulations for therapeutic administration. In one example, a subject antibody can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and can be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets,

capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols.

[00129] As such, administration of a subject antibody can be achieved in various administrations, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, subcutaneous, intramuscular, transdermal, intranasal, pulmonary, intratracheal, etc administrations. For treatment of ocular diseases, currently, the preferred method of administration is via intravitreal (IVT) injection directly into the eye. This does not exclude potential administration via alternative mechanisms which are not currently available, but which may become available in the future. If required, the anti-AP antibody may also be given systemically via subcutaneous injection or intravenous injection. Administration of the anti-AP antibodies described herein, and/or any functional derivations thereof, may be by any method known in the art. Administration can be acute or chronic (*e.g.,* daily, weekly, monthly, etc.) or in combination with other agents.

[00130] In pharmaceutical dosage forms, the anti-AP antibodies can be administered independently or in appropriate association, as well as in combination, with other pharmaceutically active compounds. The following methods and excipients are merely exemplary and are in no way limiting.

[00131] Unit dosage forms for injection or intravenous administration can comprise the anti-AP antibodies in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

[00132] An anti-AP antibody can be administered to an individual with a certain frequency and for a period of time so as to achieve the desired therapeutic effect. For example, an anti-AP antibody can be administered, for example, once per month, twice per month, three times per month, every other week (qow), once per week (qw), twice per week (biw), three times per week (tiw), four times per week, five times per week, six times per week, every other day (qod), daily (qd), twice a day (qid), or three times a day (tid), or substantially continuously, or continuously, over a period of time ranging from about one day to about one week, from about two weeks to about four weeks, from about one month to about two months, from about two months to about four months, from about four months to about six months, or longer.

Combination Therapy

[00133] The anti-AP antibody can, in some embodiments, be administered in an effective amount in combination therapy with a second therapeutic agent.

Disease Conditions

[00134] In some embodiments, the anti-AP antibodies described herein can be used in a prophylactic treatment for a subject undergoing an ophthalmologic procedure who has been identified as being at risk for developing a complement mediated ocular disorder post procedure. In some embodiments, the anti-AP antibodies can inhibit fibrosis, hemorrhage and inflammation associated with the ocular procedure. In still other embodiments, the anti-AP antibodies can prevent neovascularization following the ophthalmologic procedure without inhibiting tissue repair.

[00135] In another embodiment, the invention provides a process for inhibiting fibrosis and hemorrhage with normal tissue repair, in a subject undergoing an ocular surgical procedure (or other physical ocular trauma), wherein an anti-AP antibody described herein is administered in order to promote wound healing. In one embodiment of the invention, the invention provides a process for treating AP mediated ocular pathologies occurring during an ocular surgical procedure wherein the subject undergoing the procedure suffers from condition characterized by retinal hemorrhage or inflammation which may/may not lead to vision loss. This embodiment includes the step of administering a qualifying anti-P antibody either immediate before, during or after the surgical procedure.

[00136] In other embodiments, an anti-AP antibody can be used to prevent fibrosis and hemorrhage secondary to a pathology of uveitis, including but not limited to; Iritis, Pars planitis, Choroiditis, Chorioretinitis, Anterior uveitis, Posterior uveitis, Scleritis, ocular neovascularization, atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, Purtscher's retinopathy, Sorsby's fundus dystrophy, Doyne Honeycomb Retinal Dystrophy, Malattia Leventinese, Familial Dominant Drusen, North Carolina macular dystrophy, Juvenile Macular degeneration, Stargardt's disease,

Vitelliform Macular Dystrophy, Adult-Onset Foveomacular Vitelliform Dystrophy (AOFVD), Sorsby's fundus dystrophy, and Best's Disease.

[00137] In other embodiments, one or more of the claimed anti-AP antibodies can be used to prevent inflammation, neovascularization, cellular atrophy, tissue degradation, release of LDH, fibrosis and/or hemorrhage secondary to a pathology of uveitis, including but not limited to; Iritis, Pars planitis, Choroiditis, Chorioretinitis, Anterior uveitis, Posterior uveitis, or Scleritis, ocular neovascularization, diabetic retinopathy or other inflammatory disorder of the eye associated with diabetes, prevent hypertensive retinopathy, prevent autoimmune uveitis or uveitis secondary to an autoimmune disorder, Behçet's Disease, Eales Disease, or other autoimmune inflammtory disease of the eye, atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, Purtscher's retinopathy, AMD, Sorsby's fundus dystrophy, Doyne Honeycomb Retinal Dystrophy, Malattia Leventinese, Familial Dominant Drusen, North Carolina macular dystrophy, Juvenile Macular degeneration, Stargardt's disease, Vitelliform Macular Dystrophy, Adult-Onset Foveomacular Vitelliform Dystrophy (AOFVD), Sorsby's fundus dystrophy, or Best's Disease, vascular occlusion including, but not limited to; Central retinal vein occlusion (CRVO), occlusive peripheral arterial disease, ocular ischemic syndrome secondary to atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, or Purtscher's retinopathy, retinopathy of prematurity or familial exudative vitreoretinopathy, ocular pathology occurring in the anterior segments of the eye, and Fuchs' corneal endothelial dystrophy.

[00138] In some embodiments, an anti-AP antibody is used to prevent fibrosis and/or hemorrhage secondary to a pathology characterized by vascular occlusion. Such pathologies associated with vascular occlusion can include: Central retinal vein occlusion (CRVO), occlusive peripheral arterial disease, ocular ischemic syndrome secondary to atherosclerosis, retinal artery occlusion secondary to antiphospholipid syndrome, neovascular glaucoma, rubeosis iridis, and Purtscher's retinopathy.

[00139] In one embodiment, the anti-AP antibody is used to prevent fibrosis and hemorrhage secondary to diabetic retinopathy. In another embodiment, an anti-P, anti-C3b, or anti-Bb antibody is used to treat any or all AP mediated pathologies associated with retinal

fibrosis or hemorrhage in a diabetic patient, hypertensive retinopathy, an autoimmune disorder, autoimmune uveitis or uveitis, Behçet's Disease, Eales Disease, or other autoimmune disease of the eye.

[00140] In some embodiments, the anti-AP antibody is used to prevent fibrosis and/or hemorrhage secondary to retinopathy of prematurity or familial exudative vitreoretinopathy, ocular pathology occurring in the anterior segments of the eye, Fuchs' corneal endothelial dystrophy, repeated treatment with anti-VEGF agents for prevention of neovascularization.

[00141] In some embodiments, the anti-AP antibody used to treat ocular hemorrhage and/or fibrosis is one which binds to one of the group of complement factors which includes Ba, Bb, C3b, D, C5, C6, C7 or C8. In other embodiments of the invention, the anti-AP antibody used to treat ocular hemorrhage and/or fibrosis is one which also inhibits the classical or lectin pathway.

[00142] In one example, an elderly patient being treated with an anti-VEGF agent for prevention of CNV, arrives at a hospital for ocular surgery. The patient can be required to discontinue the anti-VEGF treatment prior to undergoing the surgical procedure because anti-VEGF agents jeopardize post-surgical healing and recovery. The surgery causes inflammation and hemorrhage immediately, due to trauma caused by the surgery. Without the anti-VEGF treatment, the uncontrolled inflammation results in the patient developing postoperative CNV. To prevent CNV in the absence of an anti-VEGF agent, the surgeon could administer to the patient an anti-P antibody of this invention. This anti-P agent inhibits progression of inflammation, and thereby inhibits formation of VEGF responsible for neovascularization. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00143] In another example, a patient arrives at a healthcare center seeking treatment for CNV or fibrovascular PED and as per instructions the ocular specialist gives the patient an injection of Ranibizumab. The patient undergoes RPE tear occurring less than a minute after intravitreal injection of Ranibizumab for a fibrovascular PED. Such cases do not use Ranibizumab as the drug is not indicated for tear. However, the drug of the present invention does not block tissue repair and therefore would be indicated for such a patient without having the fear of not healing lesions.

[00144] In yet another example, patient suffering from ocular defects in one or both eyes visits the hospital for ocular surgery for correction of pathologies associated with birth defects, lens changes, cataracts, or glaucoma. The patient may be undergoing ocular surgery for cosmetic reasons or for natural lens replacement. As a result of surgery, or due to spontaneous or congenital causes, the patient develops neovascularization. Under such conditions, Ranibizumab cannot be administered as it is contraindicated for ocular surgery. Anti-P antibodies of this invention can be used to prevent CNV and the tissue repair will proceed normally. Thus anti-P antibodies can be used in ocular conditions where neovascularization and surgery are both part of the disease process.

[00145] In still another example, a patient who received monthly or bi-monthly injections of Lucentis to prevent CNV will have continuous lesions as Lucentis prevents tissue repair. The ultimate result is formation of scar and fibrosis and loss of vision. Anti-AP antibodies of the current invention prevent the formation of new VEGF and therefore would control CNV, while also preventing hemorrhage and fibrosis that threaten vision. Administration of an anti-AP antibody of the current invention could be used to prevent vision loss in patients who have undergone repeated treatments of an anti-VEGF agent.

[00146] In yet another example, an elderly patient presents with vision loss after 2 years of monthly Ranibizumab therapy. An ophthalmic specialist attributes the patient's vision loss to lesion characteristics commonly associated with suppressed CNV, such as pigmentary abnormalities, atrophic scar, and the absence of leakage. Future VA improvements in patients receiving Ranibizumab therapy may require preservation of photoreceptor and RPE function rather than strategies that target CNV. Administration of an anti-AP antibody of the invention would inhibit production of MAC, along with other inflammatory cytokines and mediators which jeopardize RPE cell viability. Preservation of the RPE cells by the anti-AP agent would preserve vision when the anti-VEGF agent is no longer able to prevent vision loss.

[00147] In another example, a patient having been treated with an anti-VEGF agent for tumor growth suppression presents with ongoing lesions and hemorrhaging due to lack of healing at the site of tumor regression. Anti-VEGF agents are well known to be effective for tumor regression. Anti-VEGF agents inhibit vascular growth to the tumor, and thereby inhibit

tumor growth. However, anti-VEGF agents also inhibit post tumor recession healing and healthy tissue regrowth. An ophthalmic specialist could administer an anti-AP agent of the invention in order to preserve the tumor suppression accomplished by the anti-VEGF agent, while also providing treatment for wound healing and healthy tissue regrowth. The invention of this application could be used to promote tumor regression by inhibiting VEGF produced by the AP, without jeopardizing the VEGF needed for healthy tissue regrowth and healing.

[00148] In another example, an older patient suffering from ocular defects in one or both eyes visits the hospital for ocular surgery. Surgery of the eye causes immediate inflammation and hemorrhage as a result of trauma. Inflammatory cytokines and mediators begin to proliferate immediately during and after surgery. In the days and weeks following surgery, inflammation continues, resulting in the release of growth factors and activation of immune system cells. Post operative complications of ocular surgery include fibrosis, neovascularization, vascular leakage and edema. To improve surgical outcome, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery. Administration of the anti-P antibody prior to surgery immediately reduces inflammation and hemorrhaging during surgery and inhibits the release of growth factors and activation of immune system cells following surgery. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00149] In another example, an older patient suffering from non-proliferative diabetic retinopathy in one or both eyes visits the hospital for ocular surgery. Inflammatory cytokines and mediators begin to proliferate immediately during and after surgery. In the days and weeks following surgery, inflammation continues, resulting in the release of growth factors and activation of immune system cells. Inflammation and the release of growth factors cause the patient's diseased blood vessels to grow abnormally, resulting in neovascularization. The onset of neovascularization advances the patients non-proliferative diabetic retinopathy into proliferative diabetic retinopathy, which jeopardizes the patient's vision. To improve surgical outcome and to prevent post-surgical advancement of the patient's disease condition, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery. Administration of the anti-P antibody prior to surgery immediately reduces inflammation and

hemorrhaging during surgery and inhibits the release of growth factors and activation of immune system cells following surgery. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00150] In another, example an older patient suffering from proliferative diabetic retinopathy in one or both eyes visits the hospital for ocular surgery. In patients with proliferative diabetic retinopathy, there is neovascularization of the blood vessels supplying the retina. The standard treatment for proliferative diabetic retinopathy includes administration of an anti-VEGF agent. Anti-VEGF agents are counter-indicated for ocular surgery. The patient will be required to discontinue use of the anti-VEGF agent in order to undergo ocular surgery. Without the anti-VEGF agent, the inflammation caused by the ocular surgery causes release of inflammatory mediators, cytokines and growth factors which can cause neovascularization in the patient with proliferative diabetic retinopathy. To improve surgical outcome and to prevent post-surgical advancement of the patient's disease condition, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery. Administration of the anti-P antibody prior to surgery immediately reduces inflammation and hemorrhaging during surgery and inhibits the release of growth factors and activation of immune system cells following surgery. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00151] In yet another example, a patient who has been diagnosed with a disorder associated with occlusive retinal vasculitis, such as Bechet's or Eales' disease, visits the hospital for ocular surgery. Occlusive retinal vasculitis is an inflammatory condition in which chronic inflammation can lead to retinal neovascularization. Ocular surgery causes trauma-induced inflammation which causes the immediate release of inflammatory cytokines and mediators which begin to proliferate immediately during surgery. In the days and weeks following surgery, inflammation continues, resulting in the release of growth factors and activation of immune system cells. To improve surgical outcome and to prevent post-surgical advancement of the patient's disease condition, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery. Administration of the anti-P antibody prior to surgery immediately reduces inflammation and hemorrhaging during surgery and inhibits the release of

growth factors and activation of immune system cells following surgery. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00152] In yet another example, an adult patient, who has previously been exposed to Histoplasma capsulatum**,** visits the hospital for an ocular surgery unrelated to OHS. The patient is experiencing some ocular inflammation prior to surgery, but has not yet developed "histo spots" or any other noticeable signs of ocular histoplasmosis syndrome (OHS). Ocular surgery causes trauma, inflammation and hemorrhage which make the patient more vulnerable to infection. In the weeks following surgery, the patient begins show the early signs of OHS. To improve surgical outcome, and to reduce inflammation and hemorrhage immediately following surgery, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery. Administration of the anti-P antibody does not jeopardize the patient's ability to fight infection. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00153] In another example, an adult patient who has been previously diagnosed with Ocular Histoplasmosis Syndrome (OHS) visits the hospital for an ocular surgery. Chronic inflammation caused by exposure to the pathogen causes some patients with OHS to develop ocular edema, neovascularization, and fibrosis. Ocular surgery causes trauma, inflammation and hemorrhage which render the patient more vulnerable to infection. To improve surgical outcome and to prevent post-surgical advancement of the patient's disease condition, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery without jeopardizing the patient's ability to fight infection. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00154] In yet another example, a patient who has been diagnosed with a congenital disorder associated with excessive deposition of drusen visits the hospital for ocular surgery. In patients with familial drusen, large deposits of drusen can cause ocular inflammation and a break in the blood-eye barrier, which can lead to neovascularization and vision loss. Ocular surgery causes inflammation and hemorrhage which can stress the retinal epithelial layer which is already under stress from the drusen deposits. The inflammation caused by the ocular surgery immediately causes further release of inflammatory mediators and cytokines. In the days and

weeks following surgery, continued inflammation causes the release of growth factors, MAC production, and activation of immune system cells which can cause retinal cell death, breakage of the blood-retinal barrier and neovascularization. To improve surgical outcome and to prevent post-surgical advancement of the patient's disease condition, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery. Administration of the anti-P antibody prior to surgery reduces inflammation and the release of cytokines and growth factors immediately following surgery. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00155] In still another example, an adult patient, who has a history of developing excessive fibrotic tissue and scarring following surgical procedures, visits the hospital for ocular surgery. Ocular surgery causes immediate trauma and inflammation. In the days and weeks following surgery, inflammation causes the release of growth factors and activation of cells involved in scar formation and fibrosis. Without a prophylactic treatment for ocular fibrosis, the patient develops excessive scar tissue at the surgical site. To improve surgical outcome and to inhibit post-surgical fibrosis and scarring, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery. Administration of the anti-P antibody prior to surgery reduces inflammation and inhibits post-surgical release of growth factors and cell activations involved in fibrosis. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

[00156] In another example, an adult patient, who has a history of Von Willebrand Disease (VWD), visits the hospital for ocular surgery. Ocular surgery causes immediate trauma, inflammation and hemorrhage. Due to the patient's disorder, bleeding at the surgical site is excessive and prolonged. Without a prophylactic treatment for ocular hemolysis, the patient struggles to recover from surgery due to unresolved hemolysis. To improve surgical outcome, the surgeon can administer an anti-P antibody of the present invention immediately prior to surgery. Administration of the anti-P antibody prior to surgery reduces inflammation and hemolysis. The reduction in hemolysis improves healing at the surgical site. Post-operative wound healing occurs without development of neovascularization, fibrosis, vascular leakage or edema.

EXAMPLES

[00157] It is to be understood that this invention is not limited to the particular embodiments described herein, as such may, of course, vary. It is also to be understood that the terminology used herein is for describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

EXAMPLE 1: Alternative Pathway Inhibiting Antibodies of the Invention Inhibit Production of VEGF, PDGF, TNF-a, and IL-1b

[00158] An anti-AP antibody as described in Example 3was added to human blood during an extracorporeal model of dialysis, wherein complement activation is known to occur. After incubation at 37°C, the levels of VEGF, PDGF, TNF-alpha, and IL-1b were measured using conventional methods. The data from these experiments demonstrate that the anti-AP antibody was able to inhibit production of VEGF, PDGF, TNF-alpha, and IL-1b in human blood wherein complement activation would otherwise occur. Graphical representations of the data from these experiments are presented in FIG. 3 (VEGF), FIG. 4 (PDGF), FIG. 5 (TNF-alpha), and FIG. 6 (IL-1b).

EXAMPLE 2: Anti-AP antibodies inhibit AP and LDH *Ex Vivo*

[00159] To test the activity of the antibody for AP inhibition, rabbit erythrocytes were incubated in 10% normal human serum in buffer that allows only AP activation to occur. (/Mg^{2+}/EGTA). These rRBCs activate the AP, Lysis of the cells results in a gradual decrease in light scattered by cells. When an AP specific antibody of the present invention was incubated with rRBCs at 37°C in 10% NHS, the lysis was prevented y this antibody. This implies that the AP specific antibody of the present invention blocks AP. Plasma was evaluated by LDH to demonstrate that the AP specific antibody prevents LDH formation. Both lysis and LDH are critical parameters in ocular disease, the former demonstrates cell injury and the latter demonstrates cell death as dead cells release LDH. As shown in FIG. 7, both cell injury/lysis and LDH overlap.

EXAMPLE 3: Anti-P Antibody Fab Inhibits CNV in Rhesus Model of Wet AMD

[00160] A humanized anti-properdin antibody used for this study is the Fab fragment of one of the full-length antibodies having the light chain variable domain 3CDRs of SEQ ID NO: 12 and the heavy chain variable domain 3CDRs of SEQ ID NO: 55. The material used for the study was evaluated at a concentration of 25.5 mg/mL. We used the Fab of the anti-P antibody instead of the IgG because the study involved a comparison with an anti-VEGF antibody in fab form Lucentis® (Genentech). The concentration of Lucentis in the vial is 10 mg/ml and the volume is 300 ul/vial. Concentration of the anti-P antibody was 25 mg/ml in phosphate buffered saline. The test article, reference article and control article were each administered via a single intravitreal injection performed in naive female rhesus monkeys which were 2.9 – 3.9 years old at the time of study assignment. Subjects weighed 3.0 – 4.8 kg on Day -1 (n=9).

[00161] Lucentis was administered at a dose of 500 ug/eye (the therapeutic dose for use in humans), while 1.25 mg/eye was used for the anti-P antibody (the highest concentration allowable based on our current formulation). Following administration of the injection, a laser was used to create nine spots of tissue injury on the retina of each eye of each animal. These lasered spots are known in the art to induce CNV in other animal models. Following the laser induction, a period of two weeks was allowed for healing and CNV formation. Following the two week post-op period, FA images were taken at the end of Week2, Week3 and Week4. Color images were taken at the end of Week2, Week3 and Week4. FA images were evaluated with the aid of the ImageJ program.

[00162] CNV appearing on FA images was quantified using an ImageJ program which is known and accepted within the art. FIG. 8 displays the images taken at Week2, Week3, and Week4. Due to overexposure of Week4 images, meaningful FA data analysis was only possible for images taken at the end of Week2 and Week3. The results of the ImageJ analysis are presented in FIG. 9 (corresponding to Week2). As the results of this study demonstrate, the anti-P antibody was effective in inhibiting CNV. As expected, the anti-VEGF inhibitor was more effective at preventing vascular growth in the weeks following laser induction. As previously discussed in this application, anti-VEGF agents inhibit all new vessel growth. The purpose of

this invention is to offer a treatment for CNV which inhibits excessive growth of new vessels without inhibiting new vessel growth which will be required for wound healing.

EXAMPLE 4: Anti-P Antibody Fab Inhibits Hemolysis in Rhesus Model of Wet AMD

[00163] Hemorrhage quantification was conducted using the FA images which were originally taken for evaluation of the CNV study described in Example 3 above. The black areas around the CNV and laser spots were identified by as hemorrhage (see FIG. 10). The black regions were present mostly around the areas of CNV and underneath the CNV. Black spots were also noted in the centers of the circular tissue injuries created by the laser-induction of CNV. These regions were quantified using the ImageJ, using methods similar to those used for quantification of CNV, as discussed in Example 3. The results of the quantitative evaluation for hemorrhage after Week 3 are presented in FIG. 11.

EXAMPLE 5: Anti-P Antibody Fab Inhibits Retinal Fibrosis in Rhesus Model of Wet AMD

[00164] FIG. 12 shows the color images (converted to grayscale for purposes of this application) taken from the rhesus monkey study described in examples 3 through 4 above were used to evaluate the study subjects for development of retinal fibrosis following treatment and induction of CNV. Retinal fibrosis appears in the color images as lightly colored "stringy" or obscurely patterned areas surrounding and extending from the laser spots. Using a scale from 0 to 6, with zero being no appearance of fibrosis and 6 being the appearance of the most extensive fibrosis, multiple observers scored the full color images for visualization of fibrosis on each image. Observers were blinded to the identification of the images as being from the test, reference or control group. Examples of visualized fibrosis and the grading key provided to the observers are provided in FIG. 13. FIG. 14 provides a graphical representation of the quantitative results of the observers' evaluation for fibrosis. As can be seen from the data, the anti-P antibody substantially reduced fibrosis in 2 out of the 3 animals treated. While some improvement in fibrosis was also seen in 2 out of 3 animals in the Lucentis treated group, the improvement in fibrosis seen in the anti-P antibody treated animals was significantly greater than was seen in the Lucentis treated group.

[00165] From the above description of the invention, those skilled in the art will perceive improvements, changes and modifications. Such improvements, changes and modifications within the skill of the art are intended to be covered by the appended claims. All references, publications, and patents cited in the present application are herein incorporated by reference in their entirety.

CLAIMS

1. A method of treating ocular pathologies associated with fibrosis and hemorrhage within and around the macula of a subject in need thereof, the method comprising: administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that binds to a component of alternative pathway and inhibits alternative pathway activation.

2. The method of claim 1, wherein the antibody or antigen binding fragment thereof inhibits alternative complement pathway activation without inhibiting classical pathway activation.

3. The method of claim 1, wherein the antibody or antigen binding fragment thereof binds to a component of alternative pathway selected from the group consisting of C3b, Properdin (factor P), Factors Ba and Bb, C5, C6, C7, C8, C9.

4. The method of claim 1, wherein the antibody or antigen binding fragment thereof binds to a complement regulator that controls complement activation.

5. The method of claim 1, wherein the antibody or antigen binding fragment thereof selectively inhibits C3a, C5a, C3b, C5b, and C5b-9 produced by the alternative pathway, without inhibiting any of the classical pathway's ability to produce C3a, C5a, C3b, C5b, and C5b-9.

6. The method of claim 1, wherein the antibody or antigen binding fragment thereof selectively inhibits formation of PC3bBb produced by the alternative pathway.

7. The method of any of claim 3, wherein the antibody or antigen binding fragment thereof neutralizes the component of the alternative pathway function.

8. The method of claim 1, wherein the antibody or antigen binding fragment thereof binds to at least one of P, Bb, or C3b.

9. The method of any of claims 1 to 8, wherein the therapeutically effective amount of antibody or antigen binding fragment thereof is an amount effective for comprehensive treatment of macular degeneration, geographic atrophy and retinal fibrosis.

10. The method of any of claims 1 to 8, wherein the subject has dry age-related macular degeneration and the therapeutically effective amount of antibody or antigen binding fragment thereof is an amount of antibody effective to treat the dry age-related macular degeneration.

11. The method of any of claims 1 to 8, wherein the subject has wet age-related macular degeneration and the therapeutically effective amount of antibody or antigen binding fragment thereof is an amount of anti-properdin antibody effective to treat the wet age-related macular degeneration.

12. The method of any of claims 1 to 8, wherein the subject has geographic atrophy and the therapeutically effective amount of antibody or antigen binding fragment thereof is an amount of antibody or antigen binding fragment thereof effective to treat the geographic atrophy.

13. The method of any of claims 1 to 8, wherein the subject has geographic atrophy post onset of wet age-related macular degeneration and the therapeutically effective amount of antibody or antigen binding fragment thereof is an amount of antibody or antigen binding fragment thereof effective to treat the geographic atrophy.

14. The method of any of claims 1 to 8, wherein the subject has geographic atrophy post onset of dry age-related macular degeneration and the therapeutically effective amount of antibody or antigen binding fragment thereof is an amount of antibody or antigen binding fragment thereof effective to treat the geographic atrophy.

15. The method of any of claims 1 to 8, wherein the subject has early-stage age-related macular degeneration or excessive drusen pre-age-related macular degeneration and the therapeutically effective amount of antibody or antigen binding fragment thereof is an amount of antibody or antigen binding fragment thereof effective to inhibit onset of age-related macular degeneration.

16. A method of treating ocular disorders in a subject in need thereof, comprising administering to the subject undergoing anti-VEGF, anti-PDGF treatment a therapeutically effective amount of an antibody or antigen binding fragment thereof that binds to a component of alternative pathway and inhibits alternative pathway activation.

17. The method of claim 16, wherein the antibody or antigen binding fragment thereof has a reduced effector function.

18. The method of claim 16, wherein the antibody is a hybrid of two antibody isoforms.

19. The method of claim 16, wherein the antibody or antigen binding fragment thereof binds to a component of alternative pathway C3 convertase and inhibits alternative pathway activation.

20. The method of claim 16, wherein the antibody or antigen binding fragment thereof selectively inhibits C3a, C5a, C3b, C5b, and C5b-9 produced by the alternative pathway but not the classical pathway.

21. The method of claim 16, wherein the antibody or antigen binding fragment thereof binds to at least one of P, Bb, or C3b.

22. The method of any of claims 15 to 21, wherein the ocular disorder is associated with and/or results from a surgical procedure of the subject.

23. The method of claim 22, wherein the surgical procedure is cardiopulmonary bypass surgery.

24. The method of claim 22, wherein the surgical procedure is an ocular surgical procedure.

25. The method of any of claims 15 to 21, wherein the ocular disorder is associated with and/or results from diabetes of the subject.

26. The method of any of claims 15 to 21, wherein the ocular disorder is associated with and/or results from physical injury to the retina.

27. The method of any of claim 15 to 12, wherein the ocular disorder is aberrant choroidal neovascularization.

28. The method of any of claims 15 to 21, wherein the ocular disorder is retinal fibrosis.

29. The method of any of claims 15 to 21, wherein the ocular disorder is ocular inflammation.

30. The method of any of claims 15 to21, wherein the ocular disorder includes anterior and posterior chamber ocular diseases.

31. The method of any of claims 15 to 21, wherein the ocular disorder is selected from the group consisting of Angioid Streaks, Arterial Macroaneurysm, Arterial Occlusive Disease, Central Retinal Vein Occlusion, Central Serous Chorioretinopathy, Chorioretinal Degenerations, Choroidal Rupture, Choroiditis, Circinate Retinopathy, Cone Degenerations, Cone-Rod Dystrophies, Cystoid Macular Edema, Degenerative Myopia, Dominant/Excessive Drusen, Endophthalmitis, Exudative Retinopathy, Histoplasmosis Of The Eye, Hypertensive Retinopathy, Ischemic Eye Injury, Leukemic Retinopathy, Macular Edema, Malattia Leventinese, Mucopolysaccharidoses, Neoplasm, North Carolina Macular Dystrophy, Peripheral Retinal Neovascularization, Photoreceptor Degenerations, Polypoidal Choroidal Vasculopathy, Preretinal Fibrosis, Proliferative Retinopathy, Proliferative Vitreoretinopathy, Purtscher's Retinopathy, Radiation-Induced Retinopathy, Renal Retinopathy, Retinal Angiomatosis, Retinal Detachment, Retinal Scarring, Retinal Telangiectasia, Retinal Vein Occlusion, Retinopathy Of Prematurity, Rhegmatogenous Retinal Detachment, Rod-Cone Dystrophies, RPE Degenerations, Rubeosis Iridis, Sickle Cell Retinopathy, Sorsby's Fundus Dystrophy, Stellate Retinopathy, Subretinal Choroidal Neovascularization , Uveitis, and Venous Occlusive Disease.

32. The method of any of claims 15 to 21, wherein the ocular disorder is selected from the group consisting of diabetic retinopathy, diabetic microvasculopathy, pericyte cell death, intraretinal microvascular, microaneurysms, altered vascular permeability, macular edema, subhyaloid and vitreous hemorrhage, and subretinal choroidal neovascularization.

33. A method of treating ocular disorder associated with and/or results from a surgical procedure of the subject in a subject in need thereof, comprising administering to the subject therapeutically effective amount of an antibody or antigen binding fragment thereof that binds to a component of alternative pathway and inhibits alternative pathway activation.

34. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject down-regulates vascular permeability in the subject.

35. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject down-regulates epithelial permeability in the subject.

36. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject inhibits neovascularization in the subject.

37. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject inhibits retinal fibrosis in the subject.

38. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject inhibits of retinal pigment epithelial cell atrophy in the subject.

39. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject inhibits LDH in the subject.

40. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject inhibits photoreceptor cell death in the subject.

41. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject down-regulates vascular endothelial growth factor (VEGF) in the subject.

42. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject down-regulates platelet derived growth factor (PDGF) in the subject.

43. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject down-regulates angiopoietin-2 in the subject.

44. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject down-regulates fibroblast growth factor (FGF) in the subject.

45. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject down-regulates connective tissue growth factor (CTGF) in the subject.

46. The method of any of claims 1 to 33, wherein the antibody upon administration to the subject C3b formation.

47. The method of any of claims 1 to 33, wherein the antibody or antigen binding fragment thereof upon administration to the subject inhibits C5a formation.

48. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator of vascular permeability.

49. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator of epithelial permeability.

50. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator of epithelial permeability.

51. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof an inhibitor of neovascularization.

52. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator of epithelial permeability.

53. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof an inhibitor of neovacularization.

54. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof an inhibitor of retinal fibrosis.

55. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof an inhibitor of RPE cell atrophy.

56. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof an inhibitor of LDH.

57. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof an inhibitor of photoreceptor cell death.

58. The method of any of claims 1 to47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down regulator of VEGF.

59. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator of PDGF.

60. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator of angiopoietin-2.

61. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator of FGF.

62. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator CTGF.

63. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a down-regulator of retinal glial cell activation.

64. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof an inhibitor of C3b.

65. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof an inhibitor of C5a.

66. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof a selective inhibitor of intraocular activation.

67. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, antibody and/or small molecule agents which directly target VEGF.

68. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, antibody and/or small molecule agents which directly target PDGF.

69. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, antibody and/or small molecule agents which directly target Angiopoietin-2.

70. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, antibody and/or small molecule agents which directly target CTGF.

71. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, antibody and small molecule agents which directly target C5a.

72. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, antibody and/or small molecule agents which directly target C3b.

73. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, antibody and/or small molecule agents which directly target C4.

74. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, antibody and/or small molecule agents which inhibit the Classical Pathway.

75. The method of any of claims 1 to 47, further comprising administering in combination with the antibody or antigen binding fragment thereof, at least one agent selected from the group consisting of Ranibizumab, bevacizumab, aflibercept, KH902 VEGF receptor-Fc fusion protein, 2C3 antibody, ORAl 02, pegaptanib, bevasiranib, SIRNA-027, decursin, decursinol, picropodophyllin, guggulsterone, PLGlOl, eicosanoid LXA4, PTK787, pazopanib, axitinib, CDDO-Me, CDDO-Imm, shikonin, beta- hydroxyisovalerylshikonin, or ganglioside GM3, DClOl antibody, Mab25 antibody, Mab73 antibody, 4A5 antibody, 4E10 antibody, 5F12 antibody, VAOl antibody, BL2 antibody, VEGF-related protein, sFLTOl, sFLT02, Peptide B3, TG100801, sorafenib, and G6-31 antibody.

76. The method of any of claims 1-75, wherein the antibody is an anti-properdin antibody or antigen binding portion thereof that specifically binds to properdin and inhibits alternative complement pathway activation, the anti-properdin antibody comprising a heavy chain having at least two CDR(s) having at least 80% sequence identity to the CDRs of the heavy chain variable domains of SEQ ID NOs: 44, 46-48, 51-78 or 86, or (ii) competitively inhibits binding of an isolated anti-properdin antibody or antigen binding portion thereof, a heavy chain variable region having at least two CDR(s) having at least 80% sequence identity to the CDRs of the heavy chain variable domains of SEQ ID NOs: 44, 46-48, 51-78 or 86, to properdin.

77. The method of any of claims 1-75, wherein the antibody is an anti-properdin antibody or antigen binding portion thereof that specifically binds to properdin and inhibits alternative complement pathway activation, the anti-properdin antibody comprising a light chain having at least two CDR(s) having at least 80sequence identity to the CDRs of the light chain variable domains of SEQ ID NOs: 2, 3, 4, 7-33, 41, 42, or 43, or (ii) competitively inhibits

binding of an isolated anti-properdin antibody or antigen binding portion thereof, a heavy chain variable region having at least two CDR(s) having at least 80% sequence identity to the CDRs of the light chain variable domains of SEQ ID NOs: 2, 3, 4, 7-33, 41, 42, or 43, to properdin.

78. The method of any of claims 1-75, wherein the antibody is an anti-properdin antibody or antigen binding portion thereof that specifically binds to properdin and inhibits alternative complement pathway activation, the anti-properdin antibody comprising a heavy chain including three CDRs of heavy chain variable domains selected from the group consisting of SEQ ID NOs: 44, 46-48, 51-78 and 86, or (ii) competitively inhibits binding of an isolated anti-properdin antibody or antigen binding portion thereof, which comprises a heavy chain including three CDRs of heavy chain variable domains selected from the group consisting of SEQ ID NOs: SEQ ID NOs: 44, 46-48, 51-78 and 86, to properdin.

79. The method of any of claims 1-75, wherein the antibody is an anti-properdin antibody or antigen binding portion thereof that specifically binds to properdin and inhibits alternative complement pathway activation, the anti-properdin antibody comprising a light chain including three CDRs of light chain variable domains selected from the group consisting of SEQ ID NOs: 2, 3, 4, 7-33, 41, 42, and 43, or (ii) competitively inhibits binding of an isolated anti-properdin antibody or antigen binding portion thereof, which comprises a light chain including three CDRs of light chain variable domains selected from the group consisting of SEQ ID NOs: 2, 3, 4, 7-33, 41, 42, and 43, to properdin.

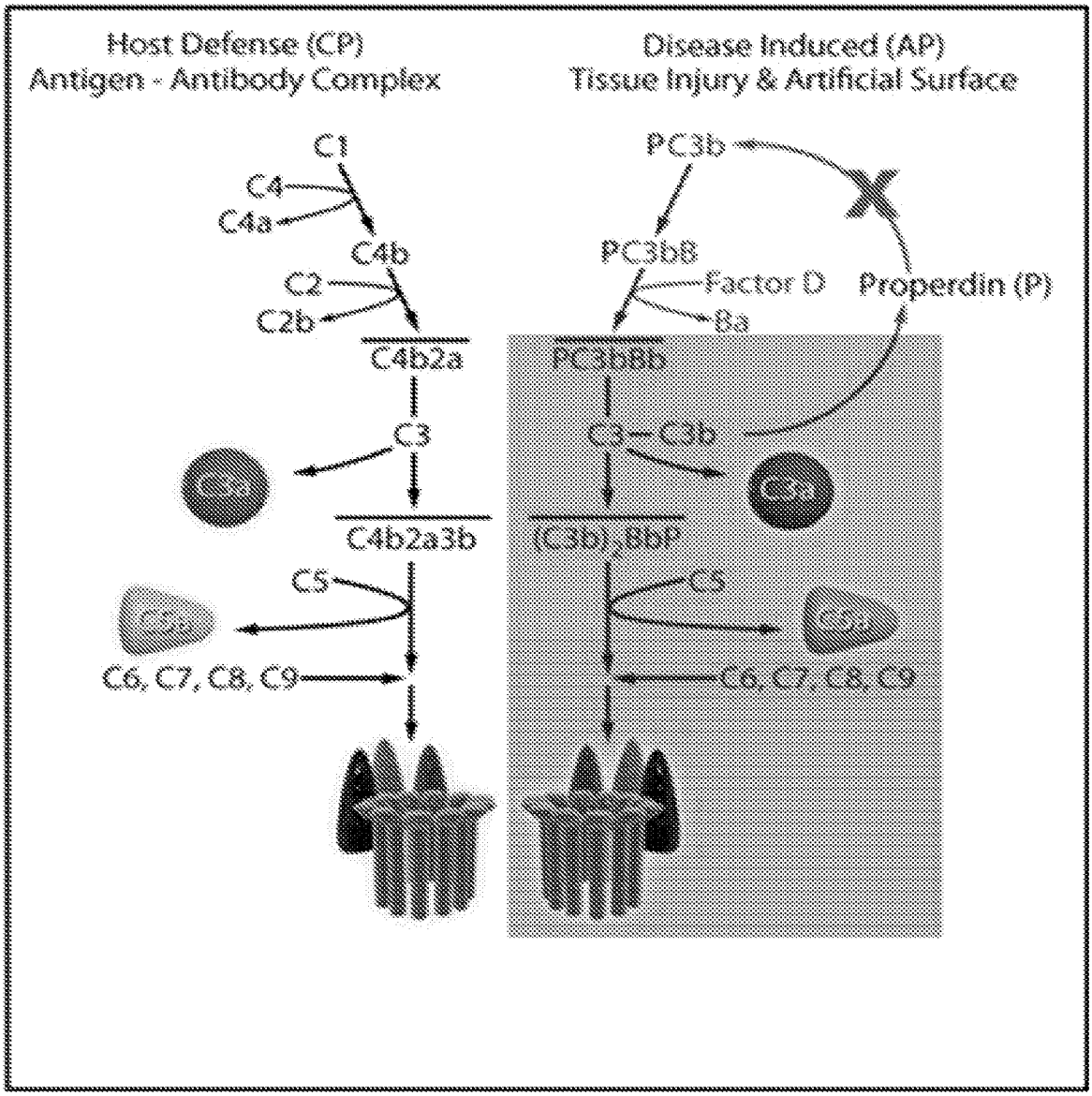

Host Defense (CP)
Antigen - Antibody Complex
Disease Induced (AP)
Tissue Injury & Artificial Surface
C1
C4
C4a
C4b
C2
C2b
C4b2a
C3
C4b2a3b
C5
C6, C7, C8, C9
PC3b
PC3b8
Factor D
Properdin (P)
8a
PC3b8b
C3—C3b
(C3b)nBbP
C5
C6, C7, C8, C9

Fig. 1

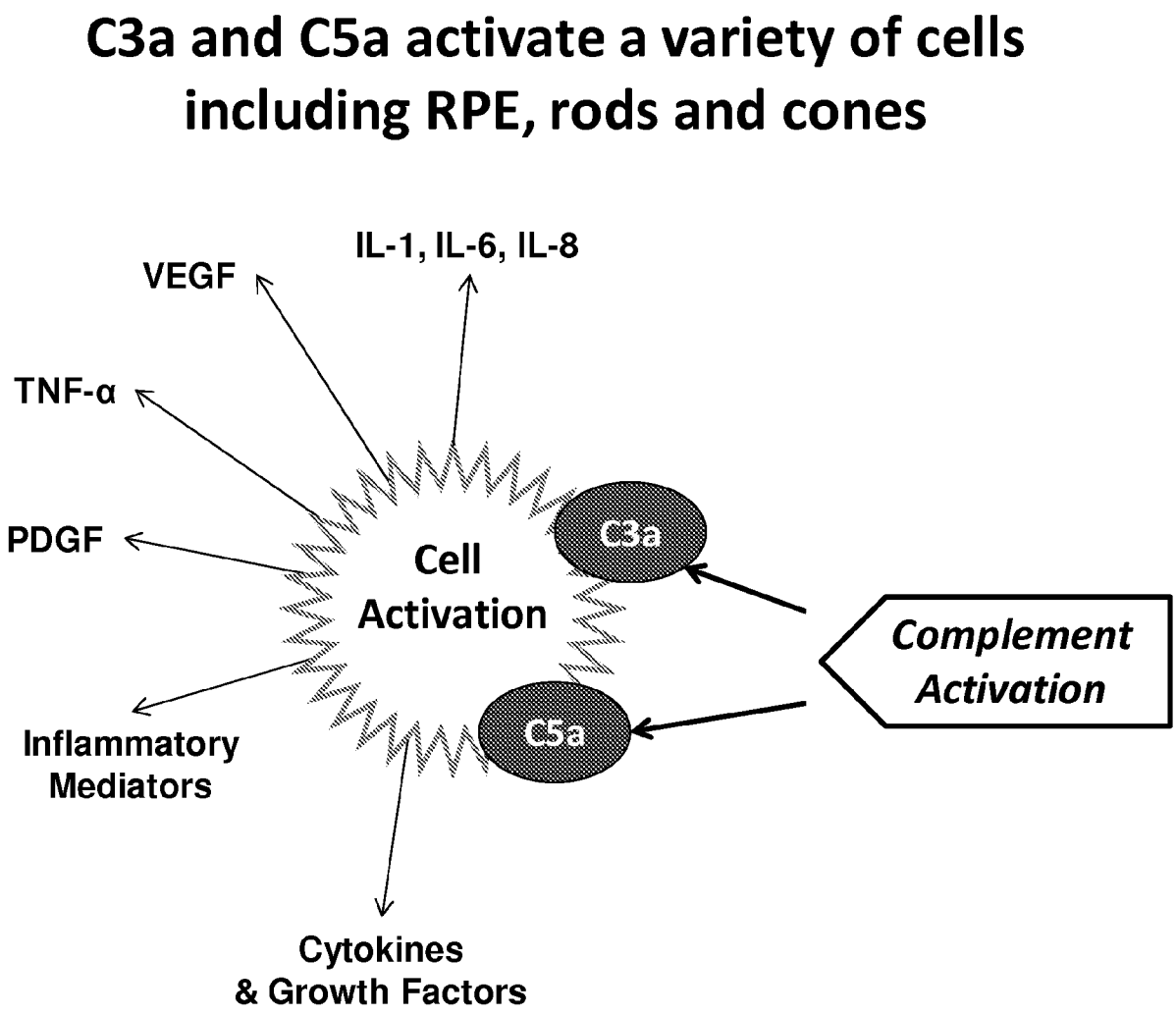

C3a and C5a activate a variety of cells including RPE, rods and cones
IL-1, IL-6, IL-8
VEGF
TNF-α
PDGF
Cell Activation
C3a
C5a
Complement Activation
Inflammatory Mediators
Cytokines & Growth Factors

Fig. 2

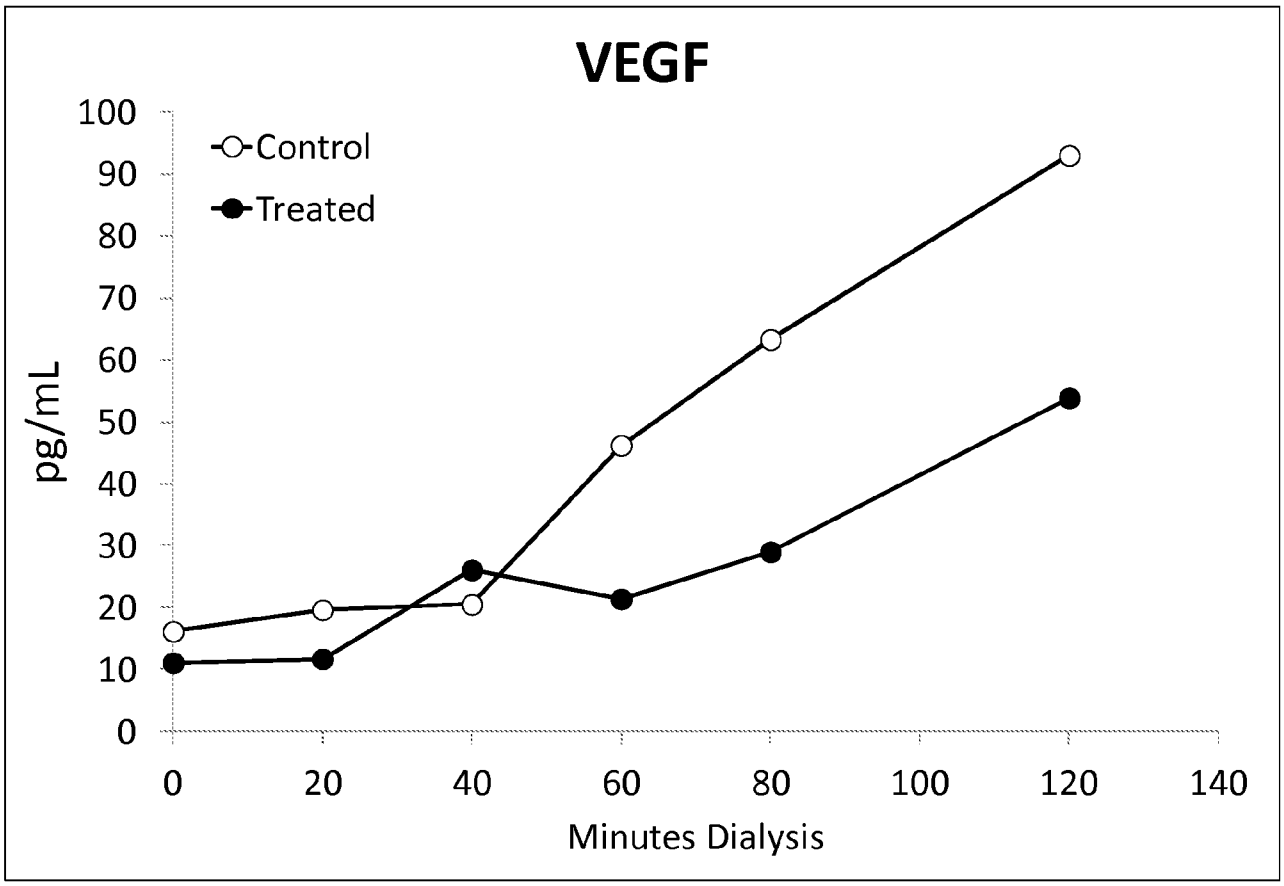

VEGF
Control
Treated
pg/mL
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
140
Minutes Dialysis

Fig. 3

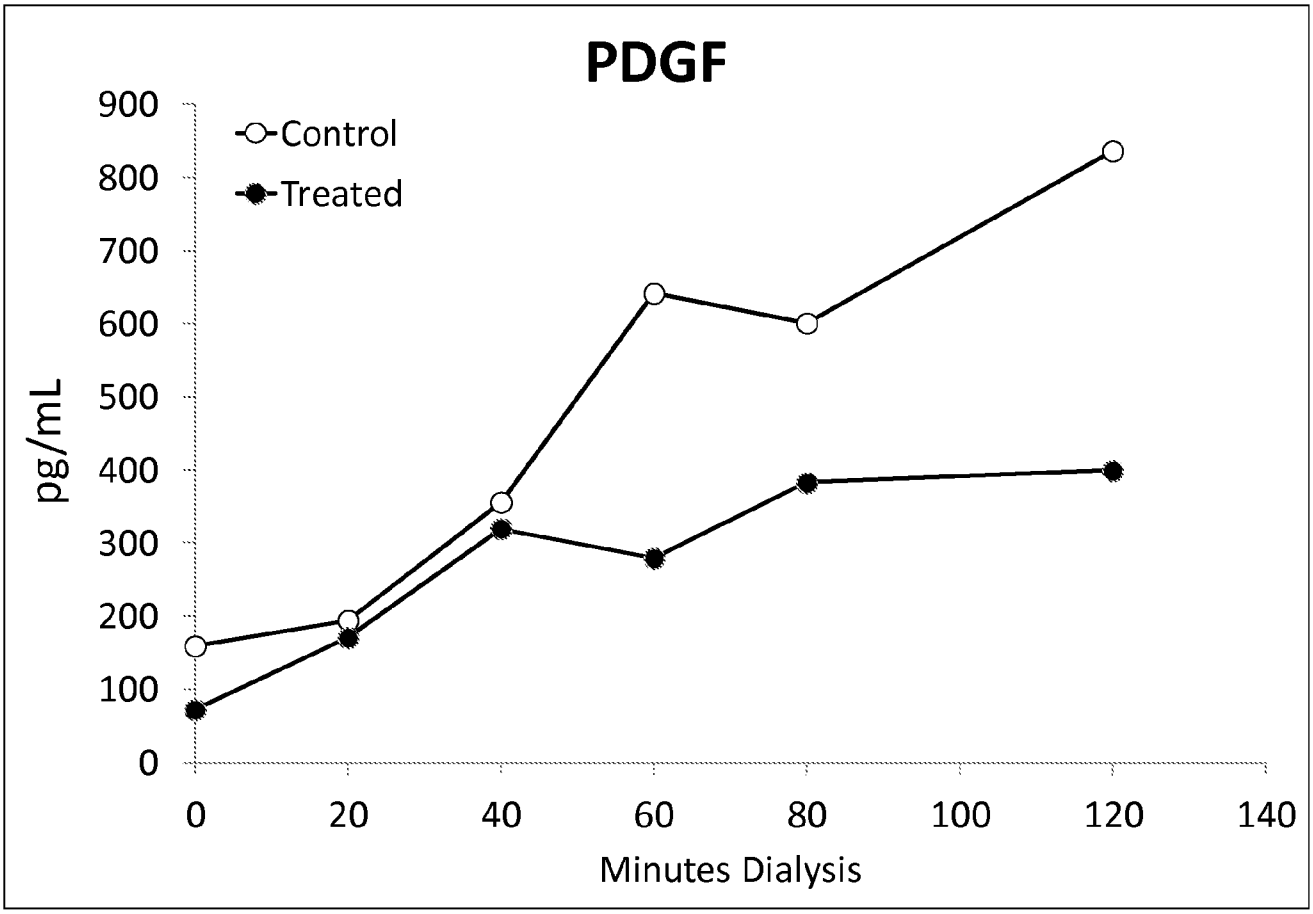

PDGF
Control
Treated
pg/mL
900
800
700
600
500
400
300
200
100
0
0
20
40
60
80
100
120
140
Minutes Dialysis

Fig. 4

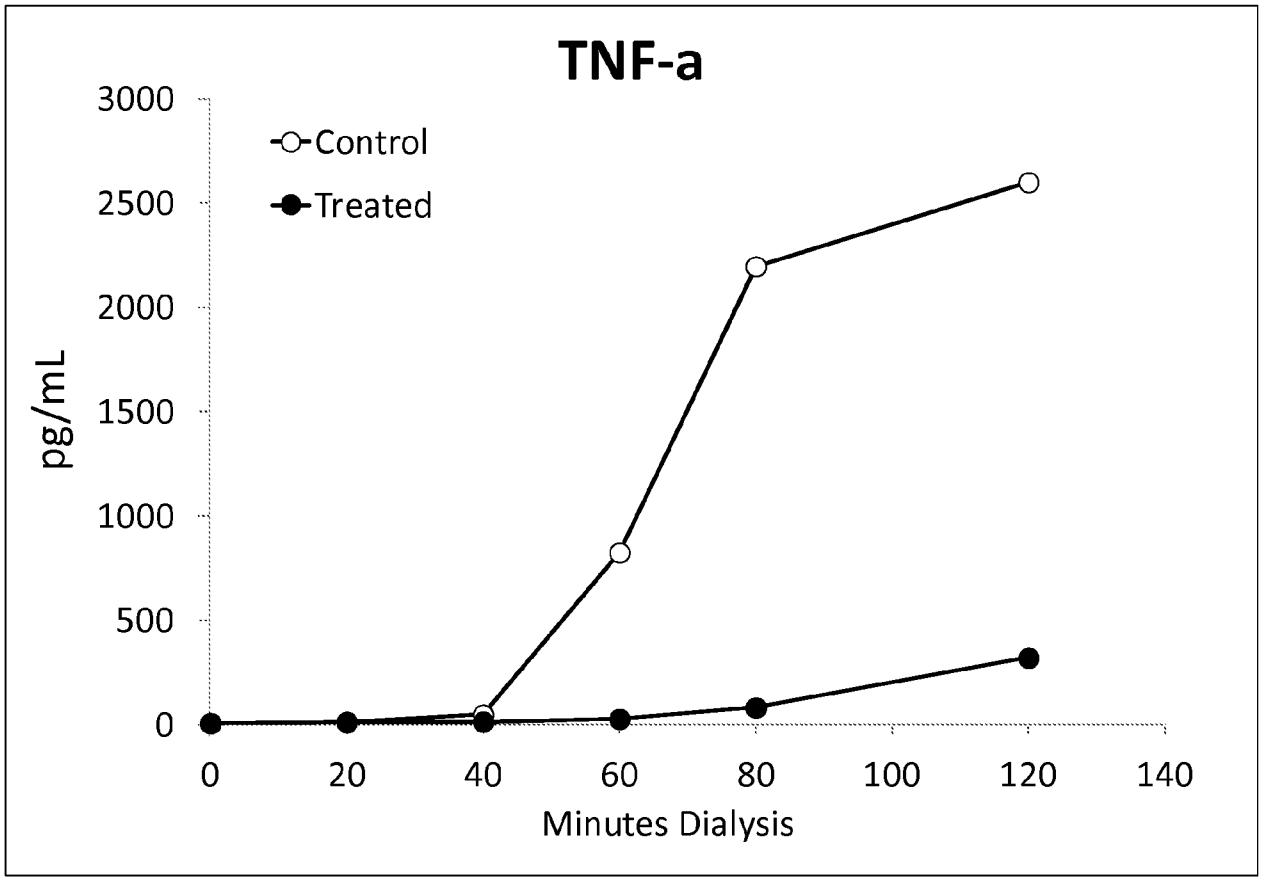

TNF-a
3000
2500
2000
1500
1000
500
0
pg/mL
Control
Treated
0
20
40
60
80
100
120
140
Minutes Dialysis

Fig. 5

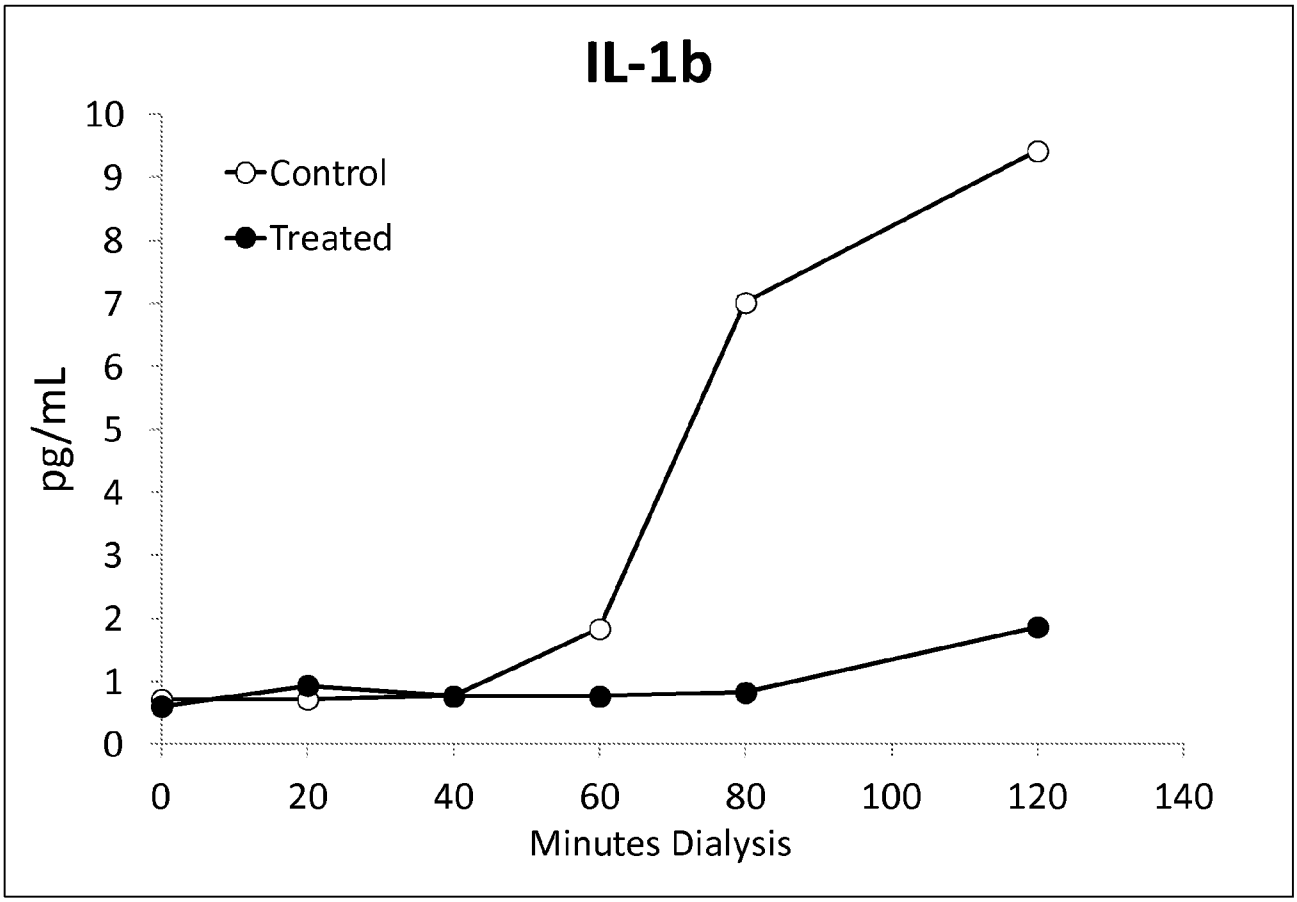

IL-1b
Control
Treated
pg/mL
10
9
8
7
6
5
4
3
2
1
0
0
20
40
60
80
100
120
140
Minutes Dialysis

Fig. 6

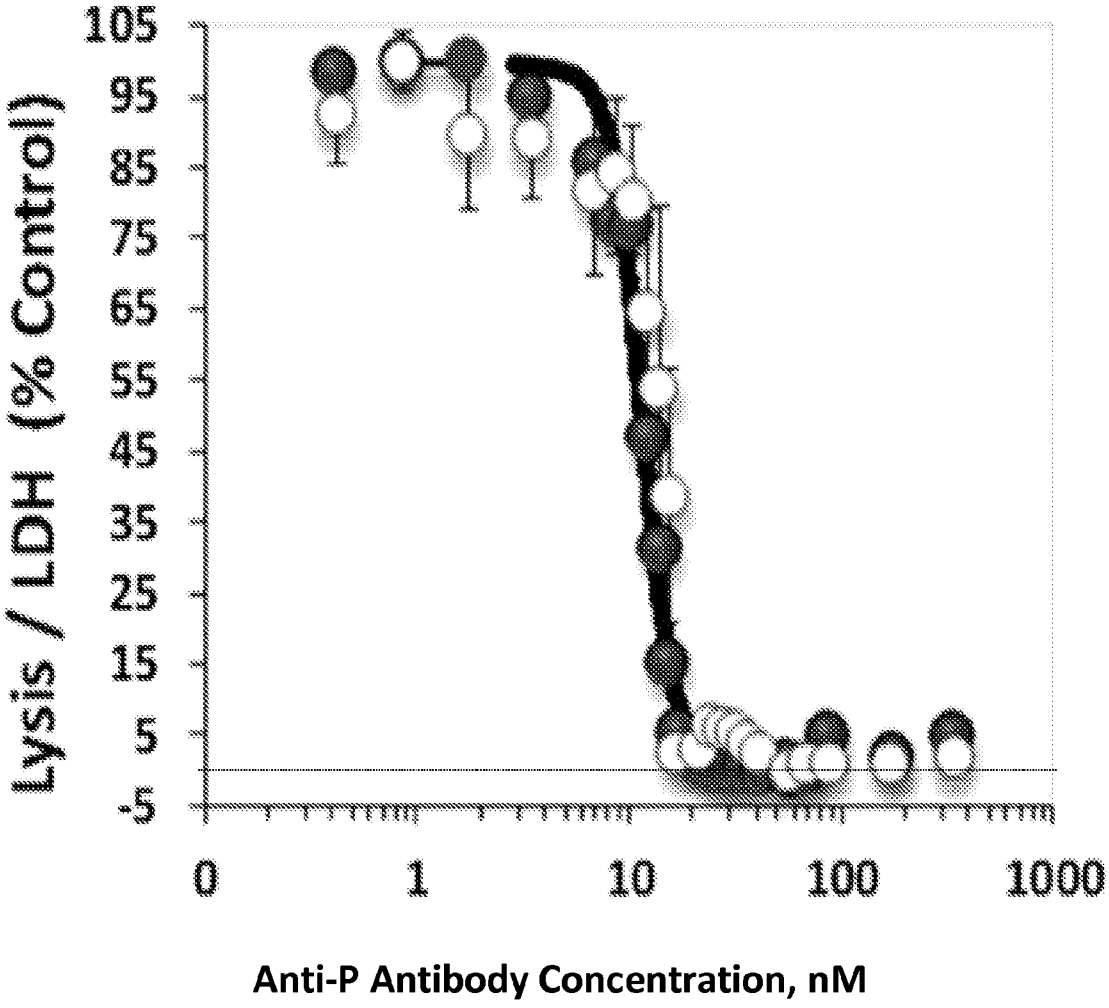

Lysis / LDH (% Control)
105
95
85
75
65
55
45
35
25
15
5
-5
0
1
10
100
1000
Anti-P Antibody Concentration, nM

Fig. 7

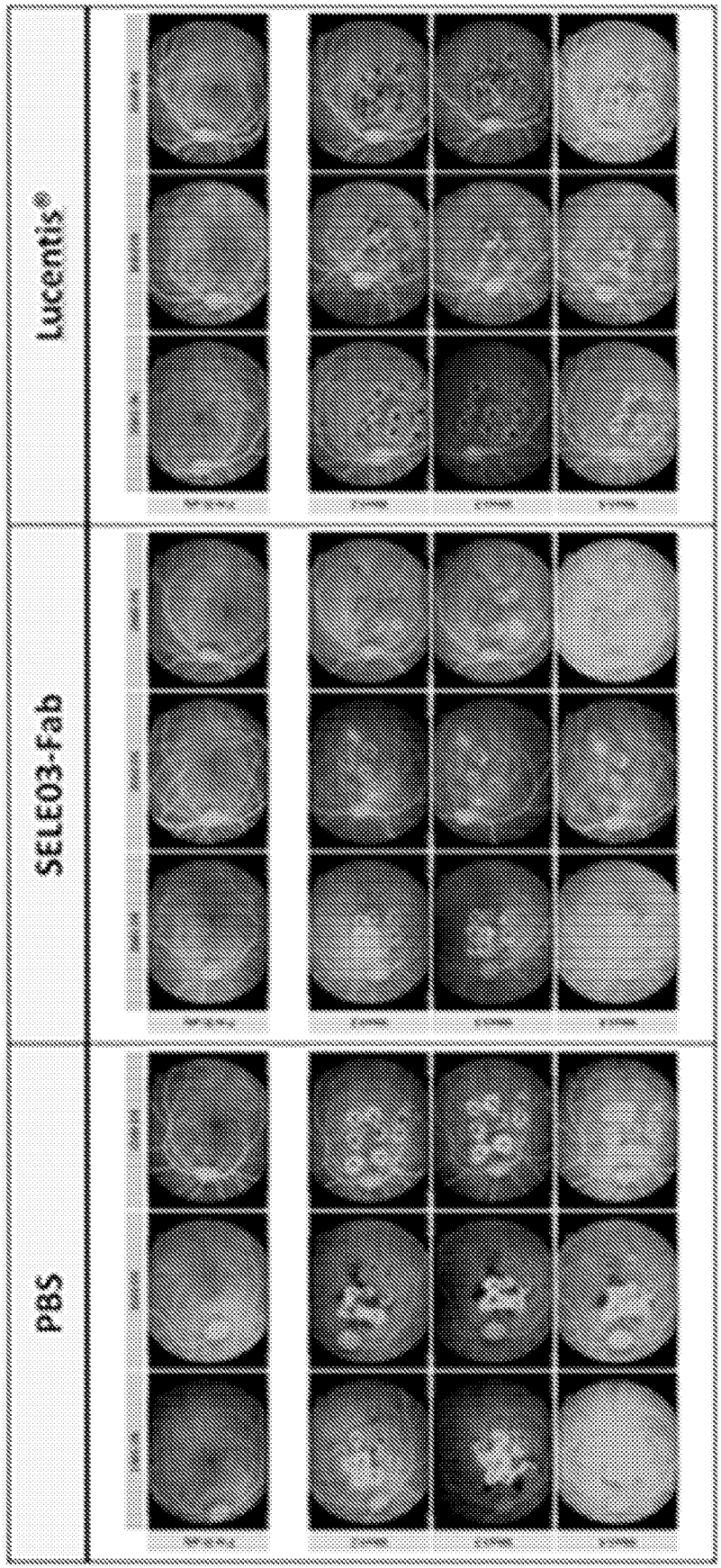


Fig. 8

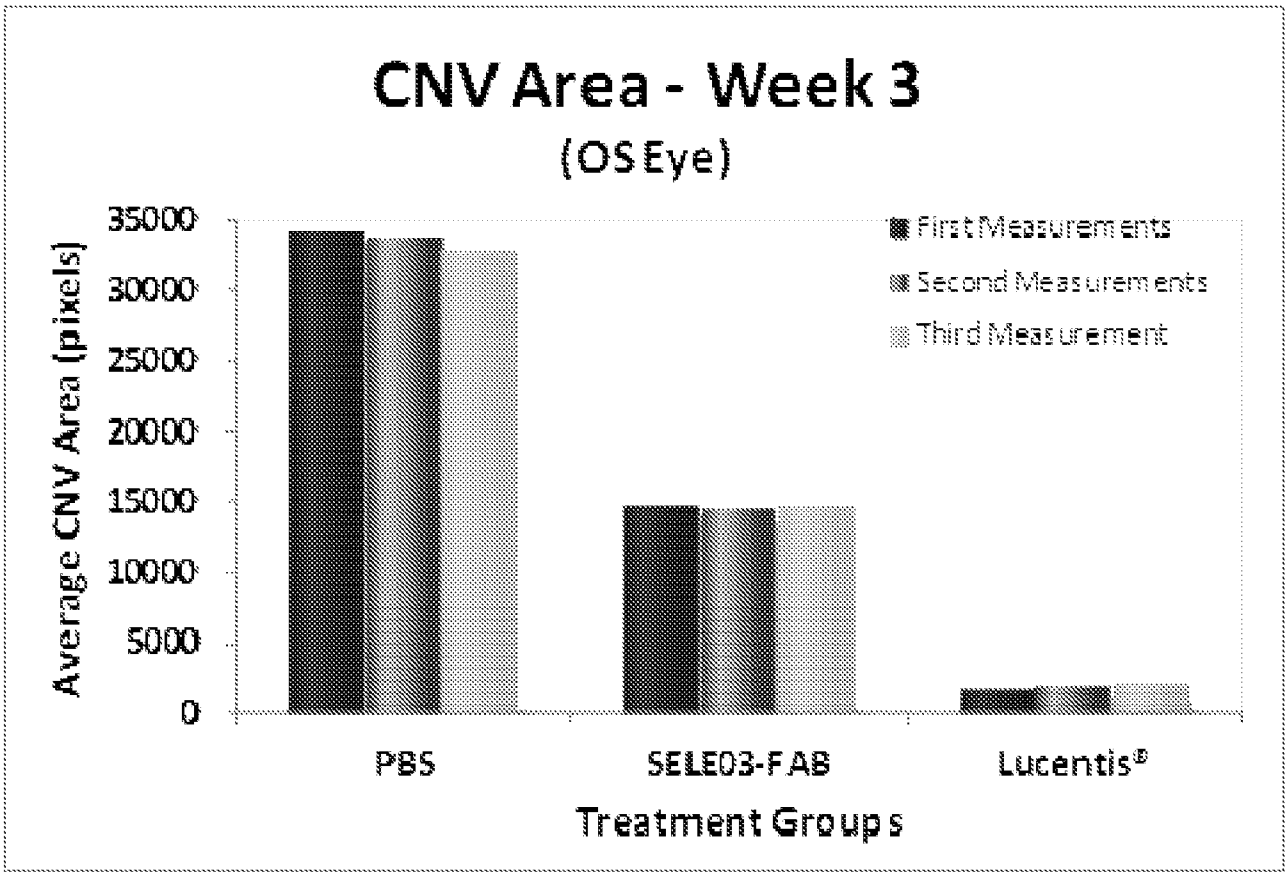
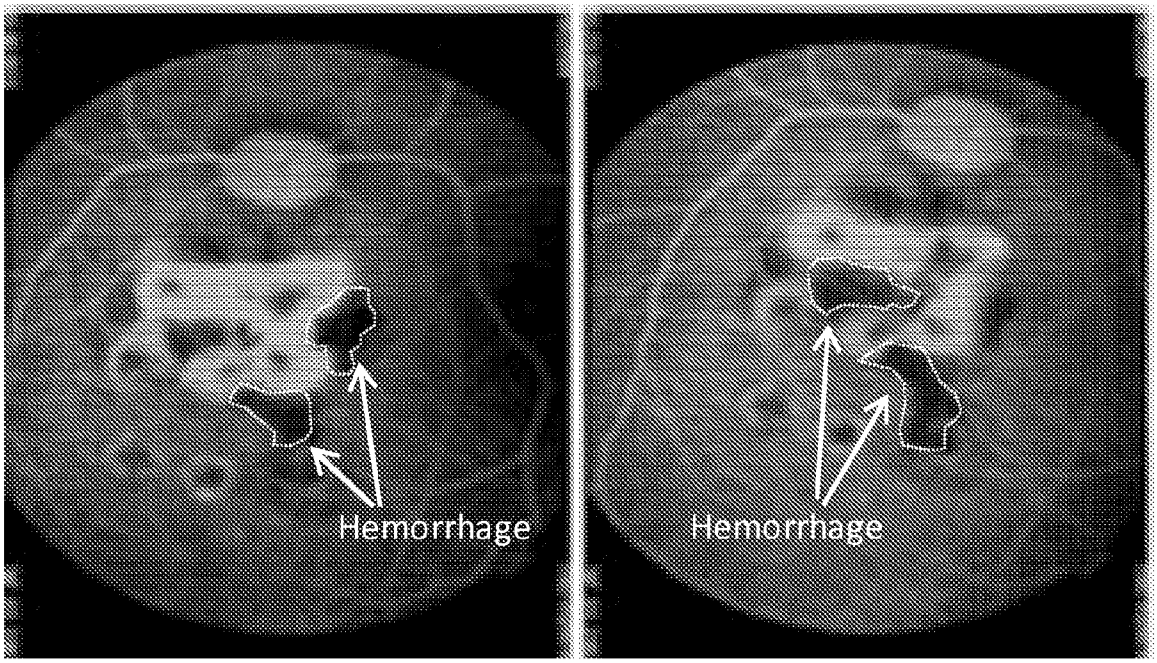
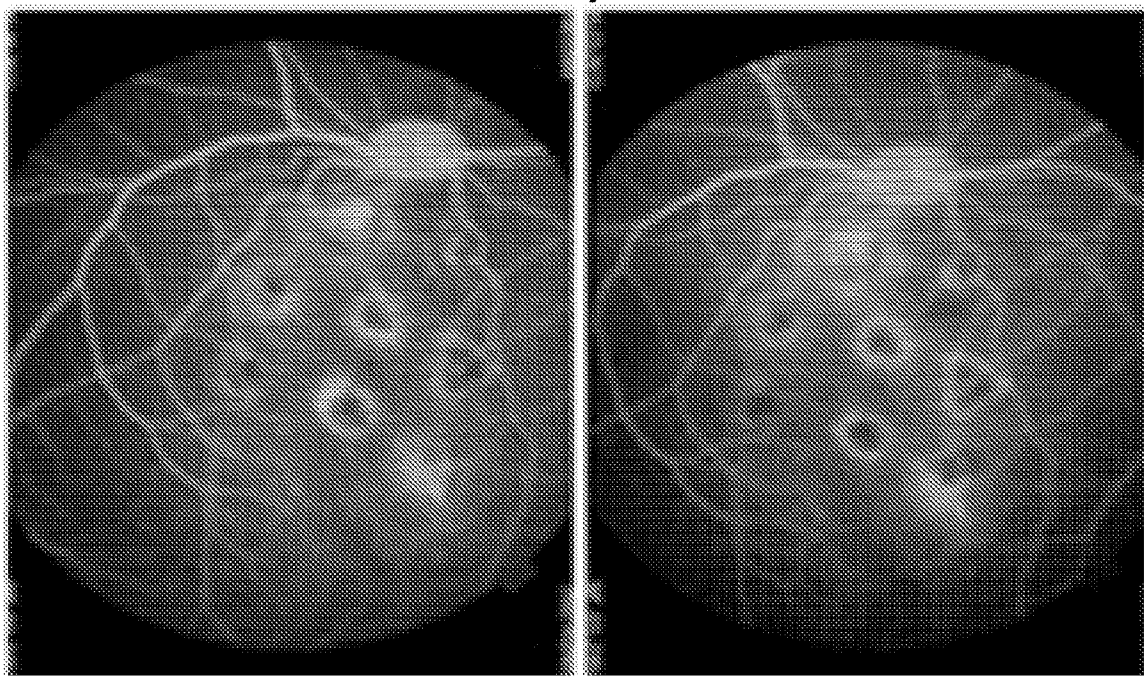

CNV Area - Week 3
(OS Eye)
Average CNV Area (pixels)
35000
30000
25000
20000
15000
10000
5000
0
First Measurements
Second Measurements
Third Measurement
PBS
SELE03-FAB
Lucentis®
Treatment Groups

Fig. 9

A: Hemorrhage in Control Eyes



B: Treated Eyes



Figs. 10A-B

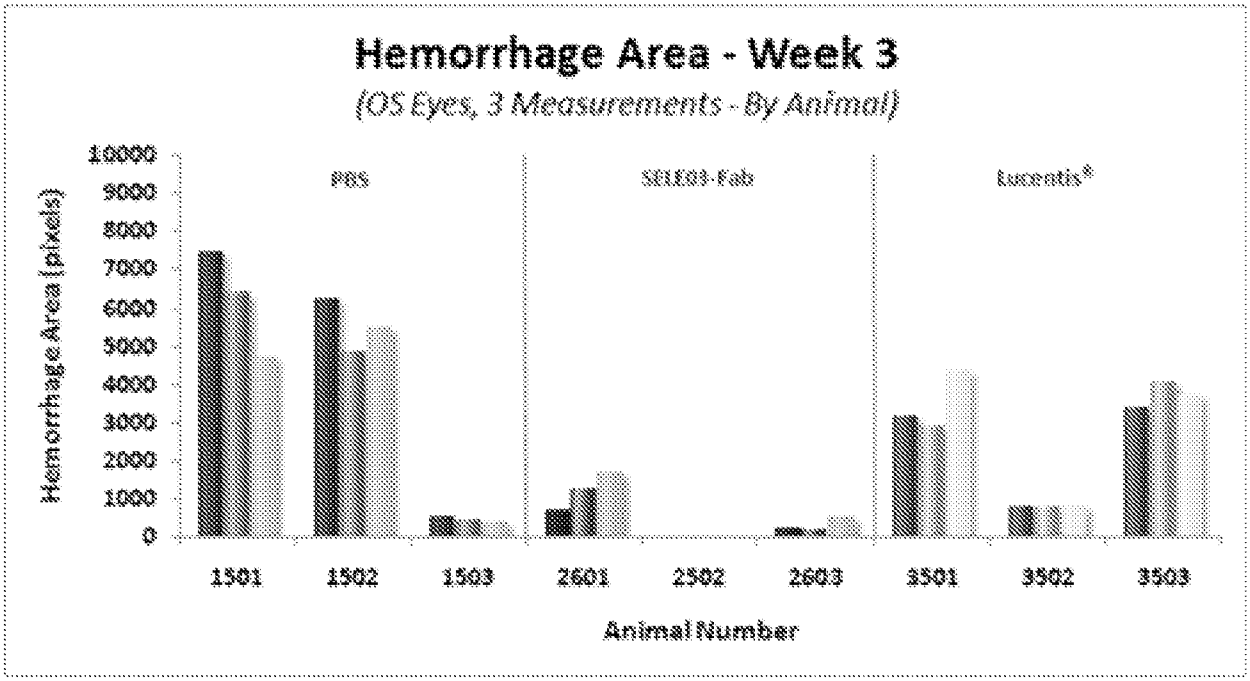

Hemorrhage Area - Week 3
(OS Eyes, 3 Measurements - By Animal)
Hemorrhage Area (pixels)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
PBS
SEED3-Fab
Lucentis®
1501
1502
1503
2601
2502
2603
3501
3502
3503
Animal Number

Fig. 11

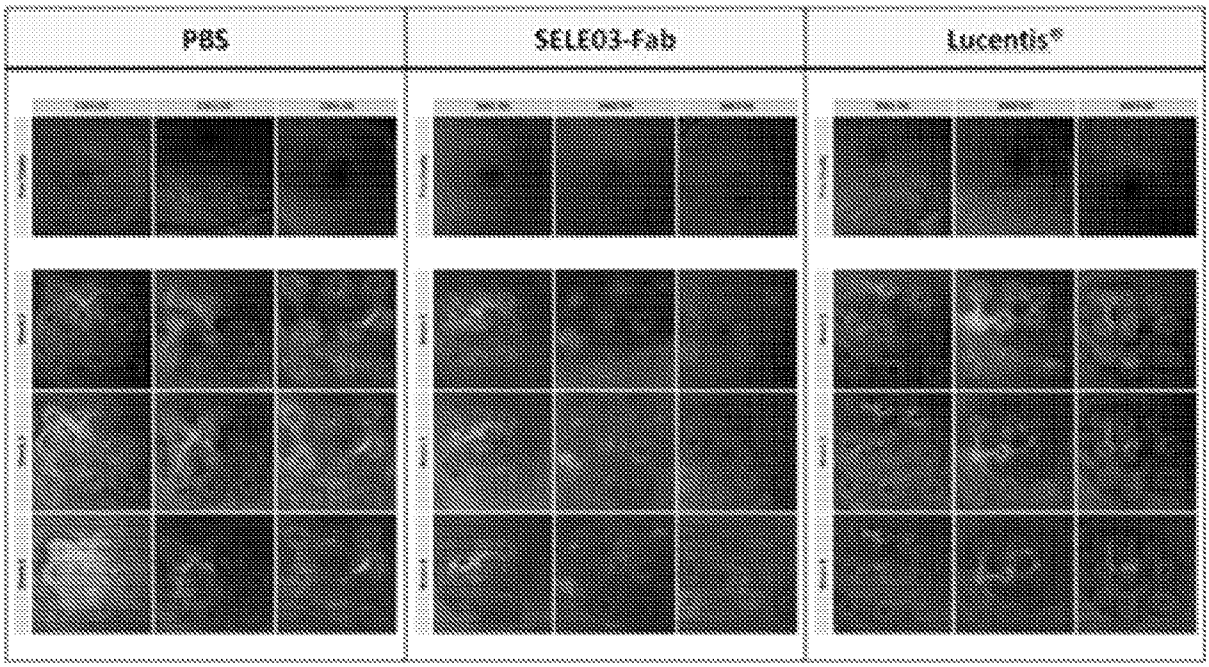
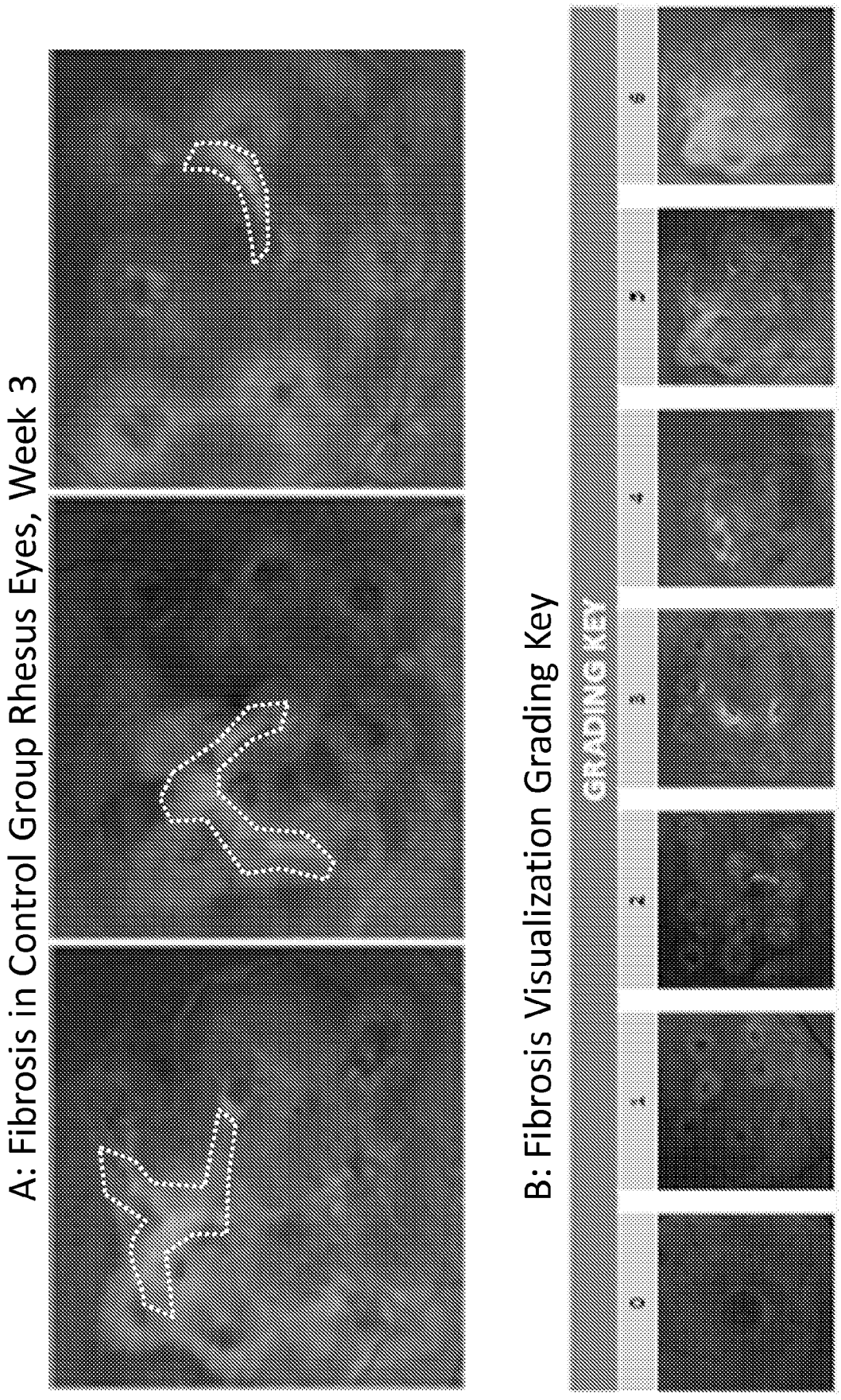


Fig. 12


A: Fibrosis in Control Group Rhesus Eyes, Week 3
B: Fibrosis Visualization Grading Key
GRADING KEY
0
1
2
3
4
5

Figs. 13A-B

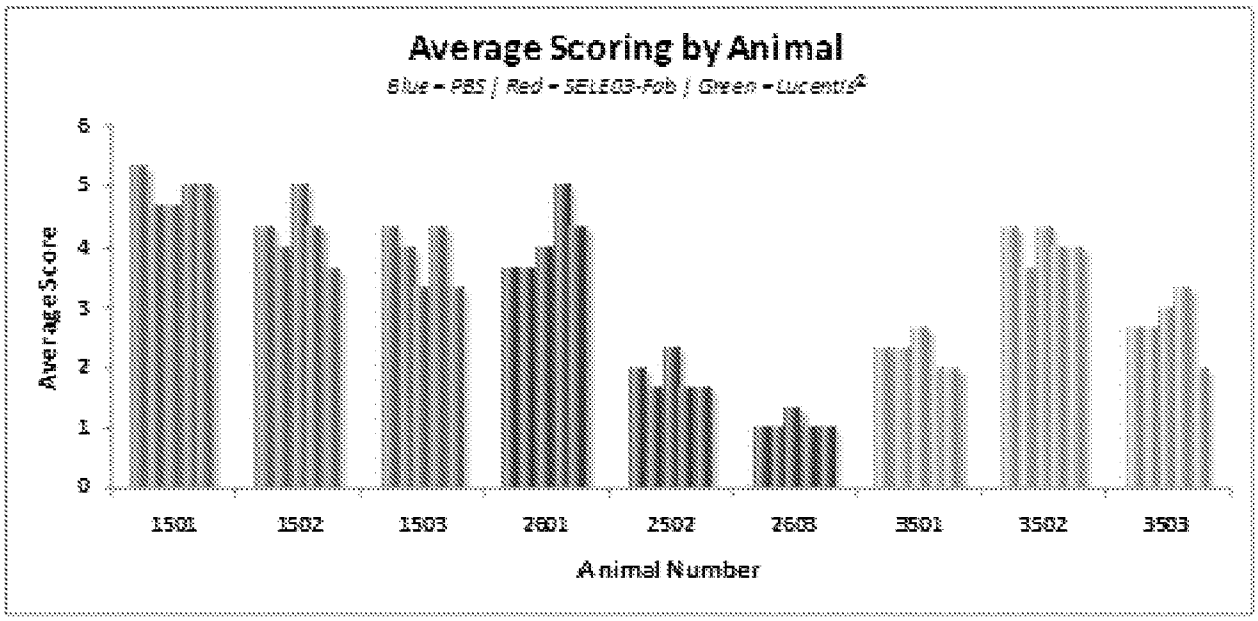

Average Scoring by Animal
Blue = PBS / Red = SELE03-Fab / Green = Lucentis®
Average Score
0
1
2
3
4
5
6
1501
1502
1503
2601
2502
2603
3501
3502
3503
Animal Number

Fig. 14