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(54) Title: COMPOSITIONS AND METHODS FOR TREATING OCULAR DISEASES

(57) Abstract: The present disclosure relates generally to compositions and methods of preventing, reducing risk of developing, or treating an inherited retinal disease (IRD) (e.g., retinitis pigmentosa, choroideremia, Stargardt disease, cone-rod dystrophy, leber congenital amaurosis), X-linked RP, and Usher Syndrome or retinal detachment.

COMPOSITIONS AND METHODS FOR TREATING OCULAR DISEASES

RELATED APPLICATIONS

This patent application claims priority to U.S. Provisional Patent Application No. 63/336,539, filed April 29, 2022, which is hereby incorporated by reference in its
5 entirety.

BACKGROUND

Inherited retinal diseases (IRDs) are a group of diseases that can cause severe vision loss or even blindness. Each IRD is caused by at least one gene that is not working as it should. IRDs (such as Retinitis Pigmentosa) can affect individuals of all ages, can
10 progress at different rates, and are rare. However, most are progressive, which means that the symptoms of the disease will get worse over time. Current approaches to therapy aim to fix the genetic defect, but there are numerous genetic defects and each defect affects only a small number of patients. The only approved treatment voretigene neparvovec-
rxyzl, is indicated for the genetic mutation RPE65, but this gene is present in only 1-2% of
15 IRD patients. Another approach uses a device called a “retinal prosthetic” To convert light to electrical energy to directly stimulate the retina, but this approach does not address the pathophysiology of the disease. At present, there are no gene agnostic approved treatments or therapies for IRDs. Therefore, there is a significant unmet need for treatments for patients with IRDs.

20 Retinal detachment is a disorder of the eye in which the retina peels away from its underlying layer of support tissue. Retinal detachment occurs about 10-12 cases per 100,000 annually. In about 50% of cases, the central retina detaches resulting in a macula-off retinal detachment. When the central retina detaches, the recovery of visual acuity reaches only about 50% of pre-detachment visual acuity, despite success in re-
25 attaching the retina. The cause of this limited visual recovery is photoreceptor degeneration. There are no approved treatments or therapies to improve the visual function following successful macula-off retinal detachment surgery. Therefore, there is a significant unmet need for treatments for patients with retinal detachment.

SUMMARY

The present disclosure is generally directed to compositions and methods of preventing, reducing risk of developing, or treating an inherited retinal disease (IRD) (e.g., retinitis pigmentosa/rod-cone dystrophy, choroideremia, Stargardt disease, cone-rod dystrophy, leber congenital amaurosis, X-linked RP, Usher Syndrome) and/or retinal detachment in a human patient. In some embodiments, the anti-C1q antibody is administered before retinal detachment surgery, after retinal detachment surgery, and/or simultaneous with retinal detachment surgery. Such methods may restore vision in the human patient and/or improve vision in the human patient.

Such methods include administering to the patient a composition comprising about 1 mg to about 10 mg of an anti-C1q antibody via an intravitreal injection, wherein the antibody comprises a light chain variable domain comprising an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7; and a heavy chain variable domain comprising an HVR-H1 having the amino acid sequence of SEQ ID NO: 9, an HVR-H2 having the amino acid of SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11. In some embodiments, the antibody comprises a light chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected from SEQ ID NO: 4 and 35-38 and wherein the light chain variable domain comprises an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7. In some embodiments, the light chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 4 and 35-38. In some embodiments, the antibody comprises a heavy chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected from SEQ ID NO: 8 and 31-34 and wherein the heavy chain variable domain comprises an HVR-H1 having the amino acid sequence of SEQ ID NO: 9, an HVR-H2 having the amino acid of SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11. In some embodiments, the heavy chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 8 and 31-34. In some embodiments, the antibody comprises a light chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected

from SEQ ID NO: 4 and 35-38, and wherein the light chain variable domain comprises an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7, and a heavy chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected from SEQ ID NO: 8 and 31-34 and wherein the heavy chain variable domain comprises an HVR-H1 having the amino acid sequence of SEQ ID NO: 9, an HVR-H2 having the amino acid of SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11. In some embodiments, the antibody comprises a light chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 4 and 35-38, and a heavy chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 8 and 31-34. The antibody may be a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody, an antibody fragment, or antibody derivative thereof. The antibody fragment may be a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a diabody, or a single chain antibody molecule. In some embodiments, the Fab fragment comprises a heavy chain Fab fragment of SEQ ID NO: 39 and a light chain Fab fragment of SEQ ID NO: 40.

In some embodiments, the antibody is administered once a week, once every other week, once every three weeks, once a month, once every 4 weeks, once every 6 weeks, once every 8 weeks, once every other month, once every 10 weeks, once every 12 weeks, once every three months, or once every 4 months. In some embodiments, the antibody is administered for at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, or at least 12 months.

In some embodiments, the administered composition comprises about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 6.5 mg, about 7 mg, about 7.5 mg, about 8 mg, about 8.5 mg, about 9 mg, about 9.5 mg, or about 10 mg of the anti-C1q antibody. The administered composition may comprise about 1 mg to about 5 mg of the anti-C1q antibody. The administered composition may comprise about 1 mg to about 2.5 mg, about 2.5 mg to about 5 mg, about 5 mg to about 7.5 mg, or about 7.5 mg to about 10 mg of the anti-C1q antibody. The administered composition may comprise about 5 mg of the anti-C1q antibody. The administered composition may comprise about 10 mg of the anti-C1q antibody.

DESCRIPTION OF THE FIGURES

Figures 1A-1F show photoreceptor damage and microgliosis following light exposure. **Figures 1A-1C** show immunofluorescence (IF) image and quantification showing progressive loss of photoreceptor synapses (Bassoon) and cell bodies (Dapi) following light damage. **Figures 1D-1F** show IF image and quantification showing increased microglia/macrophage reactivity (Iba1 and CD68) following light damage. Distribution of phagocytic microglia in the synaptic layer peaked at Day 1, when significant synapse loss was first observed.

Figures 2A-2E show complement signature and C1q distribution in retina following light exposure. **Figures 2A-2C** show ELISA assays showing increased levels of the initiating classical complement components C1q and C1s, as well as the downstream activation product C3d, in retina lysate following light damage. **Figure 2D** shows IF showing retinal C1q distribution and its co-localization with microglia/macrophage (Iba1) and synapses (Bassoon). **Figure 2E** shows correlation analysis showing significant negative correlation between C1q levels in the OPL and photoreceptor synaptic density, consistent with causal relationship.

Figures 3A-3E show microglia synaptic engulfment following light exposure. **Figure 3A** shows IF showing increased C1q levels in the OPL of light damaged retina and its proximity to Bassoon+ve synapses (i). **Figure 3B** shows high resolution and 3D surface rendered images showing microglia engulfment of C1q tagged synapses in light damaged retina. **Figures 3C-3E** show quantitative analysis showing significant decrease in synapse density (**Figure 3C**), increase in the percentage of C1q tagged synapses (**Figure 3D**), and increase in microglia engulfed C1q tagged synapses (**Figure 3E**) in light damaged retina, as compared to naïve.

Figure 4A-4F show phosphatidylserine (PS) externalization on photoreceptor Synapses and in vitro binding to C1q. **Figure 4A** show IF showing PSVue labelling of PS in the OPL of light damaged retina. 3D surface rendered images (i-ii) showing PSVue proximity to Bassoon and C1q, indicating PS externalization on synapses. **Figure 4B** shows assay showing binding of C1q to PS lipid beads. No binding to control phosphatidylcholine (PC) beads. **Figures 4C-4D** show assay showing deposition of C1q and C4 on serum exposed PS lipid beads. NO deposition observed on PC beads. **Figures**

4E-4F show competition assay showing reduced deposition of C1q and C4 on serum exposed PS lipid beads in presence of anti-C1q neutralizing antibody.

Figures 5A-5D show retina PK/PD following anti-C1q treatment. **Figures 5A-5D** show PK/PD data showing measurable drug levels in retina lysates from anti-C1q treated animals, together with significant decrease in C1q, C1s and C3d levels upon anti-C1q treatment.

Figures 6A-6C show C1q distribution in human GA retina: **Figures 6A-6B** show IF showing reduced immunoreactivity for the pre-synaptic marker Vglut1 (**Figure 6A**) and increased labelling for C1q (**Figure 6B**) in the photoreceptor synaptic layer OPL, confirming synaptic loss and C1q accumulation occurring in GA retina, compared to healthy donors. **Figure 6C** show triple immunolabelling for C1q (grey), presynaptic marker Vglut1 and postsynaptic marker (HOMER1) confirming co-localization of C1q with photoreceptor synapses in human GA donor retina.

Figure 7 shows human C1q binding assay. Binding of Mab2-Fab, FabA and Mab2 to human C1q in a one-sided ELISA. Bound antibody or Fab molecules were detected using an enzyme-tagged anti-human-Fc or anti-human kappa antibody followed by enzyme substrate. The antibodies showed comparable binding affinity for human C1q. EC50 for Mab2-Fab, FabA and Mab2 = 4.4, 2.5, and 4.9 ng/mL, respectively (range of 34–95 pM).

Figure 8 shows that FabA inhibits the classical, but not the lectin and alternate complement pathways. FabA and Mab2 were evaluated for their ability to inhibit the classical, lectin and alternate pathways using ELISA based assay kits from Eurodiagnostica (Weislab™). The wells are coated with specific activators of the classical pathway (IgM), the lectin pathway (mannan), or the alternate pathway (lipopolysaccharide), and activation of all pathways was assessed using a C5b-9 terminal complex detection antibody. An inhibitory antibody against C5 was used as a positive control. FabA and Mab2 selectively block the classical pathway with an IC50 of ≤ 0.3 μ g/mL, while anti-C5 inhibits all three pathways.

Figure 9 shows inhibition of hemolysis of IgM-coated RBC in human serum. Sheep RBCs, pre-sensitized with a surface-reactive polyclonal IgM antibody, were co-incubated with human serum (diluted 100x) at 37°C for 20–30 minutes. RBC hemolysis

was quantified by measuring release of hemoglobin, and is expressed as a percentage of hemolysis induced by no-treatment.

Figure 10 shows reduction in the number of damaged axons in the optic nerves of eyes treated with Mab1-Fab, Mab1, or Mab2. Increased IOP was induced in one eye of each animal by injection of 1 μ l of 6 μ m polystyrene beads, 1 μ l of 10 μ m polystyrene beads (Polybead Microspheres; Polysciences, Inc., Warrington, PA, USA) and 1 μ l of viscoelastic solution (10 mg/mL sodium hyaluronate; Advanced Medical Optics Inc., USA) into the anterior chamber of the eye on Day 1. The contralateral eye was left untouched to serve as a control. Antibodies Mab2, Mab1, and Mab1-Fab (Fab derived by enzymatic digest of Mab1) vs. saline were administered to the microbead-injected eyes intravitreally, one day prior to microbead injection and one week later (Day 0 and Day 7; 2 μ L of a 10 mg/mL antibody saline solution for each injection vs. saline alone). Two weeks post injury, optic nerves were collected from animals (perfused with saline and 4% paraformaldehyde), postfixed with 4% paraformaldehyde and 1% osmium, dehydrated in ascending alcohol concentration and placed in 1% uranyl acetate / ethanol. Nerves were embedded in epoxy resin and semi-thin sections (1 μ m) were cut. The total number of degenerating axons was estimated using StereoInvestigator software (MicroBrightfield, Inc, VT, USA). Scale bar = 20 μ m. Mab1-Fab and Mab2 both significantly reduced formation of damaged axons in the optic nerve, while antibody Mab1 showed a similar trend.

Figures 11A-11D show protection of photoreceptor neuron loss and retinal function in a mouse photodamage model with Mab1 antibody. **Figure 11A** shows photodamage model in mouse for 7 days followed by intravitreal (IVT) administration of Mab1 antibody and assessment of retinal function and histology at Day 14. Mice were administered 1 μ L of 7.5 mg/mL Mab1 or isotype control antibody via IVT administration on Day 7. **Figure 11B** shows that Mab1 treatment led to a significant reduction in Tunel +ve photoreceptor cells in the outer nuclear layer of the retina, when compared to isotype control. **Figure 11C** shows that Mab1 treatment led to an increase in the number of photoreceptor cell rows in the outer nuclear layer, when compared to isotype control. **Figure 11D** shows that Mab1 antibody treatment led to a significant increase in the A-wave and B-wave in electroretinogram on Day 14, when compared to isotype control antibody.

Figure 12 shows free C1q in aqueous humor after a single IVT injection.

Figures 13A-13D show immunofluorescence (IF) data. **Figure 13B** shows reduced microgliosis in the outer plexiform layer (OPL) (aka outer synaptic layer) of the Retina at day 3 post-treatment. A reduction in microgliosis is associated with decreased inflammation. **Figure 13C** shows the significant preservation of photoreceptor synapses and **Figure 13D** shows the significant preservation of cell bodies at day 5 post-treatment.

Figures 14A-14B show measurable PK and target engagement in the retina.

Figure 15A is a bar graph showing a quantification of immunofluorescence images.

Figure 15B shows immunofluorescence images demonstrating the preservation of the photoreceptor synapses (BSN marker) upon treatment with a C1q inhibitor.

DETAILED DESCRIPTION

General

The present disclosure is generally directed to compositions and methods of preventing, reducing risk of developing, or treating an inherited retinal disease (IRD) (e.g., retinitis pigmentosa, choroideremia, Stargardt disease, cone-rod dystrophy, and leber congenital amaurosis) or retinal detachment.

Disclosed herein is a recombinant humanized Immunoglobulin G (IgG1) antigen-binding fragment (Fab) that inhibits the classical complement cascade, without affecting the lectin or alternative complement pathways. Anti-C1q Fab (e.g., FabA, an anti-C1q Fab comprising heavy chain Fab fragment of SEQ ID NO: 39 and light chain Fab fragment of SEQ ID NO: 40) is developed as an intravitreally (IVT) administered agent for the treatment for Inherited retinal diseases (IRDs) (e.g., retinitis pigmentosa, choroideremia, Stargardt disease, cone-rod dystrophy, and leber congenital amaurosis) and retinal detachment. The hypervariable regions derived from the murine antibody M1 (Mab1 antibody comprising heavy chain variable domain of SEQ ID NO: 3 and light chain variable domain of SEQ ID NO: 7) were expressed as a human IgG1 Fab fragment construct (FabA). A full-length human IgG4 antibody (Mab2, an antibody comprising heavy chain variable domain of SEQ ID NO: 8 and light chain variable domain of SEQ ID NO: 4) comprising the hypervariable regions derived from Mab1 was also expressed. Mab1 and Mab2, as well as their Fabs (Mab1-Fab and Mab2-Fab), were used as surrogate molecules for FabA in pharmacology studies. As a monovalent Fab construct lacking Fc

heavy chain constant domains 2 and 3 (CH2 and CH3), FabA cannot bind to C1q through Fc domain interactions. Furthermore, with only a single antigen-binding arm, FabA does not exhibit agonistic activity for C1q over a broad range of concentrations of FabA.

The complement cascade is a critical component of innate immunity and can be activated through 3 distinct pathways: the classical, lectin, and alternative complement pathways. All 3 pathways lead to the activation of complement component C3, which ultimately leads to immune cell recruitment, inflammation, membrane lysis through the membrane attack complex, and cell death.

C1q, the initiating molecule of the classical complement cascade, has been implicated in the initiation and propagation of neurodegenerative disease. C1q inhibition may block initiation of the classical complement cascade and slow down neuronal and synaptic damage via directly reducing damage to nerve cell membranes and by reducing the inflammatory consequences of complement activation.

Mab2-Fab and/or FabA exhibit high affinity binding to human C1q as measured by Biacore (< 10 pM) and by enzyme-linked immunosorbent assay (ELISA) (40–50 pM; Figure 7). Mab1 binds to the isolated globular head domains of C1q, but not to C1q's collagen tail (as determined by ELISA). Consistent with this finding, Mab1 inhibits substrate interactions mediated by C1q's globular head domain (IgM, C-reactive protein [CRP], and phosphatidylserine); and FabA inhibits C1q functional interaction with immunoglobulin M (IgM)-coated red blood cells (RBCs) (blocking hemolysis; Figure 9). Antibody Mab1 specifically recognizes C1q, showing no binding to the other complement components (C3b and C5), or to other C1q/tumor necrosis factor (TNF) superfamily members, including TNF and adiponectin, a protein that shares the highest sequence identity to C1q in its globular head domain. Consistent with these results, FabA does not inhibit the lectin complement pathway, which is initiated by the mannose-binding lectin (MBL, another member of the C1q/TNF superfamily), nor does it inhibit the alternative complement pathway (initiated by C3b) (Figure 8).

Definitions

As used herein the specification, “a” or “an” may mean one or more. As used herein in the claim(s), when used in conjunction with the word “comprising”, the words “a” or “an” may mean one or more than one. For example, reference to an “antibody” is a

reference from one to many antibodies. As used herein “another” may mean at least a second or more.

As used herein, administration “*conjointly*” with another compound or composition includes simultaneous administration and/or administration at different times. Administration in conjunction also encompasses administration as a co-
5 formulation or administration as separate compositions, including at different dosing frequencies or intervals, and using the same route of administration or different routes of administration.

The term “*immunoglobulin*” (Ig) is used interchangeably with “*antibody*” herein.
10 The term “antibody” herein is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies) formed from at least two intact antibodies, antibody fragments so long as they exhibit biological activity, and antibody derivatives.

The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of
15 two identical light (L) chains and two identical heavy (H) chains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, *see, e.g., Basic and Clinical Immunology*, 8th Ed., Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

20 The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (“κ”) and lambda (“λ”), based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (CH), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM,
25 having heavy chains designated alpha (“α”), delta (“δ”), epsilon (“ε”), gamma (“γ”) and mu (“μ”), respectively. The γ and α classes are further divided into subclasses (isotypes) on the basis of relatively minor differences in the CH sequence and function, *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The subunit structures and three dimensional configurations of different classes of immunoglobulins
30 are well known and described generally in, for example, Abbas *et al.*, Cellular and Molecular Immunology, 4th ed. (W.B. Saunders Co., 2000).

“Full-length antibodies” are usually heterotetrameric glycoproteins of about 150,000 daltons, comprising two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different

5 immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable
10 domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains.

An “isolated” molecule or cell is a molecule or a cell that is identified and separated from at least one contaminant molecule or cell with which it is ordinarily
15 associated in the environment in which it was produced. Preferably, the isolated molecule or cell is free of association with all components associated with the production environment. The isolated molecule or cell is in a form other than in the form or setting in which it is found in nature. Isolated molecules therefore are distinguished from molecules existing naturally in cells; isolated cells are distinguished from cells existing
20 naturally in tissues, organs, or individuals. In some embodiments, the isolated molecule is an anti-C1q antibody of the present disclosure. In other embodiments, the isolated cell is a host cell or hybridoma cell producing anti-C1q antibody of the present disclosure.

An “isolated” antibody is one that has been identified, separated and/or recovered from a component of its production environment (*e.g.*, naturally or recombinantly).
25 Preferably, the isolated polypeptide is free of association with all other contaminant components from its production environment. Contaminant components from its production environment, such as those resulting from recombinant transfected cells, are materials that would typically interfere with research, diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-
30 proteinaceous solutes. In certain preferred embodiments, the polypeptide will be purified: (1) to greater than 95% by weight of antibody as determined by, for example, the Lowry method, and in some embodiments, to greater than 99% by weight; (2) to a

degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. An isolated antibody includes the antibody *in situ* within recombinant T-cells since
5 at least one component of the antibody's natural environment will not be present. Ordinarily, however, an isolated polypeptide or antibody will be prepared by a process including at least one purification step.

The "*variable region*" or "*variable domain*" of an antibody refers to the amino-terminal domains of the heavy or light chain of the antibody. The variable domains of the
10 heavy chain and light chain may be referred to as "V_H" and "V_L", respectively. These domains are generally the most variable parts of the antibody (relative to other antibodies of the same class) and contain the antigen binding sites.

The term "*variable*" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates
15 antigen binding and defines the specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the entire span of the variable domains. Instead, it is concentrated in three segments called hypervariable regions (HVRs) both in the light-chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FR).
20 The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a beta-sheet configuration, connected by three HVRs, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The HVRs in each chain are held together in close proximity by the FR regions and, with the HVRs from the other chain, contribute to the formation of the antigen binding site of antibodies
25 (*see* Kabat et al., *Sequences of Immunological Interest*, Fifth Edition, National Institute of Health, Bethesda, MD (1991)). The constant domains are not involved directly in the binding of antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent-cellular toxicity.

As used herein, the term "CDR" or "complementarity determining region" is
30 intended to mean the non-contiguous antigen binding sites found within the variable region of both heavy and light chain polypeptides. CDRs have been described by Kabat et al., J. Biol. Chem. 252:6609-6616 (1977); Kabat et al., U.S. Dept. of Health and Human

Services, "Sequences of proteins of immunological interest" (1991) (also referred to herein as Kabat 1991); by Chothia et al., J. Mol. Biol. 196:901-917 (1987) (also referred to herein as Chothia 1987); and MacCallum et al., J. Mol. Biol. 262:732-745 (1996), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or grafted antibodies or variants thereof is intended to be within the scope of the term as defined and used herein.

As used herein, the terms "CDR-L1", "CDR-L2", and "CDR-L3" refer, respectively, to the first, second, and third CDRs in a light chain variable region. As used herein, the terms "CDR-H1", "CDR-H2", and "CDR-H3" refer, respectively, to the first, second, and third CDRs in a heavy chain variable region. As used herein, the terms "CDR-1", "CDR-2", and "CDR-3" refer, respectively, to the first, second and third CDRs of either chain's variable region.

The term "*monoclonal antibody*" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies of the population are identical except for possible naturally occurring mutations and/or post-translation modifications (*e.g.*, isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, monoclonal antibodies are advantageous since they are typically synthesized by hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained as a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by a variety of techniques, including, for example, the hybridoma method (*e.g.*, Kohler and Milstein., *Nature*, 256:495-97 (1975); Hongo et al., *Hybridoma*, 14 (3):253-260 (1995), Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2d ed. 1988); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981)), recombinant DNA methods (see, *e.g.*, U.S.

Patent No. 4,816,567), phage-display technologies (*see, e.g.,* Clackson *et al.*, *Nature*, 352:624-628 (1991); Marks *et al.*, *J. Mol. Biol.* 222:581-597 (1992); Sidhu *et al.*, *J. Mol. Biol.* 338(2): 299-310 (2004); Lee *et al.*, *J. Mol. Biol.* 340(5):1073-1093 (2004); Fellouse, *Proc. Nat'l Acad. Sci. USA* 101(34):12467-472 (2004); and Lee *et al.*, *J. Immunol. Methods* 284(1-2):119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (*see, e.g.,* WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits *et al.*, *Proc. Nat'l Acad. Sci. USA* 90:2551 (1993); Jakobovits *et al.*, *Nature* 362:255-258 (1993); Bruggemann *et al.*, *Year in Immunol.* 7:33 (1993); U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks *et al.*, *Bio/Technology* 10:779-783 (1992); Lonberg *et al.*, *Nature* 368:856-859 (1994); Morrison, *Nature* 368:812-813 (1994); Fishwild *et al.*, *Nature Biotechnol.* 14:845-851 (1996); Neuberger, *Nature Biotechnol.* 14:826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995).

The terms “*full-length antibody*,” “*intact antibody*” and “*whole antibody*” are used interchangeably to refer to an antibody in its substantially intact form, as opposed to an antibody fragment or antibody derivative. Specifically, whole antibodies include those with heavy and light chains including an Fc region. The constant domains may be native sequence constant domains (*e.g.,* human native sequence constant domains) or amino acid sequence variants thereof. In some cases, the intact antibody may have one or more effector functions.

An “*antibody fragment*” or “*antigen-binding fragment*” or “*functional fragments*” of antibodies comprises a portion of an intact antibody, preferably the antigen binding and/or the variable region of the intact antibody or the F region of an antibody which retains or has modified FcR binding capability. Examples of antibody fragments include Fab, Fab', F(ab')₂ and Fv fragments; diabodies; and linear antibodies (*see* U.S. Patent 5,641,870, Example 2; Zapata *et al.*, *Protein Eng.* 8(10):1057-1062 (1995)). Additional examples of antibody fragments include antibody derivatives such as single-chain antibody molecules, monovalent antibodies and multispecific antibodies formed from antibody fragments

An “antibody derivative” is any construct that comprises the antigen-binding region of an antibody. Examples of antibody derivatives include single-chain antibody

molecules, monovalent antibodies and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called “*Fab*” fragments, and a residual “*Fc*” fragment, a designation reflecting the ability to crystallize readily. The *Fab* fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_{H1}). Each *Fab* fragment is monovalent with respect to antigen binding, *i.e.*, it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment which roughly corresponds to two disulfide linked *Fab* fragments having different antigen-binding activity and is still capable of cross-linking antigen. *Fab'* fragments differ from *Fab* fragments by having a few additional residues at the carboxy terminus of the C_{H1} domain including one or more cysteines from the antibody hinge region. *Fab'*-SH is the designation herein for *Fab'* in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of *Fab'* fragments with hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The *Fc* fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the *Fc* region, the region which is also recognized by *Fc* receptors (*FcR*) found on certain types of cells.

The term “*Fc region*” herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence *Fc* regions and variant *Fc* regions. Although the boundaries of the *Fc* region of an immunoglobulin heavy chain might vary, the human IgG heavy-chain *Fc* region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the *Fc* region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue.

Suitable native-sequence Fc regions for use in the antibodies of the disclosure include human IgG1, IgG2, IgG3 and IgG4.

A “*native sequence Fc region*” comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

A “*variant Fc region*” comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, *e.g.*, from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

“*Fc receptor*” or “*FcR*” describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc γ RI, Fc γ RII, and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors, Fc γ RII receptors include Fc γ RIIA (an “activating receptor”) and Fc γ RIIB (an “inhibiting receptor”), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc γ RIIA contains an immunoreceptor tyrosine-based activation motif (“ITAM”) in its cytoplasmic domain. Inhibiting receptor Fc γ RIIB contains an immunoreceptor tyrosine-based inhibition motif (“ITIM”) in its cytoplasmic domain. (*See, e.g.*, M. Daëron, *Annu. Rev. Immunol.* 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-92 (1991); Capel et al., *Immunomethods* 4:25-34 (1994); and de Haas et al., *J. Lab. Clin. Med.* 126: 330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term “FcR” herein. FcRs can also increase the serum half-life of antibodies.

Binding to FcRn *in vivo* and serum half-life of human FcRn high-affinity binding polypeptides can be assayed, *e.g.*, in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides having a variant Fc region are administered. WO 2004/42072 (Presta) describes antibody variants with improved or diminished binding to FcRs. *See also, e.g.*, Shields et al., *J. Biol. Chem.* 9(2):6591-6604 (2001).

“Fv” is the minimum antibody fragment, which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three HVRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

“Single-chain Fv” also abbreviated as “sFv” or “scFv” are antibody fragments that comprise the VH and VL antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the sFv to form the desired structure for antigen binding. For a review of the sFv, *see* Plückthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term “diabodies” refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10) residues between the VH and VL domains such that inter-chain but not intra-chain pairing of the V domains is achieved, thereby resulting in a bivalent fragment, *i.e.*, a fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two “crossover” sFv fragments in which the VH and VL domains of the two antibodies are present on different polypeptide chains. Diabodies are described in greater detail in, for example, EP 404,097; WO 1993/011161; WO/2009/121948; WO/2014/191493; Hollinger et al., *Proc. Nat’l Acad. Sci. USA* 90:6444-48 (1993).

As used herein, a “chimeric antibody” refers to an antibody (immunoglobulin) in which a portion of the heavy and/or light chain is identical with or homologous to

corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is(are) identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison et al., *Proc. Nat'l Acad. Sci. USA*, 81:6851-55 (1984)). Chimeric antibodies of interest herein include PRIMATIZED[®] antibodies wherein the antigen-binding region of the antibody is derived from an antibody produced by, e.g., immunizing macaque monkeys with an antigen of interest. As used herein, "humanized antibody" is a subset of "chimeric antibodies."

"Humanized" forms of non-human (e.g., murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. In some embodiments, a humanized antibody is a human immunoglobulin (recipient antibody) in which residues from an HVR of the recipient are replaced by residues from an HVR of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired specificity, affinity, and/or capacity. In some instances, FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications may be made to further refine antibody performance, such as binding affinity. In general, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin sequence, and all or substantially all of the FR regions are those of a human immunoglobulin sequence, although the FR regions may include one or more individual FR residue substitutions that improve antibody performance, such as binding affinity, isomerization, immunogenicity, and the like. The number of these amino acid substitutions in the FR is typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see, e.g., Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992). See also, for example, Vaswani and Hamilton, *Ann. Allergy, Asthma*

& *Immunol.* 1:105-115 (1998); Harris, *Biochem. Soc. Transactions* 23:1035-1038 (1995); Hurle and Gross, *Curr. Op. Biotech.* 5:428-433 (1994); and U.S. Patent Nos. 6,982,321 and 7,087,409.

A “*human antibody*” is one that possesses an amino-acid sequence corresponding
5 to that of an antibody produced by a human and/or has been made using any of the
techniques for making human antibodies as disclosed herein. This definition of a human
antibody specifically excludes a humanized antibody comprising non-human antigen-
binding residues. Human antibodies can be produced using various techniques known in
the art, including phage-display libraries. Hoogenboom and Winter, *J. Mol. Biol.*,
10 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991). Also available for the
preparation of human monoclonal antibodies are methods described in Cole et al.,
Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985); Boerner et al., *J.*
Immunol., 147(1):86-95 (1991). See also van Dijk and van de Winkel, *Curr. Opin.*
Pharmacol. 5:368-74 (2001). Human antibodies can be prepared by administering the
15 antigen to a transgenic animal that has been modified to produce such antibodies in
response to antigenic challenge, but whose endogenous loci have been disabled, e.g.,
immunized xenomice (see, e.g., U.S. Patent Nos. 6,075,181 and 6,150,584 regarding
XENOMOUSE™ technology). See also, for example, Li et al., *Proc. Nat’l Acad. Sci.*
USA, 103:3557-3562 (2006) regarding human antibodies generated via a human B-cell
20 hybridoma technology.

The term “*hypervariable region*,” “*HVR*,” or “*HV*,” when used herein refers to the
regions of an antibody-variable domain that are hypervariable in sequence and/or form
structurally defined loops. Generally, antibodies comprise six HVRs; three in the VH
(H1, H2, H3), and three in the VL (L1, L2, L3). In native antibodies, H3 and L3 display
25 the most diversity of the six HVRs, and H3 in particular is believed to play a unique role
in conferring fine specificity to antibodies. See, e.g., Xu et al., *Immunity* 13:37-45
(2000); Johnson and Wu in *Methods in Molecular Biology* 248:1-25 (Lo, ed., Human
Press, Totowa, NJ, 2003)). Indeed, naturally occurring camelid antibodies consisting of a
heavy chain only are functional and stable in the absence of light chain. See, e.g.,
30 Hamers-Casterman et al., *Nature* 363:446-448 (1993) and Sheriff et al., *Nature Struct.*
Biol. 3:733-736 (1996).

A number of HVR delineations are in use and are encompassed herein. The HVRs that are Kabat complementarity-determining regions (CDRs) are based on sequence variability and are the most commonly used (Kabat et al., *supra*). Chothia refers instead to the location of the structural loops (Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). The AbM HVRs represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody-modeling software. The “contact” HVRs are based on an analysis of the available complex crystal structures. The residues from each of these HVRs are noted below.

Loop	Kabat	AbM	Chothia	Contact
L1	L24-L34	L24-L34	L26-L32	L30-L36
L2	L50-L56	L50-L56	L50-L52	L46-L55
L3	L89-L97	L89-L97	L91-L96	L89-L96
H1	H31-H35B	H26-H35B	H26-H32	H30-H35B (Kabat numbering)
H1	H31-H35	H26-H35	H26-H32	H30-H35 (Chothia numbering)
H2	H50-H65	H50-H58	H53-H55	H47-H58
H3	H95-H102	H95-H102	H96-H101	H93-H101

HVRs may comprise “extended HVRs” as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2), and 89-97 or 89-96 (L3) in the VL, and 26-35 (H1), 50-65 or 49-65 (a preferred embodiment) (H2), and 93-102, 94-102, or 95-102 (H3) in the VH. The variable-domain residues are numbered according to Kabat et al., *supra*, for each of these extended-HVR definitions.

“*Framework*” or “*FR*” residues are those variable-domain residues other than the HVR residues as herein defined.

The phrase “*variable-domain residue-numbering as in Kabat*” or “*amino-acid-position numbering as in Kabat*,” and variations thereof, refers to the numbering system used for heavy-chain variable domains or light-chain variable domains of the compilation of antibodies in Kabat et al., *supra*. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or HVR of the variable domain. For example, a heavy-chain variable domain may include a single amino acid insert (residue 52a according to Kabat)

after residue 52 of H2 and inserted residues (*e.g.*, residues 82a, 82b, and 82c, *etc.* according to Kabat) after heavy-chain FR residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a “standard” Kabat numbered sequence.

5 The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.*, Kabat et al., Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The “EU numbering system” or “EU index” is generally used when referring to a residue in an immunoglobulin heavy chain constant region (*e.g.*, the EU index reported in Kabat *et al.*, *supra*). The “EU index as in Kabat” refers to the residue numbering of the human IgG1 EU antibody. Unless stated otherwise herein, references to residue numbers in the variable domain of antibodies means residue numbering by the Kabat numbering system. Unless stated otherwise herein, references to residue numbers in the constant domain of antibodies means residue numbering by the EU numbering system (*e.g.*, see United States Patent Publication No. 2010-280227).

 An “*acceptor human framework*” as used herein is a framework comprising the amino acid sequence of a VL or VH framework derived from a human immunoglobulin framework or a human consensus framework. An acceptor human framework “derived from” a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain pre-existing amino acid sequence changes. In some embodiments, the number of pre-existing amino acid changes are 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, or 2 or fewer. Where pre-existing amino acid changes are present in a VH, preferable those changes occur at only three, two, or one of positions 71H, 73H and 78H; for instance, the amino acid residues at those positions may be 71A, 73T and/or 78A. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

30 A “*human consensus framework*” is a framework that represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH

sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991). Examples include for the VL, the subgroup may be subgroup kappa I, kappa II, kappa III or kappa IV as in Kabat *et al.*, *supra*. Additionally, for the VH, the subgroup may be subgroup I, subgroup II, or subgroup III as in Kabat *et al.*, *supra*.

An “*amino-acid modification*” at a specified position refers to the substitution or deletion of the specified residue, or the insertion of at least one amino acid residue adjacent the specified residue. Insertion “adjacent” to a specified residue means insertion within one to two residues thereof. The insertion may be N-terminal or C-terminal to the specified residue. The preferred amino acid modification herein is a substitution.

An “*affinity-matured*” antibody is one with one or more alterations in one or more HVRs thereof that result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody that does not possess those alteration(s). In some embodiments, an affinity-matured antibody has nanomolar or even picomolar affinities for the target antigen. Affinity-matured antibodies are produced by procedures known in the art. For example, Marks et al., *Bio/Technology* 10:779-783 (1992) describes affinity maturation by VH- and VL-domain shuffling. Random mutagenesis of HVR and/or framework residues is described by, for example: Barbas et al. *Proc Nat. Acad. Sci. USA* 91:3809-3813 (1994); Schier et al. *Gene* 169:147-155 (1995); Yelton et al. *J. Immunol.* 155:1994-2004 (1995); Jackson et al., *J. Immunol.* 154(7):3310-9 (1995); and Hawkins *et al.*, *J. Mol. Biol.* 226:889-896 (1992).

As use herein, the term “*specifically recognizes*” or “*specifically binds*” refers to measurable and reproducible interactions such as attraction or binding between a target and an antibody that is determinative of the presence of the target in the presence of a heterogeneous population of molecules including biological molecules. For example, an antibody that specifically or preferentially binds to a target or an epitope is an antibody that binds this target or epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other targets or other epitopes of the target. It is also understood that, for example, an antibody (or a moiety) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, “*specific binding*” or “*preferential binding*” does not necessarily require

(although it can include) exclusive binding. An antibody that specifically binds to a target may have an association constant of at least about 10^3 M^{-1} or 10^4 M^{-1} , sometimes about 10^5 M^{-1} or 10^6 M^{-1} , in other instances about 10^6 M^{-1} or 10^7 M^{-1} , about 10^8 M^{-1} to 10^9 M^{-1} , or about 10^{10} M^{-1} to 10^{11} M^{-1} or higher. A variety of immunoassay formats can be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select monoclonal antibodies specifically immunoreactive with a protein. *See, e.g.,* Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Publications, New York, for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity.

“*Identity*”, as used herein, indicates that at any particular position in the aligned sequences, the amino acid residue is identical between the sequences. “*Similarity*”, as used herein, indicates that, at any particular position in the aligned sequences, the amino acid residue is of a similar type between the sequences. For example, leucine may be substituted for isoleucine or valine. Other amino acids which can often be substituted for one another include but are not limited to:

- phenylalanine, tyrosine and tryptophan (amino acids having aromatic side chains);
- lysine, arginine and histidine (amino acids having basic side chains);
- aspartate and glutamate (amino acids having acidic side chains);
- asparagine and glutamine (amino acids having amide side chains); and
- cysteine and methionine (amino acids having sulphur-containing side chains).

Degrees of identity and similarity can be readily calculated. (*See e.g.,* Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing. Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991)

As used herein, an “*interaction*” between a complement protein and a second protein encompasses, without limitation, protein-protein interaction, a physical interaction, a chemical interaction, binding, covalent binding, and ionic binding. As used

herein, an antibody “inhibits interaction” between two proteins when the antibody disrupts, reduces, or completely eliminates an interaction between the two proteins. An antibody of the present disclosure, or fragment thereof, “inhibits interaction” between two proteins when the antibody or fragment thereof binds to one of the two proteins.

5 A “*blocking*” antibody, an “*antagonist*” antibody, an “*inhibitory*” antibody, or a “*neutralizing*” antibody is an antibody that inhibits or reduces one or more biological activities of the antigen it binds, such as interactions with one or more proteins. In some embodiments, blocking antibodies, antagonist antibodies, inhibitory antibodies, or “*neutralizing*” antibodies substantially or completely inhibit one or more biological
10 activities or interactions of the antigen.

The term “inhibitor” refers to a compound having the ability to inhibit a biological function of a target biomolecule, for example, an mRNA or a protein, whether by decreasing the activity or expression of the target biomolecule. An inhibitor may be an antibody, a small molecule, or a nucleic acid molecule. The term “antagonist” refers to a
15 compound that binds to a receptor, and blocks or dampens the receptor’s biological response. The term “inhibitor” may also refer to an “antagonist.”

Antibody “*effector functions*” refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype.

20 As used herein, the term “affinity” refers to the equilibrium constant for the reversible binding of two agents (*e.g.*, an antibody and an antigen) and is expressed as a dissociation constant (KD). Affinity can be at least 1-fold greater, at least 2-fold greater, at least 3-fold greater, at least 4-fold greater, at least 5-fold greater, at least 6-fold greater, at least 7-fold greater, at least 8-fold greater, at least 9-fold greater, at least 10-fold
25 greater, at least 20-fold greater, at least 30-fold greater, at least 40-fold greater, at least 50-fold greater, at least 60-fold greater, at least 70-fold greater, at least 80-fold greater, at least 90-fold greater, at least 100-fold greater, or at least 1,000-fold greater, or more, than the affinity of an antibody for unrelated amino acid sequences. Affinity of an antibody to a target protein can be, for example, from about 100 nanomolar (nM) to about 0.1 nM,
30 from about 100 nM to about 1 picomolar (pM), or from about 100 nM to about 1 femtomolar (fM) or more. As used herein, the term “avidity” refers to the resistance of a complex of two or more agents to dissociation after dilution. The terms

“immunoreactive” and “preferentially binds” are used interchangeably herein with respect to antibodies and/or antigen-binding fragments.

The term “binding” refers to a direct association between two molecules, due to, for example, covalent, electrostatic, hydrophobic, and ionic and/or hydrogen-bond interactions, including interactions such as salt bridges and water bridges. For example, a subject anti-C1q antibody binds specifically to an epitope within a complement C1q protein. “Specific binding” refers to binding with an affinity of at least about 10^{-7} M or greater, *e.g.*, 5×10^{-7} M, 10^{-8} M, 5×10^{-8} M, and greater. “Non-specific binding” refers to binding with an affinity of less than about 10^{-7} M, *e.g.*, binding with an affinity of 10^{-6} M, 10^{-5} M, 10^{-4} M, etc.

The term “ k_{on} ”, as used herein, is intended to refer to the rate constant for association of an antibody to an antigen.

The term “ k_{off} ”, as used herein, is intended to refer to the rate constant for dissociation of an antibody from the antibody/antigen complex.

The term “ K_D ”, as used herein, is intended to refer to the equilibrium dissociation constant of an antibody-antigen interaction.

As used herein, “*percent (%) amino acid sequence identity*” and “*homology*” with respect to a peptide, polypeptide or antibody sequence refers to the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or MEGALIGN™ (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms known in the art needed to achieve maximal alignment over the full length of the sequences being compared.

A “biological sample” encompasses a variety of sample types obtained from an individual and can be used in a diagnostic or monitoring assay. The definition encompasses blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures or cells derived therefrom and the progeny

thereof. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components, such as polynucleotides. The term “biological sample” encompasses a clinical sample, and also includes cells in culture, cell supernatants, cell lysates, serum, plasma, biological fluid, and tissue samples. The term “biological sample” includes urine, saliva, cerebrospinal fluid, interstitial fluid, ocular fluid, synovial fluid, blood fractions such as plasma and serum, and the like. The term “biological sample” also includes solid tissue samples, tissue culture samples, and cellular samples.

An “*isolated*” nucleic acid molecule is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the environment in which it was produced. Preferably, the isolated nucleic acid is free of association with all components associated with the production environment. The isolated nucleic acid molecules encoding the polypeptides and antibodies herein is in a form other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from nucleic acids encoding any polypeptides and antibodies herein that exist naturally in cells.

The term “*vector*,” as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a “*plasmid*,” which refers to a circular double stranded DNA into which additional DNA segments may be ligated. Another type of vector is a phage vector. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors,” or simply, “expression vectors.” In general, expression vectors useful in recombinant DNA techniques are often in the form of plasmids. In the present specification, “plasmid” and “vector” may be used interchangeably as the plasmid is the most commonly used form of vector.

“*Polynucleotide*,” or “*nucleic acid*,” as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase or by a synthetic reaction. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may comprise modification(s) made after synthesis, such as conjugation to a label. Other types of modifications include, for example, “caps,” substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, *etc.*) and with charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, *etc.*), those containing pendant moieties, such as, for example, proteins (*e.g.*, nucleases, toxins, antibodies, signal peptides, poly-L-lysine, *etc.*), those with intercalators (*e.g.*, acridine, psoralen, *etc.*), those containing chelators (*e.g.*, metals, radioactive metals, boron, oxidative metals, *etc.*), those containing alkylators, those with modified linkages (*e.g.*, alpha anomeric nucleic acids, *etc.*), as well as unmodified forms of the polynucleotides(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid or semi-solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl-, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α -anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs, and basic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S (“thioate”), P(S)S

(“dithioate”), (O)NR₂ (“amidate”), P(O)R, P(O)OR’, CO, or CH₂ (“formacetal”), in which each R or R’ is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or aralkyl. Not all linkages in a polynucleotide need be identical. The preceding description
5 applies to all polynucleotides referred to herein, including RNA and DNA.

A “*host cell*” includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to
10 natural, accidental, or deliberate mutation. A host cell includes cells transfected *in vivo* with a polynucleotide(s) of this disclosure.

“*Carriers*” as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is
15 an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or
20 lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

The term “*preventing*” is art-recognized, and when used in relation to a condition,
25 such as an inherited retinal disease (IRD) (e.g., retinitis pigmentosa/rod-cone dystrophy, choroideremia, Stargardt disease, cone-rod dystrophy, leber congenital amaurosis, X-linked RP, and Usher Syndrome) or retinal detachment or related symptoms, relative to a patient who does not receive the therapy.

The term “*subject*” as used herein refers to a living mammal and may be
30 interchangeably used with the term “patient”. Examples of mammals include, but are not limited to, any member of the mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses,

sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. The term does not denote a particular age or gender.

As used herein, the term “*treating*” or “*treatment*” includes reducing, arresting, or reversing the symptoms, clinical signs, or underlying pathology of a condition to stabilize or improve a subject's condition or to reduce the likelihood that the subject's condition will worsen as much as if the subject did not receive the treatment.

“Restoring” refers to the act of returning to a normal or healthy condition. The restoration may be partial (e.g., when the subject returns to a condition which is below the normal or healthy condition) or total (e.g., when the subject returns to a condition which is identical or almost identical to a normal or healthy condition). An example of a normal or healthy condition is the visual acuity of a patient prior to retinal detachment.

“Improving vision” refers to the act of enhancing the faculty or state of being able to see, relative to before treatment, including improving acuity, sensitivity, and/or range of visual field.

The term “*therapeutically effective amount*” of a compound with respect to the subject method of treatment refers to an amount of the compound(s) in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment. A therapeutically effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the antibody to elicit a desired response in the individual.

As used herein, an individual “*at risk*” of developing a particular disease, disorder, or condition may or may not have detectable disease or symptoms of disease, and may or may not have displayed detectable disease or symptoms of disease prior to the treatment methods described herein. “At risk” denotes that an individual has one or more risk factors, which are measurable parameters that correlate with development of a particular disease, disorder, or condition, as known in the art. An individual having one or more of these risk factors has a higher probability of developing a particular disease, disorder, or condition than an individual without one or more of these risk factors.

“Chronic” administration refers to administration of the medicament(s) in a continuous as opposed to acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. “Intermittent” administration refers to treatment that is not administered consecutively without interruption, but rather is cyclic/periodic in nature.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. such as, for example, the widely utilized methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 3d edition (2001) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; *Current Protocols in Molecular Biology* (F.M. Ausubel, et al. eds., (2003)); the series *Methods in Enzymology* (Academic Press, Inc.): *PCR 2: A Practical Approach* (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) *Antibodies, A Laboratory Manual*, and *Animal Cell Culture* (R.I. Freshney, ed. (1987)); *Oligonucleotide Synthesis* (M.J. Gait, ed., 1984); *Methods in Molecular Biology*, Humana Press; *Cell Biology: A Laboratory Notebook* (J.E. Cellis, ed., 1998) Academic Press; *Animal Cell Culture* (R.I. Freshney), ed., 1987); *Introduction to Cell and Tissue Culture* (J.P. Mather and P.E. Roberts, 1998) Plenum Press; *Cell and Tissue Culture: Laboratory Procedures* (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-8) J. Wiley and Sons; *Handbook of Experimental Immunology* (D.M. Weir and C.C. Blackwell, eds.); *Gene Transfer Vectors for Mammalian Cells* (J.M. Miller and M.P. Calos, eds., 1987); *PCR: The Polymerase Chain Reaction*, (Mullis et al., eds., 1994); *Current Protocols in Immunology* (J.E. Coligan et al., eds., 1991); *Short Protocols in Molecular Biology* (Wiley and Sons, 1999); *Immunobiology* (C.A. Janeway and P. Travers, 1997); *Antibodies* (P. Finch, 1997); *Antibodies: A Practical Approach* (D. Catty., ed., IRL Press, 1988-1989); *Monoclonal Antibodies: A Practical Approach* (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); *Using Antibodies: A Laboratory Manual* (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); *The Antibodies* (M.

Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995); and *Cancer: Principles and Practice of Oncology* (V.T. DeVita et al., eds., J.B. Lippincott Company, 1993).

5 *Antibodies*

All sequences mentioned in the present disclosure are incorporated by reference from U.S. Pat. App. No. 14/933,517, U.S. Pat. App. No. 14/890,811, U.S. Pat. No. 8,877,197, U.S. Pat. No. 9,708,394, U.S. Pat. App. No. 15/360,549, U.S. Pat. No. 9,562,106, U.S. Pat. No. 10,450,382, U.S. Pat. No. 10,457,745, International Patent
10 Application No. PCT/US2018/022462 each of which is hereby incorporated by reference for the antibodies and related compositions that it discloses.

Full-length antibodies may be prepared by the use of recombinant DNA engineering techniques. Such engineered versions include those created, for example, from natural antibody variable regions by insertions, deletions or changes in or to the
15 amino acid sequences of the natural antibodies. Particular examples of this type include those engineered variable region domains containing at least one CDR and optionally one or more framework amino acids from one antibody and the remainder of the variable region domain from a second antibody. The DNA encoding the antibody may be prepared by deleting all but the desired portion of the DNA that encodes the full length antibody.
20 DNA encoding chimerized antibodies may be prepared by recombining DNA substantially or exclusively encoding human constant regions and DNA encoding variable regions derived substantially or exclusively from the sequence of the variable region of a mammal other than a human. DNA encoding humanized antibodies may be prepared by recombining DNA encoding constant regions and variable regions other than
25 the complementarity determining regions (CDRs) derived substantially or exclusively from the corresponding human antibody regions and DNA encoding CDRs derived substantially or exclusively from a mammal other than a human.

Suitable sources of DNA molecules that encode antibodies include cells, such as hybridomas, that express the full length antibody. For example, the antibody may be
30 isolated from a host cell that expresses an expression vector that encodes the heavy and/or light chain of the antibody.

Antibody fragments, including but not limited to Fab fragments, and/or antibody derivatives may also be prepared by the use of recombinant DNA engineering techniques involving the manipulation and re-expression of DNA encoding antibody variable and constant regions. Standard molecular biology techniques may be used to modify, add or delete further amino acids or domains as desired. Any alterations to the variable or constant regions are still encompassed by the terms 'variable' and 'constant' regions as used herein. In some instances, PCR is used to generate an antibody fragment by introducing a stop codon immediately following the codon encoding the interchain cysteine of C_H1, such that translation of the C_H1 domain stops at the interchain cysteine. Methods for designing suitable PCR primers are well known in the art and the sequences of antibody C_H1 domains are readily available. In some embodiments, stop codons may be introduced using site-directed mutagenesis techniques.

An antibody of the present disclosure may be derived from any antibody isotype ("class") including for example IgG, IgM, IgA, IgD and IgE and subclasses thereof, including for example IgG1, IgG2, IgG3 and IgG4. In certain preferred embodiments, the heavy and light chains of the antibody are from IgG. The heavy and/or light chains of the antibody may be from murine IgG or human IgG. In certain other preferred embodiments, the heavy and/or light chains of the antibody are from human IgG1. In still other preferred embodiments, the heavy and/or light chains of the antibody are from human IgG4.

An antibody of the present disclosure may bind to and inhibit a biological activity of C1q, C1r, or C1s. For example, (1) C1q binding to an autoantibody, (2) C1q binding to C1r, (3) C1q binding to C1s, (4) C1q binding to phosphatidylserine, (5) C1q binding to pentraxin-3, (6) C1q binding to C-reactive protein (CRP), (7) C1q binding to globular C1q receptor (gC1qR), (8) C1q binding to complement receptor 1 (CR1), (9) C1q binding to B-amyloid, or (10) C1q binding to calreticulin. In other embodiments, the biological activity of C1q is (1) activation of the classical complement activation pathway, (2) reduction in lysis and/or reduction in C3 deposition, (3) activation of antibody and complement dependent cytotoxicity, (4) CH50 hemolysis, (5) a reduction in red blood cell lysis, (6) a reduction in red blood cell phagocytosis, (7) a reduction in dendritic cell infiltration, (8) inhibition of complement-mediated red blood cell lysis, (9) a reduction in lymphocyte infiltration, (10) a reduction in macrophage infiltration, (11) a reduction in

antibody deposition, (12) a reduction in neutrophil infiltration, (13) a reduction in platelet phagocytosis, (14) a reduction in platelet lysis, (15) an improvement in transplant graft survival, (16) a reduction in macrophage mediated phagocytosis, (17) a reduction in autoantibody mediated complement activation, (18) a reduction in red blood cell destruction due to transfusion reactions, (19) a reduction in red blood cell lysis due to alloantibodies, (20) a reduction in hemolysis due to transfusion reactions, (21) a reduction in alloantibody mediated platelet lysis, (22) an improvement in anemia, (23) a reduction in eosinophilia, (24) a reduction in C3 deposition on red blood cells (*e.g.*, a reduction of deposition of C3b, iC3b, etc., on RBCs), (25) a reduction in C3 deposition on platelets (*e.g.*, a reduction of deposition of C3b, iC3b, etc., on platelets), (26) reduction in anaphylatoxin production, (27) a reduction in autoantibody mediated blister formation, (28) a reduction in autoantibody induced erythematosis, (29) a reduction in red blood cell destruction due to transfusion reactions, (30) a reduction in platelet lysis due to transfusion reactions, (31) a reduction in mast cell activation, (32) a reduction in mast cell histamine release, (33) a reduction in vascular permeability, (34) a reduction in complement deposition on transplant graft endothelium, (35) B-cell antibody production, (36) dendritic cell maturation, (37) T-cell proliferation, (38) cytokine production, (39) microglia activation, (40) Arthus reaction, (41) a reduction of anaphylatoxin generation in transplant graft endothelium, or (42) activation of complement receptor 3 (CR3/C3) expressing cells.

In some embodiments, CH50 hemolysis comprises human, mouse, and/or rat CH50 hemolysis. In some embodiments, the antibody is capable of neutralizing from at least about 50%, to at least about 95% of CH50 hemolysis. In some embodiments, the antibody is capable of neutralizing 50%, 60%, 70%, 80, 90%, or 100% of CH50 hemolysis. The antibody may also be capable of neutralizing at least 50% of CH50 hemolysis at a dose of less than 150 ng/ml, less than 100 ng/ml, less than 50 ng/ml, or less than 20 ng/ml.

Other *in vitro* assays to measure complement activity include ELISA assays for the measurement of split products of complement components or complexes that form during complement activation. Complement activation via the classical pathway can be measured by following the levels of C4d and C4 in the serum. Activation of the alternative pathway can be measured in an ELISA by assessing the levels of Bb or

C3bBbP complexes in circulation. An *in vitro* antibody-mediated complement activation assay may also be used to evaluate inhibition of C3a production.

An antibody of the present disclosure may be a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody, an antibody fragment thereof, or a derivative thereof. In some embodiments, the antibody is humanized antibody.

The antibodies of the present disclosure may also be an antibody fragment, such as a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a diabody, or a single chain antibody molecule. In some embodiments, the antibody fragment is a Fab fragment.

In some embodiments, antibodies are human monoclonal antibodies which may be prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline and/or non-germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

In some embodiments, antibodies are humanized and/or chimeric monoclonal antibodies, which can be raised by immunizing rodents (*e.g.*, mice, rats, hamsters and guinea pigs) with either (1) the native complement component (*e.g.*, C1q) derived from enzymatic digestion of a purified complement component from human plasma or serum, or (2) a recombinant complement component, or its derived fragment, expressed by either eukaryotic or prokaryotic systems. Other animals can be used for immunization, *e.g.*,

non-human primates, transgenic mice expressing human immunoglobulins, and severe combined immunodeficient (SCID) mice transplanted with human B-lymphocytes.

Polyclonal and monoclonal antibodies are naturally generated as immunoglobulin (Ig) molecules in the immune system's response to a pathogen. A dominating format with
5 a concentration of 8 mg/ml in human serum, the ~150-kDa IgG1 molecule is composed of two identical ~50-kDa heavy chains and two identical ~25-kDa light chains.

Hybridomas can be generated by conventional procedures by fusing B-lymphocytes from the immunized animals with myeloma cells. In addition, anti-C1q antibodies can be generated by screening recombinant single-chain Fv or Fab libraries
10 from human B-lymphocytes in a phage-display system. The specificity of the MAbs to human C1q can be tested by enzyme linked immunosorbent assay (ELISA), Western immunoblotting, or other immunochemical techniques.

The inhibitory activity on complement activation of antibodies identified in the screening process can be assessed by hemolytic assays using either unsensitized rabbit or
15 guinea pig RBCs for the alternative complement pathway, or sensitized chicken or sheep RBCs for the classical complement pathway. Those hybridomas that exhibit an inhibitory activity specific for the classical complement pathway are cloned by limiting dilution. The antibodies are purified for characterization for specificity to human C1q by the assays described above.

20 Anti-Complement C1q Antibodies

The anti-C1q antibodies disclosed herein are potent inhibitors of C1q and can be dosed for continuous inhibition of C1q function over any period, and then optionally withdrawn to allow for return of normal C1q function at times when its activity may be important. Results obtained with anti-C1q antibodies disclosed herein in animal studies
25 can be readily carried forward into the clinic with humanized or human antibodies, as well as with fragments and/or derivatives thereof.

C1q is a large multimeric protein of 460 kDa consisting of 18 polypeptide chains (6 C1q A chains, 6 C1q B chains, and 6 C1q C chains). C1r and C1s complement proteins bind to the C1q tail region to form the C1 complex (C1qr₂s₂).

30 The antibodies of this disclosure specifically recognize complement factor C1q and/or C1q in the C1 complex of the classical complement activation pathway. The bound complement factor may be derived, without limitation, from any organism having

a complement system, including any mammalian organism such as human, mouse, rat, rabbit, monkey, dog, cat, cow, horse, camel, sheep, goat, or pig.

As used herein “C1 complex” refers to a protein complex that may include, without limitation, one C1q protein, two C1r proteins, and two C1s proteins (e.g.,
5 C1qr²s²).

Anti-C1q antibodies disclosed herein may inhibit C1 complex formation.

As used herein “complement factor C1q” refers to both wild type sequences and naturally occurring variant sequences.

A non-limiting example of a complement factor C1q recognized by antibodies of
10 this disclosure is human C1q, including the three polypeptide chains A, B, and C:

C1q, chain A (homo sapiens), Accession No. Protein

Data Base: NP_057075.1; GenBank No.: NM_015991:

>gi|7705753|ref|NP_057075.1|complement C1q

subcomponent subunit A precursor [Homo sapiens]

15 (SEQ ID NO:1)

MEGPRGWLVLCLVLAISLASMVTEDLCRAPDGKKGEAGRPGRRRGRPGLKGEQGE
PGAPGIRTGIQGLKGDQGEPPSGNPGKVGYPGPGPLGARGIPGIKGTKGSPGNI
KDQPRPAFSAIRRNPPMGGNVVIFDTVITNQEOPYQNHSGRFVCTVPGYYYFTFQ
VLSQWEICLSIVSSSRGQVRRSLGFCDTTNKGLFQVVSGGMVLQLQQGDQVWVE
20 KDPKKGHIYQGSEADSVFSGFLIFPSA.

C1q, chain B (homo sapiens), Accession No. Protein

Data Base: NP_000482.3; GenBank No.: NM_000491.3:

>gi|87298828|ref|NP_000482.3|complement C1q

25 subcomponent subunit B precursor [Homo sapiens]

(SEQ ID NO:2)

MMMIPWGSIPVLMLLLLGLIDISQAQLSCTGPPAIPGIPGIPGTPGPDGQPGTPGI
KGEKGLPGLAGDHGEFGEKGDPIPGNPGKVGPKGPMGPKGGPGAPGAPGPKGE
SGDYKATQKIAFSATRTINVPLRRDQTIRFDHVITNMNNNYEPRSGKFTCKVPGL
30 YYFTYHASSRGNLCVNLMRGRERAQKVVTFCDYAYNTFQVTTGGMVLKLEQGE
NVFLQATDKNSLLGMEGANSIFSGFLLFPDMEA.

C1q, chain C (homo sapiens), Accession No. Protein

Data Base: NP_001107573.1; GenBank No.:

NM_001114101.1:

>gi|166235903|ref|NP_001107573.1|complement C1q

5 subcomponent subunit C precursor [Homo sapiens]

(SEQ ID NO:3)

MDVGPSSLPHLGLKLLLLLLLLLPLRGQANTGCYGIPGMPGLPGAPGKDG YDGLP
GPKGEPGIPAIPGIRGPKGQKGEPGLPGHPGKNGPMGPPGMPGVPGPMGIPGEPGE
EGRYKQKFQSVFTVTRQTHQPPAPNSLIRFNAVL TNPQGDYDTSTGKFTCKVPGL
10 YYFVYHASHTANLCVLLYRSGVKVVTFCGHTSKTNQVNSGGVLLRLQVGEEVW
LAVNDYYDMVGIQGS DSVFSGFLLFPD.

Accordingly, an anti-C1q antibody of the present disclosure may bind to polypeptide chain A, polypeptide chain B, and/or polypeptide chain C of a C1q protein. In some embodiments, an anti-C1q antibody of the present disclosure binds to
15 polypeptide chain A, polypeptide chain B, and/or polypeptide chain C of human C1q or a homolog thereof, such as mouse, rat, rabbit, monkey, dog, cat, cow, horse, camel, sheep, goat, or pig C1q. In some embodiments, the anti-C1q antibody is a human antibody, a humanized antibody, a chimeric antibody, or a fragment thereof or a derivative thereof. In some embodiments, the antibody is humanized antibody. In some embodiments, the
20 antibody is antibody fragment, such as, a Fab fragment.

All sequences mentioned in the following twenty paragraphs are incorporated by reference from U.S. Pat. No. 9,708,394, which is hereby incorporated by reference for the antibodies and related compositions that it discloses.

Light Chain and Heavy Chain Variable Domain Sequences of Antibody M1 (Mab1)

25 Using standard techniques, the nucleic acid and amino acid sequences encoding the light chain variable and the heavy chain variable domain of antibody M1 were determined. The amino acid sequence of the light chain variable domain of antibody M1 is:

DVQITQSPSYLAASPGETITINCRASKSINKYLAWYQEKP GKTNKLIIYSGSTLOS
30 GIPSRFSGSGSGTDFTLTISSELPEDFAMYYCQOHNEYPLTFGAGTKLELK (SEQ
ID NO:4).

The hyper variable regions (HVRs) of the light chain variable domain are depicted in bolded and underlined text. In some embodiments, the HVR-L1 of the M1 light chain variable domain has the sequence RASKSINKYLA (SEQ ID NO:5), the HVR-L2 of the M1 light chain variable domain has the sequence SGSTLQS (SEQ ID NO:6), and the HVR-L3 of the M1 light chain variable domain has the sequence QQHNEYPLT (SEQ ID NO:7).

The amino acid sequence of the heavy chain variable domain of antibody M1 is:
 QVQLQQPGAELVKPGASVKLSCKSS**GYHFTSYWMH**HWVKQRPGQGLEWIG**VIH**
PNSGSINYNEKFESKATLTVDKSSSTAYMQLSSLTSEDSAVYYCAG**ERDSTEVL**
PMDYWGQGTSVTVSS (SEQ ID NO:8).

The hyper variable regions (HVRs) of the heavy chain variable domain are depicted in bolded and underlined text. In some embodiments, the HVR-H1 of the M1 heavy chain variable domain has the sequence GYHFTSYWMH (SEQ ID NO:9), the HVR-H2 of the M1 heavy chain variable domain has the sequence VIHPNSGSINYNEKFES (SEQ ID NO:10), and the HVR-H3 of the M1 heavy chain variable domain has the sequence ERDSTEVL**PMDY** (SEQ ID NO:11).

The nucleic acid sequence encoding the light chain variable domain was determined to be:
 GATGTCCAGATAACCCAGTCTCCATCTTATCTTGCTGCATCTCCTGGAGAAAC
 CATTACTATTAATTGCAGGGCAAGTAAGAGCATTAACAAATATTTAGCCTGGT
 ATCAAGAGAAACCTGGGAAAATAATAAGCTTCTTATCTACTCTGGATCCACT
 TTGCAATCTGGAATTCCATCAAGGTTCAAGTGGCAGTGGATCTGGTACAGATTT
 CACTCTCACCATCAGTAGCCTGGAGCCTGAAGATTTTGCAATGTATTACTGTC
 AACAACATAATGAATACCCGCTCACGTTTCGGTGCTGGGACCAAGCTGGAGCT
 GAAA (SEQ ID NO:12).

The nucleic acid sequence encoding the heavy chain variable domain was determined to be:
 CAGGTCCAAGTGCAGCAGCCTGGGGCTGAGCTGGTAAAGCCTGGGGCTTCAG
 TGAAGTTGTCCTGCAAGTCTTCTGGCTACCATTTCACCAGCTACTGGATGCAC
 TGGGTGAAGCAGAGGCCTGGACAAGGCCTTGAGTGGATTGGAGTGATTCATC
 CTAATAGTGGTAGTATTAATACTACAATGAGAAGTTCGAGAGCAAGGCCACACT
 GACTGTAGACAAATCCTCCAGCACAGCCTACATGCAACTCAGCAGCCTGACA

TCTGAGGACTCGGCGGTCTATTATTGTGCAGGAGAGAGAGATTCTACGGAGG
 TTCTCCCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ
 ID NO:13).

The Mab1-Fab is the Fab of the Mab1 (M1) antibody.

- 5 Mab3 is a murine anti-C1q antibody that is derived from Mab 1 antibody and optimized for murine experiments, and Mab3-Fab is the Fab of the Mab3 antibody.

Deposit of Material

- The following materials have been deposited according to the Budapest Treaty in the American Type Culture Collection, ATCC Patent Depository, 10801 University
 10 Blvd., Manassas, Va. 20110-2209, USA (ATCC):

Sample ID	Deposit ATCC		
	Isotype	Date	Accession No.
Mouse hybridoma C1qM1 7788-1(M) 051613 producing anti-C1q antibody M1	IgG1, kappa	Jun. 6, 2013	PTA-120399

- The hybridoma cell line producing the M1 antibody (mouse hybridoma C1qM1 7788-1(M) 051613) has been deposited with ATCC under conditions that assure that access to the culture will be available during pendency of the patent application and for a
 15 period of 30 years, or 5 years after the most recent request, or for the effective life of the patent, whichever is longer. A deposit will be replaced if the deposit becomes nonviable during that period. The deposit is available as required by foreign patent laws in countries wherein counterparts of the subject application, or its progeny are filed. However, it should be understood that the availability of the deposit does not constitute a license to
 20 practice the subject invention in derogation of patent rights granted by governmental action.

- Disclosed herein are methods of administering an anti-C1q antibody comprising a light chain variable domain and a heavy chain variable domain. The antibody may bind to at least human C1q, mouse C1q, or rat C1q. The antibody may be a humanized
 25 antibody, a chimeric antibody, or a human antibody. The antibody may be a monoclonal antibody, an antibody fragment thereof, and/or an antibody derivative thereof. In some

embodiments, the antibody is humanized antibody. In some embodiments, the antibody is antibody fragment, such as, a Fab fragment. The light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 of the monoclonal antibody M1 produced by a hybridoma cell line deposited with Accession Number PTA-120399. The heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 of the monoclonal antibody M1 produced by a hybridoma cell line deposited with ATCC Accession Number PTA-120399.

In some embodiments, the amino acid sequence of the light chain variable domain and heavy chain variable domain comprise one or more of SEQ ID NO:5 of HVR-L1, SEQ ID NO:6 of HVR-L2, SEQ ID NO:7 of HVR-L3, SEQ ID NO:9 of HVR-H1, SEQ ID NO:10 of HVR-H2, and SEQ ID NO:11 of HVR-H3.

The antibody may comprise a light chain variable domain amino acid sequence that is at least 85%, 90%, or 95% identical to SEQ ID NO:4, preferably while retaining the HVR-L1 RASKSINKYLA (SEQ ID NO:5), the HVR-L2 SGSTLQS (SEQ ID NO:6), and the HVR-L3 QQHNEYPLT (SEQ ID NO:7). The antibody may comprise a heavy chain variable domain amino acid sequence that is at least 85%, 90%, or 95% identical to SEQ ID NO:8, preferably while retaining the HVR-H1 GYHFTSYWMH (SEQ ID NO:9), the HVR-H2 VIHPNSGSINYNEKFES (SEQ ID NO:10), and the HVR-H3 ERDSTEVLPM DY (SEQ ID NO:11).

Disclosed herein are methods of administering an anti-C1q antibody, which inhibits the interaction between C1q and an autoantibody. In preferred embodiments, the anti-C1q antibody causes clearance of C1q from the circulation or tissue.

In some embodiments, the anti-C1q antibody of this disclosure inhibits the interaction between C1q and C1s. In some embodiments, the anti-C1q antibody inhibits the interaction between C1q and C1r. In some embodiments the anti-C1q antibody inhibits the interaction between C1q and C1s and between C1q and C1r. In some embodiments, the anti-C1q antibody inhibits the interaction between C1q and another antibody, such as an autoantibody. In preferred embodiments, the anti-C1q antibody causes clearance of C1q from the circulation or tissue. In some embodiments, the anti-C1q antibody inhibits the respective interactions, at a stoichiometry of less than 2.5:1; 2.0:1; 1.5:1; or 1.0:1. In some embodiments, the C1q antibody inhibits an interaction, such as the C1q-C1s interaction, at approximately equimolar concentrations of C1q and

the anti-C1q antibody. In other embodiments, the anti-C1q antibody binds to C1q with a stoichiometry of less than 20:1; less than 19.5:1; less than 19:1; less than 18.5:1; less than 18:1; less than 17.5:1; less than 17:1; less than 16.5:1; less than 16:1; less than 15.5:1; less than 15:1; less than 14.5:1; less than 14:1; less than 13.5:1; less than 13:1; less than 12.5:1; less than 12:1; less than 11.5:1; less than 11:1; less than 10.5:1; less than 10:1; less than 9.5:1; less than 9:1; less than 8.5:1; less than 8:1; less than 7.5:1; less than 7:1; less than 6.5:1; less than 6:1; less than 5.5:1; less than 5:1; less than 4.5:1; less than 4:1; less than 3.5:1; less than 3:1; less than 2.5:1; less than 2.0:1; less than 1.5:1; or less than 1.0:1. In certain embodiments, the anti-C1q antibody binds C1q with a binding stoichiometry that ranges from 20:1 to 1.0:1 or less than 1.0:1. In certain embodiments, the anti-C1q antibody binds C1q with a binding stoichiometry that ranges from 6:1 to 1.0:1 or less than 1.0:1. In certain embodiments, the anti-C1q antibody binds C1q with a binding stoichiometry that ranges from 2.5:1 to 1.0:1 or less than 1.0:1. In some embodiments, the anti-C1q antibody inhibits the interaction between C1q and C1r, or between C1q and C1s, or between C1q and both C1r and C1s. In some embodiments, the anti-C1q antibody inhibits the interaction between C1q and C1r, between C1q and C1s, and/or between C1q and both C1r and C1s. In some embodiments, the anti-C1q antibody binds to the C1q A-chain. In other embodiments, the anti-C1q antibody binds to the C1q B-chain. In other embodiments, the anti-C1q antibody binds to the C1q C-chain. In some embodiments, the anti-C1q antibody binds to the C1q A-chain, the C1q B-chain and/or the C1q C-chain. In some embodiments, the anti-C1q antibody binds to the globular domain of the C1q A-chain, B-chain, and/or C-chain. In other embodiments, the anti-C1q antibody binds to the collagen-like domain of the C1q A-chain, the C1q B-chain, and/or the C1q C-chain.

Where antibodies of this disclosure inhibit the interaction between two or more complement factors, such as the interaction of C1q and C1s, or the interaction between C1q and C1r, the interaction occurring in the presence of the antibody may be reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% relative to a control wherein the antibodies of this disclosure are absent. In some embodiments, antibodies of this disclosure reduces the interaction between two or more complement factors by 50%, 60%, 70%, 80%, 90%, or 100%. In certain embodiments, the interaction occurring in the

presence of the antibody is reduced by an amount that ranges from at least 30% to at least 99% relative to a control wherein the antibodies of this disclosure are absent.

In some embodiments, the antibodies of this disclosure inhibit C2 or C4-cleavage by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99%, or by an amount that ranges from at least 30% to at least 99%, relative to a control wherein the antibodies of this disclosure are absent. Methods for measuring C2 or C4-cleavage are well known in the art. The EC₅₀ values for antibodies of this disclosure with respect C2 or C4-cleavage may be less than 3 µg/ml; 2.5 µg/ml; 2.0 µg/ml; 1.5 µg/ml; 1.0 µg/ml; 0.5 µg/ml; 0.25 µg/ml; 0.1 µg/ml; 0.05 µg/ml. In some embodiments, the antibodies of this disclosure inhibit C2 or C4-cleavage at approximately equimolar concentrations of C1q and the respective anti-C1q antibody.

In some embodiments, the antibodies of this disclosure inhibit autoantibody-dependent and complement-dependent cytotoxicity (CDC) by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99%, or by an amount that ranges from at least 30% to at least 99%, relative to a control wherein the antibodies of this disclosure are absent. The EC₅₀ values for antibodies of this disclosure with respect to inhibition of autoantibody-dependent and complement-dependent cytotoxicity may be less than 3 µg/ml; 2.5 µg/ml; 2.0 µg/ml; 1.5 µg/ml; 1.0 µg/ml; 0.5 µg/ml; 0.25 µg/ml; 0.1 µg/ml; 0.05 µg/ml.

In some embodiments, the antibodies of this disclosure inhibit complement-dependent cell-mediated cytotoxicity (CDCC) by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99%, or by an amount that ranges from at least 30% to at least 99%, relative to a control wherein the antibodies of this disclosure are absent. Methods for measuring CDCC are well known in the art. The EC₅₀ values for antibodies of this disclosure with respect CDCC inhibition may be less than 3 µg/ml; 2.5 µg/ml; 2.0 µg/ml; 1.5 µg/ml; 1.0 µg/ml; 0.5 µg/ml; 0.25 µg/ml; 0.1 µg/ml; 0.05 µg/ml. In some embodiments, the antibodies of this disclosure inhibit CDCC but not antibody-dependent cellular cytotoxicity (ADCC).

Humanized anti-complement C1q Antibodies

Humanized antibodies of the present disclosure specifically bind to a complement factor C1q and/or C1q protein in the C1 complex of the classical complement pathway. The humanized anti-C1q antibody may specifically bind to human C1q, human and mouse C1q, to rat C1q, or human C1q, mouse C1q, and rat C1q.

5 All sequences mentioned in the following sixteen paragraphs are incorporated by reference from U.S. Pat. App. No. 14/933,517, which is hereby incorporated by reference for the antibodies and related compositions that it discloses.

In some embodiments, the human heavy chain constant region is a human IgG4 heavy chain constant region comprising the amino acid sequence of SEQ ID NO:47, or
 10 with at least 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90% homology to SEQ ID NO: 47. The human IgG4 heavy chain constant region may comprise an Fc region with one or more modifications and/or amino acid substitutions according to Kabat numbering. In such cases, the Fc region comprises a leucine to glutamate amino acid substitution at position 248, wherein such a substitution
 15 inhibits the Fc region from interacting with an Fc receptor. In some embodiments, the Fc region comprises a serine to proline amino acid substitution at position 241, wherein such a substitution prevents arm switching in the antibody.

The amino acid sequence of human IgG4 (S241P L248E) heavy chain constant domain is:

20 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
 LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP
 EFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN
 AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG
 QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
 25 VLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
 (SEQ ID NO: 47).

The antibody may comprise a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence selected from any one of SEQ ID NOs: 31-34, or an amino acid sequence with
 30 at least about 90% homology to the amino acid sequence selected from any one of SEQ ID NOs: 31-34. In certain such embodiments, the light chain variable domain comprises an amino acid sequence selected from any one of SEQ ID NOs: 35-38, or an amino acid

sequence with at least about 90% homology to the amino acid sequence selected from any one of SEQ ID NOs: 35-38.

The amino acid sequence of heavy chain variable domain variant 1 (VH1) is:

QVQLVQSGAELKKPGASVKVSCCKSS**GYHFTSYWMH**WVKQAPGQGLEWIG**VIH**
 5 **PNSGSINYNEKFES**KATITVDKSTSTAYMQLSSLTSEDSAVYYCAG**ERDSTEVL**P
MDYWGQGTSTVTVSS (SEQ ID NO: 31). The hyper variable regions (HVRs) of VH1 are depicted in bolded and underlined text.

The amino acid sequence of heavy chain variable domain variant 2 (VH2) is:

QVQLVQSGAELKKPGASVKVSCCKSS**GYHFTSYWMH**WVKQAPGQGLEWIG**VIH**
 10 **PNSGSINYNEKFES**RATITVDKSTSTAYMELSSLRSEDTAVYYCAG**ERDSTEVL**P
MDYWGQGTSTVTVSS (SEQ ID NO: 32). The hyper variable regions (HVRs) of VH2 are depicted in bolded and underlined text.

The amino acid sequence of heavy chain variable domain variant 3 (VH3) is:

QVQLVQSGAELKKPGASVKVSCCKSS**GYHFTSYWMH**WVKQAPGQGLEWIG**VIH**
 15 **PNSGSINYNEKFES**RVITITVDKSTSTAYMELSSLRSEDTAVYYCAG**ERDSTEVL**P
MDYWGQGTSTVTVSS (SEQ ID NO: 33). The hyper variable regions (HVRs) of VH3 are depicted in bolded and underlined text.

The amino acid sequence of heavy chain variable domain variant 4 (VH4) is:

QVQLVQSGAELKKPGASVKVSCCKSS**GYHFTSYWMH**WVRQAPGQGLEWIG**VIH**
 20 **PNSGSINYNEKFES**RVITITVDKSTSTAYMELSSLRSEDTAVYYCAG**ERDSTEVL**P
MDYWGQGTSTVTVSS (SEQ ID NO: 34). The hyper variable regions (HVRs) of VH4 are depicted in bolded and underlined text.

The amino acid sequence of kappa light chain variable domain variant 1 (Vκ1) is:

DVQITQSPSYLAASLGERATINC**RASKSINKYLA**WYQQKPGKTNKLLIY**SGSTLQ**
 25 **SGIPARFSGSGSGTDFTL**TISSLEPEDFAMYYC**QQHNEYPLT**FGQGGTKLEIK (SEQ ID NO: 35). The hyper variable regions (HVRs) of Vκ1 are depicted in bolded and underlined text.

The amino acid sequence of kappa light chain variable domain variant 2 (Vκ2) is:

DVQITQSPSSLSASLGERATINC**RASKSINKYLA**WYQQKPGKANKLLIY**SGSTLQ**
 30 **SGIPARFSGSGSGTDFTL**TISSLEPEDFAMYYC**QQHNEYPLT**FGQGGTKLEIK (SEQ

ID NO: 36). The hyper variable regions (HVRs) of V κ 2 are depicted in bolded and underlined text.

The amino acid sequence of kappa light chain variable domain variant 3 (V κ 3) is:
 DVQITQSPSSLSASLGERATINC**RASKSINKYLA**WYQQKPGKAPKLLIY**SGSTLQS**
 5 GIPARFSGSGSGTDFTLTISSELPEDFAMYYC**QQHNEYPLT**TFGQGTKLEIK (SEQ
 ID NO: 37). The hyper variable regions (HVRs) of V κ 3 are depicted in bolded and underlined text.

The amino acid sequence of kappa light chain variable domain variant 4 (V κ 4) is:
 DIQLTQSPSSLSASLGERATINC**RASKSINKYLA**WYQQKPGKAPKLLIY**SGSTLQS**
 10 GIPARFSGSGSGTDFTLTISSELPEDFAMYYC**QQHNEYPLT**TFGQGTKLEIK (SEQ
 ID NO: 38). The hyper variable regions (HVRs) of V κ 4 are depicted in bolded and underlined text.

The antibody may comprise a light chain variable domain amino acid sequence that is at least 85%, 90%, or 95% identical to SEQ ID NO:35-38 while retaining the
 15 HVR-L1 RASKSINKYLA (SEQ ID NO:5), the HVR-L2 SGSTLQS (SEQ ID NO:6), and the HVR-L3 QQHNEYPLT (SEQ ID NO:7). The antibody may comprise a heavy chain variable domain amino acid sequence that is at least 85%, 90%, or 95% identical to SEQ ID NO:31-34 while retaining the HVR-H1 GYHFTSYWMH (SEQ ID NO:9), the HVR-H2 VIHPNSGSINYNEKFES (SEQ ID NO:10), and the HVR-H3 ERDSTEVLPMDDY
 20 (SEQ ID NO:11).

In some embodiments, the antibody comprises a light chain variable domain amino acid sequence of SEQ ID NO: 35 and a heavy chain variable domain amino acid sequence of SEQ ID NO: 31. In some embodiments, the antibody comprises a light chain variable domain amino acid sequence of SEQ ID NO: 36 and a heavy chain variable
 25 domain amino acid sequence of SEQ ID NO: 32. In some embodiments, the antibody comprises a light chain variable domain amino acid sequence of SEQ ID NO: 37 and a heavy chain variable domain amino acid sequence of SEQ ID NO: 33. In some embodiments, the antibody comprises a light chain variable domain amino acid sequence of SEQ ID NO: 38 and a heavy chain variable domain amino acid sequence of SEQ ID
 30 NO: 34.

The full-length antibody Mab2 comprises the heavy chain variable domain variant 3 (VH3)(SEQ ID NO: 33) and the kappa light chain variable domain variant 3 (Vk3) (SEQ ID NO: 37). The Mab2-Fab is the Fab of the Mab2 antibody.

In some embodiments, humanized anti-C1q antibodies of the present disclosure include a heavy chain variable region that contains an Fab region and a heavy chain constant regions that contains an Fc region, where the Fab region specifically binds to a C1q protein of the present disclosure, but the Fc region is incapable of binding the C1q protein. In some embodiments, the Fc region is from a human IgG1, IgG2, IgG3, or IgG4 isotype. In some embodiments, the Fc region is incapable of inducing complement activity and/or incapable of inducing antibody-dependent cellular cytotoxicity (ADCC). In some embodiments, the Fc region comprises one or more modifications, including, without limitation, amino acid substitutions. In certain embodiments, the Fc region of humanized anti-C1q antibodies of the present disclosure comprise an amino acid substitution at position 248 according to Kabat numbering convention or a position corresponding to position 248 according to Kabat numbering convention, and/or at position 241 according to Kabat numbering convention or a position corresponding to position 241 according to Kabat numbering convention. In some embodiments, the amino acid substitution at position 248 or a positions corresponding to position 248 inhibits the Fc region from interacting with an Fc receptor. In some embodiments, the amino acid substitution at position 248 or a positions corresponding to position 248 is a leucine to glutamate amino acid substitution. In some embodiments, the amino acid substitution at position 241 or a positions corresponding to position 241 prevents arm switching in the antibody. In some embodiments, the amino acid substitution at position 241 or a positions corresponding to position 241 is a serine to proline amino acid substitution. In certain embodiments, the Fc region of humanized anti-C1q antibodies of the present disclosure comprises the amino acid sequence of SEQ ID NO: 47, or an amino acid sequence with at least about 70%, at least about 75%, at least about 80% at least about 85% at least about 90%, or at least about 95% homology to the amino acid sequence of SEQ ID NO: 47.

Anti-C1q Fab Fragment (e.g., FabA)

Before the advent of recombinant DNA technology, proteolytic enzymes (proteases) that cleave polypeptide sequences have been used to dissect the structure of antibody molecules and to determine which parts of the molecule are responsible for its various functions. Limited digestion with the protease papain cleaves antibody molecules into three fragments. Two fragments, known as Fab fragments, are identical and contain the antigen-binding activity. The Fab fragments correspond to the two identical arms of the antibody molecule, each of which consists of a complete light chain paired with the V_H and C_{H1} domains of a heavy chain. The other fragment contains no antigen binding activity but was originally observed to crystallize readily, and for this reason was named the Fc fragment (Fragment crystallizable). When Fab molecules were compared to IgG molecules, it was found that Fab are superior to IgG for certain *in vivo* applications due to their higher mobility and tissue penetration capability, their reduced circulatory half-life, their ability to bind antigen monovalently without mediating antibody effector functions, and their lower immunogenicity.

The Fab molecule is an artificial ~50-kDa fragment of the Ig molecule with a heavy chain shortened by constant domains C_{H2} and C_{H3}. Two heterophilic (V_L-V_H and C_L-C_{H1}) domain interactions underlie the two-chain structure of the Fab molecule, which is further stabilized by a disulfide bridge between C_L and C_{H1}. Fab and IgG have identical antigen binding sites formed by six complementarity-determining regions (CDRs), three each from V_L and V_H (LCDR1, LCDR2, LCDR3 and HCDR1, HCDR2, HCDR3). The CDRs define the hypervariable antigen binding site of antibodies. The highest sequence variation is found in LCDR3 and HCDR3, which in natural immune systems are generated by the rearrangement of *V_L* and *J_L* genes or *V_H*, *D_H* and *J_H* genes, respectively. LCDR3 and HCDR3 typically form the core of the antigen binding site. The conserved regions that connect and display the six CDRs are referred to as framework regions. In the three-dimensional structure of the variable domain, the framework regions form a sandwich of two opposing antiparallel β -sheets that are linked by hypervariable CDR loops on the outside and by a conserved disulfide bridge on the inside. This unique combination of stability and versatility of the antigen binding site of Fab and IgG underlie its success in clinical practice for the diagnosis, monitoring, prevention, and treatment of disease.

All anti-C1q antibody Fab fragment sequences are incorporated by reference from U.S. Pat. App. No. 15/360,549, which is hereby incorporated by reference for the antibodies and related compositions that it discloses.

In certain embodiments, the present disclosure provides an anti-C1q antibody Fab fragment that binds to a C1q protein comprising a heavy (V_H/C_H1) and light chain (V_L/C_L), wherein the anti-C1q antibody Fab fragment has six complementarity determining regions (CDRs), three each from V_L and V_H (HCDR1, HCDR2, HCDR3, and LCDR1, LCDR2, LCDR3). The heavy chain of the antibody Fab fragment is truncated after the first heavy chain domain of IgG1 (SEQ ID NO: 39), and comprises the following amino acid sequence:

QVQLVQSGAELKKPGASVKVSCKSS**GYHFTSYWMH**WVKQAPGQGLEWIG
VIHPNSGSINYNEKFESRVITITVDKSTSTAYMELSSLRSEDTAVYYCAG**ERDS**
TEVLPMDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
 PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN
 HKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 39)

The complementarity determining regions (CDRs) of SEQ ID NO:39 are depicted in bolded and underlined text.

The light chain domain of the antibody Fab fragment comprises the following amino acid sequence (SEQ ID NO: 40):

DVQITQSPSSLSASLGERATINC**RASKSINKYLA**WYQQKPGKAPKLLIY**SGST**
LQSGIPARFSGSGSGTDFLTISSELPEDFAMYYC**QOHNEYPLT**FGQGTKLEIK
 RTVAAPSVFIFPPSDEQLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNS
 QESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
 EC (SEQ ID NO: 40)

The complementarity determining regions (CDRs) of SEQ ID NO:40 are depicted in bolded and underlined text.

The FabA is an anti-C1q antibody Fab fragment comprising the heavy chain domain comprising SEQ ID NO: 39 and the light chain domain comprising SEQ ID NO: 40.

The Mab1-Fab is the Fab of the Mab1 (M1) antibody.

The Mab2-Fab is the Fab of the Mab2 antibody.

The Mab3-Fab is the Fab of the Mab3 antibody.

Nucleic acids, vectors and host cells

Antibodies suitable for use in the methods of the present disclosure may be produced using recombinant methods and compositions, *e.g.*, as described in U.S. Patent No. 4,816,567. In some embodiments, isolated nucleic acids having a nucleotide
5 sequence encoding any of the antibodies of the present disclosure are provided. Such nucleic acids may encode an amino acid sequence containing the V_L/C_L and/or an amino acid sequence containing the V_H/C_{H1} of the anti-C1q antibody. In some embodiments, one or more vectors (*e.g.*, expression vectors) containing such nucleic acids are provided. A host cell containing such nucleic acid may also be provided. The host cell may contain
10 (*e.g.*, has been transduced with): (1) a vector containing a nucleic acid that encodes an amino acid sequence containing the V_L/C_L of the antibody and an amino acid sequence containing the V_H/C_{H1} of the antibody, or (2) a first vector containing a nucleic acid that encodes an amino acid sequence containing the V_L/C_L of the antibody and a second vector containing a nucleic acid that encodes an amino acid sequence containing the
15 V_H/C_{H1} of the antibody. In some embodiments, the host cell is eukaryotic, *e.g.*, a Chinese Hamster Ovary (CHO) cell or lymphoid cell (*e.g.*, YO, NS0, Sp20 cell). In some embodiments, the host cell is a bacterium such as *E. coli*.

Methods of making an anti-C1q antibody are disclosed herein. The method includes culturing a host cell of the present disclosure containing a nucleic acid encoding
20 the anti-C1q antibody, under conditions suitable for expression of the antibody. In some embodiments, the antibody is subsequently recovered from the host cell (or host cell culture medium).

For recombinant production of a humanized anti-C1q antibody of the present disclosure, a nucleic acid encoding the antibody is isolated and inserted into one or more
25 vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

Suitable vectors containing a nucleic acid sequence encoding any of the
30 antibodies of the present disclosure, or fragments thereof polypeptides (including antibodies) described herein include, without limitation, cloning vectors and expression vectors. Suitable cloning vectors can be constructed according to standard techniques, or

may be selected from a large number of cloning vectors available in the art. While the cloning vector selected may vary according to the host cell intended to be used, useful cloning vectors generally have the ability to self-replicate, may possess a single target for a particular restriction endonuclease, and/or may carry genes for a marker that can be used in selecting clones containing the vector. Suitable examples include plasmids and bacterial viruses, *e.g.*, pUC18, pUC19, Bluescript (*e.g.*, pBS SK+) and its derivatives, mpl8, mpl9, pBR322, pMB9, ColE1, pCR1, RP4, phage DNAs, and shuttle vectors such as pSA3 and pAT28. These and many other cloning vectors are available from commercial vendors such as BioRad, Stratagene, and Invitrogen.

The vectors containing the nucleic acids of interest can be introduced into the host cell by any of a number of appropriate means, including electroporation, transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (*e.g.*, where the vector is an infectious agent such as vaccinia virus). The choice of introducing vectors or polynucleotides will often depend on features of the host cell. In some embodiments, the vector contains a nucleic acid containing one or more amino acid sequences encoding an anti-C1q antibody of the present disclosure.

Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells. For example, an anti-C1q antibody of the present disclosure may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria (*e.g.*, U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523; and Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*). In other embodiments, the antibody of the present disclosure may be produced in eukaryotic cells, *e.g.*, a Chinese Hamster Ovary (CHO) cell or lymphoid cell (*e.g.*, Y0, NS0, Sp20 cell) (*e.g.*, U.S. Pat. App. No. 14/269,950, U.S. Pat. No. 8,981,071, *Eur J Biochem.* 1991 Jan 1;195(1):235-42). After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

Pharmaceutical Compositions and Administration

The anti-C1q antibody (*e.g.*, FabA) of the present disclosure may be administered in the form of pharmaceutical compositions.

Therapeutic formulations of an antibody, antibody fragments and/or antibody derivatives of the disclosure may be prepared for storage by mixing the antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. [1980]), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

Lipofections or liposomes may also be used to deliver an antibody or antibody fragment, or antibody derivative into a cell, wherein the epitope or smallest fragment which specifically binds to the binding domain of the target protein is preferred.

The antibody may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

The formulations to be used for administration may be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods.

The antibodies, antibody fragments and/or antibody derivatives and compositions of the present disclosure are typically administered by an intravitreal administration.

Pharmaceutical compositions may also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers of diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, buffered water, physiological saline, PBS, Ringer's solution, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may include other carriers, adjuvants, or non-toxic, nontherapeutic, non-immunogenic stabilizers, excipients and the like. The compositions may also include additional substances to approximate physiological conditions, such as pH adjusting and buffering agents, toxicity adjusting agents, wetting agents and detergents.

The composition may also include any of a variety of stabilizing agents, such as an antioxidant for example. When the pharmaceutical composition includes a polypeptide, the polypeptide may be complexed with various well-known compounds that enhance the *in vivo* stability of the polypeptide, or otherwise enhance its pharmacological properties (*e.g.*, increase the half-life of the polypeptide, reduce its toxicity, enhance other pharmacokinetic and/or pharmacodynamic characteristics, or enhance solubility or uptake). Examples of such modifications or complexing agents include sulfate, gluconate, citrate and phosphate. The polypeptides of a composition may also be complexed with

molecules that enhance their in vivo attributes. Such molecules include, for example, carbohydrates, polyamines, amino acids, other peptides, ions (*e.g.*, sodium, potassium, calcium, magnesium, manganese), and lipids. Further guidance regarding formulations that are suitable for various types of administration may be found in Remington's

- 5 Pharmaceutical Sciences, Mace Publishing Company, Philadelphia, Pa., 17th ed. (1985). For a brief review of methods for drug delivery, see, Langer, *Science* 249:1527-1533 (1990).

10 Toxicity and therapeutic efficacy of the active ingredient may be determined according to standard pharmaceutical procedures in cell cultures and/or experimental animals, including, for example, determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it may be expressed as the ratio LD₅₀/ED₅₀. Compounds that exhibit large therapeutic indices are preferred.

15 The data obtained from cell culture and/or animal studies and/or human clinical trials may be used in formulating a range of dosages for humans. The dosage of the active ingredient typically lies within a range of circulating concentrations that include the ED₅₀ with low toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

20 The components used to formulate the pharmaceutical compositions are preferably of high purity and are substantially free of potentially harmful contaminants (*e.g.*, at least National Food (NF) grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Moreover, compositions intended for parenteral use are usually sterile. To the extent that a given compound must be synthesized prior to
25 use, the resulting product is typically substantially free of any potentially toxic agents, particularly any endotoxins, which may be present during the synthesis or purification process. Compositions for parental administration are also typically substantially isotonic and made under GMP conditions.

30 The compositions of the disclosure may be administered using any medically appropriate procedure, *e.g.*, intravitreal injection.

Methods of Treatment

The role of complement in photoreceptor retinal diseases has been reported in multiple preclinical models of photoreceptor degeneration, where genetic or pharmacological inhibition of classical complement pathway resulted in increased photoreceptor survival and improved retinal function. However, the mechanisms through which C1q and classical complement pathway are driving photoreceptor degeneration is not well understood. Based on the described role of C1q in microglia mediated synaptic pruning in CNS development and disease, C1q may tag photoreceptor synapses in retinal degenerative disorders, contributing to neuronal loss via aberrant microglia mediated synapse elimination.

Using a photo-oxidative light damage model of photoreceptor degeneration, provided herein is evidence of C1q deposition on photoreceptor synapses and microglia engulfment of C1q tagged synapses. Significant correlation is shown between levels of C1q in the retina and photoreceptor synapse and cell body loss. Further, externalization of the C1q substrate, phosphatidylserine (PS), is shown on photoreceptor synapses, suggesting potential involvement of PS in C1q recruitment onto synapses. And finally, intravitreal treatment with anti-C1q antibody decreased levels of complement components in light damaged retina (confirm target engagement and neuroprotection following treatment).

Increased levels of classical complement component C1q were confirmed in retina lysates from both untreated and IgG Rd10 animals, compared to WT (Figure 14B). Anti-C1q treatment resulted in reduced C1q levels in retina lysates compared to IgG1-treated and untreated rd10 groups (Figure 14B), confirming good measurable PK and C1q engagement in retina. Photoreceptor synapses (BNS marker) were preserved upon treatment with a C1q inhibitor (Figure 15B).

The present disclosure is generally directed to compositions and methods of preventing, reducing risk of developing, or treating an inherited retinal disease (IRD) (e.g., retinitis pigmentosa, choroideremia, Stargardt disease, cone-rod dystrophy, and leber congenital amaurosis) or retinal detachment in a human patient.

Inherited retinal diseases (IRDs) are a group of diseases that can cause severe vision loss or even blindness. Each IRD is caused by at least one gene that is not working as it should. IRDs can affect individuals of all ages, can progress at different rates, and

are rare. However, many are progressive, which means that the symptoms of the disease will get worse over time.

There are many types of IRDs identified and others yet to be discovered. The most common types of IRDs include: retinitis pigmentosa/rod-cone dystrophy, choroideremia, Stargardt disease, cone-rod dystrophy, leber congenital amaurosis, X-linked RP, and Usher Syndrome. The common pathway is photoreceptor degeneration.

Retinitis pigmentosa (RP)/rod-cone dystrophy is a group of related eye disorders caused by variations in 60 genes that affect the retina. In people with RP, vision loss occurs as the light-sensing cells of the retina gradually die off. The severity and how fast the disease progresses can vary from person to person with RP, depending on the gene affected. RP can first appear during childhood (early onset RP) or during adulthood. The first sign of RP is usually loss of night vision, called night blindness. Later, RP causes blind spots to develop in the peripheral (side) vision. Over time, these blind spots progress to reduced peripheral vision. The disease progresses over time to eventually affect central vision – also called tunnel vision, necessary for tasks such as reading, driving, and recognizing faces. Choroideremia is a condition with progressive vision loss, mostly affecting males. The first symptom of this condition is usually night blindness, which can occur in early childhood. Over time, a person will develop tunnel vision and lose the ability to see details. These vision problems are due to an ongoing loss of cells in the retina and the nearby network of blood vessels (called the choroid). The vision impairment in choroideremia worsens over time, but the rate of worsening varies among affected individuals. This condition may cause complete loss of vision by late adulthood.

Stargardt disease is also called Stargardt macular dystrophy. The disease causes damage to the macula, a small area in the center of the retina that is responsible for sharp, straight-ahead vision. The disease typically causes central vision loss during childhood or adolescence. Sometimes, vision loss may not be noticed until later in adulthood. Only rarely do people with the disease lose all vision.

Cone-rod dystrophy (CRD) is a group of more than 30 IRDs that affect the cones and rods. Cones and rods are the light sensitive cells found in the retina. With progressive deterioration of the cones and rods, people with this condition experience vision loss over time. The first symptoms usually occur in childhood, and may include blurred vision and an intense sensitivity to light (called photophobia). These symptoms are followed by

blind spots in the center of vision, loss of the ability to see color, and loss of side or peripheral vision. Most individuals with this condition lose a significant amount of vision by mid-adulthood.

Leber Congenital Amaurosis (LCA) is an eye disorder that primarily affects the retina. The retina is the layer of the eye that acts like the film in the camera, capturing a visual image and sending electrical signals to the brain. LCA is one of the earliest onset forms of an IRD. People with this disorder typically have severe visual impairment beginning in infancy. LCA is also associated with other vision problems, such as Photophobia: Increased sensitivity to light; Nystagmus: Uncontrollable movements of the eyes; Extreme Farsightedness: An inability to clearly see objects up close, such as a book or watch face; Slow reacting pupils: The pupils do not react normally to light for individuals with LCA, instead, the pupils open and close more slowly than normal, or they may not respond to light at all; Misshaped corneas: The cornea may be cone-shaped and unusually thin with LCA; and Crossed eye (strabismus): The muscles of the eye do not form or work properly, causing the eyes to look in two different place at the same time.

X-linked RP (XLRP) is a severe form of retinitis pigmentosa (RP). XLRP is associated with mutations in genes located on the X chromosome, which means the condition predominantly affects males. However, some female carriers may also be clinically affected, although usually with a much less severe phenotype than males. The variability in phenotypes among female carriers is attributed to the pattern of random inactivation of the X chromosome carrying the wild-type gene during development of retinal tissue, moderated by other genetic and environmental factors. XLRP is most commonly caused by mutations in the Retinitis Pigmentosa GTPase Regulator (RPGR) gene on the X chromosome. It is characterized by early onset and rapid progression of vision loss, resulting in legal blindness by the end of the third decade. Less frequent forms of XLRP are caused by mutations in *RP2* gene and *OFD1* gene. Mutations in the *RPGR* gene can be associated with a rod-cone or cone-rod dystrophy phenotype. The majority of cases present with a rod-cone dystrophy-type disease progression, where central visual acuity is initially less impaired than the peripheral field loss. However, some also present with early cone involvement and correspondingly impaired central visual acuity during early stages of the disease. The fovea is ultimately affected in all

cases during the late stages of the disease by subsequent cone photoreceptor degeneration.

Usher syndrome, also known as Hallgren syndrome, Usher–Hallgren syndrome, retinitis pigmentosa–dysacusis syndrome or dystrophia retinae dysacusis syndrome, is a rare genetic disorder caused by a mutation in any one of at least 11 genes resulting in a combination of hearing loss and visual impairment. It is a major cause of deaf-blindness and is at present incurable. It causes deafness or hearing loss and an eye disease called retinitis pigmentosa (RP). Sometimes, it also causes problems with balance. Usher syndrome is classed into three subtypes (I, II and III) according to the genes responsible and the onset of deafness. All three subtypes are caused by mutations in genes involved in the function of the inner ear and retina. These mutations are inherited in an autosomal recessive pattern.

Retinal detachment describes a situation in which a thin layer of neuro tissue (the retina) at the back of the eye pulls away from its normal position. Retinal detachment separates the retinal photoreceptor cells from the retinal pigment epithelium (RPE), which provides oxygen and nourishment and removal of waste products. At the moment, the retina is separated from the RPE, there is photoreceptor degeneration and resulting vision loss. If the central retina is detached, and the longer the retinal detachment goes untreated, the greater the risk of permanent vision loss in the affected eye. Warning signs of retinal detachment may include one or all of the following: the sudden appearance of floaters and flashes and reduced vision. Retinal detachment occurs about 10-12 cases per 100,000 annually. In about 50% of cases, the central retina detaches. When the central retina detaches, the recovery of visual acuity only reaches about 50% of pre-detachment acuity, despite success in re-attaching the retina. The cause of this limited visual recovery is photoreceptor degeneration.

Genetic or pharmacological inhibition of classical complement pathway resulted in increased photoreceptor survival and improved retinal function. However, the mechanisms through which C1q and classical complement pathway are driving photoreceptor degeneration is not well understood. Based on the described role of C1q in microglia mediated synaptic pruning in CNS development and disease, we hypothesize three mechanisms of damage to the photoreceptors mediated by C1q: (1) C1q tags photoreceptor synapses in retinal degenerative disorders, contributing to neuronal loss via

aberrant microglia mediated synapse elimination; (2) C1q is activated by the waste products of damage photoreceptors (phosphatidyl serine, c-reactive protein, as well as altered photoreceptor cell membranes) leading to damage from recruitment of phagocytic cells which also bring in additional C1q, and (3) activation of the entire classical complement pathway and formation of the membrane-attack-complexes (MAC's) causing cell lysis.

C1q recognizes certain pathogens, modifications of self-antigens, antigen-bound antibodies, or specific molecules on the surface of cells. In normal aging, C1q accumulates on synapses – perhaps those weakened by age or neuronal stress – and following various pathophysiological stimuli can trigger activation of the classical complement cascade, leading to the inappropriate elimination of synapses. This aberrant inflammatory response, associated with synapse removal, is termed complement-mediated neurodegeneration (CMND). CMND has been implicated in Alzheimer's disease, schizophrenia, Huntington's disease, frontotemporal dementia, spinal muscular atrophy and glaucoma. With degenerative stress in the retina, C1q activation leads to synapse elimination and contributes to the loss of RGC's and the optic nerve.

Using a photo-oxidative light damage model of photoreceptor degeneration, we provide evidence of C1q deposition on photoreceptor synapses and demonstrate microglia engulfment of C1q tagged synapses. We show significant correlation between levels of C1q in the retina and photoreceptor synapse and cell body loss. We also show externalization of the C1q substrate, phosphatidylserine (PS), on photoreceptor synapses, suggesting potential involvement of PS in C1q recruitment onto synapses. And finally, we show intravitreal treatment with anti-C1q antibody decreased levels of complement components in light damaged retina. Additionally, we confirmed C1q deposition on photoreceptor synapses in human geographic atrophy retina tissue, suggesting that this mechanism is relevant in humans.

The present disclosure is generally directed to compositions and methods of preventing, reducing risk of developing, or treating an inherited retinal disease (IRD) (e.g., retinitis pigmentosa, choroideremia, Stargardt disease, cone-rod dystrophy, and leber congenital amaurosis) or retinal detachment in a human patient.

Such methods include administering to the patient a composition comprising about 1 mg to about 10 mg (e.g., about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 6.5 mg, about 7 mg, about 7.5 mg, about 8 mg, about 8.5 mg, about 9 mg, about 9.5 mg, or about 10 mg of the anti-C1q antibody) of an anti-C1q antibody via an intravitreal injection. Such methods also include administering to the patient a composition comprising about 1 mg to about 10 mg (e.g., about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 6.5 mg, about 7 mg, about 7.5 mg, about 8 mg, about 8.5 mg, about 9 mg, about 9.5 mg, or about 10 mg of the anti-C1q antibody) of an anti-C1q antibody via an intravitreal injection, wherein the antibody comprises a light chain variable domain comprising an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7; and a heavy chain variable domain comprising an HVR-H1 having the amino acid sequence of SEQ ID NO: 9, an HVR-H2 having the amino acid of SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11. The administered composition may comprise about 1 mg to about 5 mg of the anti-C1q antibody. The administered composition may comprise about 1 mg to about 2.5 mg, about 2.5 mg to about 5 mg, about 5 mg to about 7.5 mg, or about 7.5 mg to about 10 mg of the anti-C1q antibody. The administered composition may comprise about 5 mg of the anti-C1q antibody. The administered composition may comprise about 10 mg of the anti-C1q antibody. In some embodiments, the antibody comprises a light chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected from SEQ ID NO: 4 and 35-38 and wherein the light chain variable domain comprises an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7. In some embodiments, the light chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 4 and 35-38. In some embodiments, the antibody comprises a heavy chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected from SEQ ID NO: 8 and 31-34 and wherein the heavy chain variable domain comprises an HVR-H1 having the amino acid sequence of SEQ ID NO: 9, an HVR-H2

having the amino acid of SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11. In some embodiments, the heavy chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 8 and 31-34. In some embodiments, the antibody comprises a light chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected from SEQ ID NO: 4 and 35-38, and wherein the light chain variable domain comprises an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7, and a heavy chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected from SEQ ID NO: 8 and 31-34 and wherein the heavy chain variable domain comprises an HVR-H1 having the amino acid sequence of SEQ ID NO: 9, an HVR-H2 having the amino acid of SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11. In some embodiments, the antibody comprises a light chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 4 and 35-38, and a heavy chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 8 and 31-34. In some embodiments, the antibody may be a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody, an antibody fragment, or antibody derivative thereof. The antibody fragment may be a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a diabody, or a single chain antibody molecule. In some embodiments, the Fab fragment comprises a heavy chain Fab fragment of SEQ ID NO: 39 and a light chain Fab fragment of SEQ ID NO: 40.

In some embodiments, the antibody is administered once a week, once every other week, once every three weeks, once a month, once every 4 weeks, once every six weeks, once every 8 weeks, once every other month, once every 10 weeks, once every 12 weeks, once every three months, or once every 4 months. In some embodiments, the antibody is administered for at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, or at least 12 months.

In certain preferred embodiments, FabA is administered at a dose of 2.5 mg/eye once every month, once every 4 weeks, once every 6 weeks, or once every other month as an IVT injection.

In certain preferred embodiments, FabA is administered at a dose of 5 mg/eye once every month, once every 4 weeks, once every 6 weeks, or every other month as an

IVT injection. In certain preferred embodiments, FabA is administered at a dose of 5 mg/eye once every month or once every 4 weeks as an IVT injection. In certain preferred embodiments, FabA is administered at a dose of 5 mg/eye once every 6 weeks as an IVT injection. In certain preferred embodiments, FabA is administered at a dose of 5 mg/eye
5 once every other month or once every 8 weeks as an IVT injection.

In certain preferred embodiments, FabA is administered at a dose of 10 mg/eye once every month, once every 4 weeks, once every 6 weeks, or every other month as an IVT injection. In certain preferred embodiments, FabA is administered at a dose of 10 mg/eye once every month or once every 4 weeks as an IVT injection. In certain preferred
10 embodiments, FabA is administered at a dose of 10 mg/eye once every 6 weeks as an IVT injection. In certain preferred embodiments, FabA is administered at a dose of 10 mg/eye once every other month or once every 8 weeks as an IVT injection.

Injection of FabA is completed by a physician qualified by training and
15 experience to perform IVT injections, using aseptic technique.

The anti-C1q antibody may inhibit the interaction between C1q and an autoantibody or between C1q and C1r, or between C1q and C1s, or may promote clearance of C1q from circulation or a tissue. In some embodiments, the anti-C1q antibody has a dissociation constant (K_D) that ranges from 100 nM to 0.005 nM or less
20 than 0.005 nM. In some embodiments, the anti-C1q antibody binds C1q with a binding stoichiometry that ranges from 20:1 to 1.0:1 or less than 1.0:1, a binding stoichiometry that ranges from 6:1 to 1.0:1 or less than 1.0:1, or a binding stoichiometry that ranges from 2.5:1 to 1.0:1 or less than 1.0:1.

The methods inhibit a biological activity of C1q. For example, (1) C1q binding to an autoantibody, (2) C1q binding to C1r, (3) C1q binding to C1s, (4) C1q binding to
25 phosphatidylserine, (5) C1q binding to pentraxin-3, (6) C1q binding to C-reactive protein (CRP), (7) C1q binding to globular C1q receptor (gC1qR), (8) C1q binding to complement receptor 1 (CR1), (9) C1q binding to B-amyloid, or (10) C1q binding to calreticulin. In other embodiments, the biological activity of C1q is (1) activation of the
30 classical complement activation pathway, (2) reduction in lysis and/or reduction in C3 deposition, (3) activation of antibody and complement dependent cytotoxicity, (4) CH50 hemolysis, (5) a reduction in red blood cell lysis, (6) a reduction in red blood cell

phagocytosis, (7) a reduction in dendritic cell infiltration, (8) inhibition of complement-mediated red blood cell lysis, (9) a reduction in lymphocyte infiltration, (10) a reduction in macrophage infiltration, (11) a reduction in antibody deposition, (12) a reduction in neutrophil infiltration, (13) a reduction in platelet phagocytosis, (14) a reduction in platelet lysis, (15) an improvement in transplant graft survival, (16) a reduction in macrophage mediated phagocytosis, (17) a reduction in autoantibody mediated complement activation, (18) a reduction in red blood cell destruction due to transfusion reactions, (19) a reduction in red blood cell lysis due to alloantibodies, (20) a reduction in hemolysis due to transfusion reactions, (21) a reduction in alloantibody mediated platelet lysis, (22) an improvement in anemia, (23) a reduction in eosinophilia, (24) a reduction in C3 deposition on red blood cells (*e.g.*, a reduction of deposition of C3b, iC3b, etc., on RBCs), (25) a reduction in C3 deposition on platelets (*e.g.*, a reduction of deposition of C3b, iC3b, etc., on platelets), (26) reduction in anaphylatoxin production, (27) a reduction in autoantibody mediated blister formation, (28) a reduction in autoantibody induced erythematosis, (29) a reduction in red blood cell destruction due to transfusion reactions, (30) a reduction in platelet lysis due to transfusion reactions, (31) a reduction in mast cell activation, (32) a reduction in mast cell histamine release, (33) a reduction in vascular permeability, (34) a reduction in complement deposition on transplant graft endothelium, (35) B-cell antibody production, (36) dendritic cell maturation, (37) T-cell proliferation, (38) cytokine production, (39) microglia activation, (40) Arthus reaction, (41) a reduction of anaphylatoxin generation in transplant graft endothelium, or (42) activation of complement receptor 3 (CR3/C3) expressing cells.

In some embodiments, CH50 hemolysis comprises human CH50 hemolysis. The antibody may be capable of neutralizing from at least about 50%, to about 100% of human CH50 hemolysis. The antibody may be capable of neutralizing about 50%, about 60%, about 70%, about 80%, about 90%, about 100% of human CH50 hemolysis. The antibody may be capable of neutralizing at least 50% of CH50 hemolysis at a dose of less than 150 ng/ml, less than 100 ng/ml, less than 50 ng/ml, or less than 20 ng/ml.

In some embodiments, the antibody is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody, a human antibody, a chimeric antibody, a monovalent antibody, a multispecific antibody, or an antibody fragment, or antibody derivative thereof. In some embodiments, the antibody is humanized antibody.

In some embodiments, the antibody is antibody fragment, such as, a Fab fragment. Examples of an antibody fragment are a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a diabody, and a single chain antibody molecule.

It is contemplated that compositions may be obtained and used under the guidance of a physician for *in vivo* use. The dosage of the therapeutic formulation may vary widely, depending upon the nature of the disease, the frequency of administration, the manner of administration, the clearance of the agent from the host, and the like.

As used herein, “chronically administered,” “chronic treatment,” “treating chronically,” or similar grammatical variations thereof refer to a treatment regimen that is employed to maintain a certain threshold concentration of a therapeutic agent in the eye of a patient in order to completely or substantially suppress systemic complement activity in the patient over a prolonged period of time. Accordingly, a patient chronically treated with anti-C1q antibody may be treated for a period of time that is greater than or equal to 2 weeks (*e.g.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months; or 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, or 12 years or for the remainder of the patient's life) with the antibody in an amount and with a dosing frequency that are sufficient to maintain a concentration of the antibody in the patient's eye that inhibits or substantially inhibits systemic complement activity in the patient. In some embodiments, the antibody may be chronically administered to a patient in need thereof in an amount and with a frequency that are effective to maintain serum hemolytic activity at less than or equal to 20% (*e.g.*, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or even below 5%). In some embodiments, the antibody may be administered to a patient in an amount and with a frequency that are effective to maintain serum lactate dehydrogenase (LDH) levels at within at least 20% (*e.g.*, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or even below 5%) the normal range for LDH.

Therapeutic agents, *e.g.*, anti-C1q antibodies, can be incorporated into a variety of formulations for therapeutic administration by combination with appropriate pharmaceutically acceptable carriers or diluents.

EXAMPLES

Example 1: Methods

Photo-oxidative white light damage model

Male Balb/C mice (12 weeks of age; Charles River Laboratories) were used in the study described in Examples 2-7. Animals were dark adapted overnight for the experiment with a single extension of their darker period of 3-4 h until the start of light induction (acute: 25k lux for 4h; mild: 5k Lux for 30 min). Acute light settings were used for model characterization (Results Figure 1). Mild light settings were used for all other experiments (Results Figures 2-5). Animals were sacrificed and tissue collected at baseline, day 1, day 3 and day 7.

Rd10 mouse model

Rd10 mice were dark-reared from birth and transferred to housing in a light-controlled environment (normal cyclic light ~200 lux during daylight hours) at P30-P31.

Anti-C1q antibody treatment (or IgG control antibody) was administered intraperitoneally (i.p) twice a week at a dose of 100mg/kg starting at P12. For i.p injection, mice were gently restrained by hand, and an 8 mm, 31-Gauge needle was used to puncture the abdomen to deliver the antibody. Animals were sacrificed and tissue collected at P30, P33, P38.

Terminal Plasma and Ocular Tissue Collection

Animals were anesthetized and ~300-500 µl of terminal whole blood was collected via cardiac puncture. The blood was immediately placed in a K₂EDTA tube and centrifuged at 5,000 x g for 10 minutes to obtain plasma. The plasma was transferred to a 1.7 mL snap-cap tube and stored at -80°C until shipment to the client on dry ice. For biochemical assessment, animals were transcardially perfused with saline, and eyes were enucleated. Retina/RPE was isolated, weighed, snap frozen and stored at -80 °C. For histopathological assessment, animals were transcardially perfused with saline, followed by 4% PFA (min. 10 min/ min. 50 ml). After saline/PFA perfusion, eyes were collected. Posterior eye cups were drop fixed in 4% PFA for 2hs, transferred through serial sucrose gradient (10%, 20% 30%), embedded in optimal cutting temperature compound (OCT) and frozen.

Intravitreal injection

Animals were sedated by isoflurane. Under a surgical microscope, eyes were injected with a 32G needle inserted into the mid vitreous. For PSVue labelling, 2 µl of 1 mM PSVue were injected in to eye 6h prior to tissue collection. Contralateral eye was

used as uninjected control. For anti C1q treatment, 1 μ L of an optimized murine anti-C1q antibody (Mab3, optimized from Mab1) or IgG1 MOPC control antibody (7.5 μ g/ μ L) was injected bilaterally one day prior light exposure, with tissue collection performed at baseline, day3 and day 5.

5 ELISA

Animals were transcardially perfused with saline and eyes were enucleated. Retina/RPE was isolated, weighed, snap frozen and stored at -80 °C. Frozen tissue was homogenized using a pestle motor in lysis buffer (25 mM Hepes, 0.1M NaCl, 1% Triton X100, complete protease inhibitor cocktail; or 10mM EDTA and Thermo Scientific #A32965 in Tris buffered saline). Protein was quantified using the Micro BCA Assay Kit (Thermo Scientific #23235). Complement signature was determined using standard sandwich ELISA assay. Briefly, black 96 well ELISA plates (Costar #3925) were coated with 75 μ L of 10 μ g/mL of capture antibody in bicarbonate buffer (pH 9.4) overnight at 4°C. Next day, the plates were washed with dPBS (pH 7.4) and blocked with dPBS buffer containing 3% bovine serum albumin (BSA, VWR #28382). Standards and samples were prepared in assay buffer (dPBS containing 0.3% BSA, 0.1% tween and 0.05% EDTA) and added to the plate (75 μ L per well) after removal of blocking solution. Plates were incubated shaking at 300 rpm overnight at 4°C. The next day, plates were washed three times with wash buffer (dPBS containing 0.05% Tween), incubated with detection antibodies (75 μ L per well) for 1 hr shaking at room temperature. After incubation, plates were washed three times with wash buffer, developed by adding alkaline phosphatase substrate (Life Technologies, T2214) and read using a luminometer. For PK assay, mouse C1q (M099, Complement Tech) and AP-conjugated anti-mouse antibody (115-055-071, Jackson ImmunoResearch) were used as capture and detection antibodies, respectively. For C1q assay, in house capture antibody (JL1 clone, Atum) and detection antibody (M1-AP, Antibody Solutions 1:3000) were used. C1s assay was performed using anti-mouse C1s (LSBio, 2 μ g/ml) and anti-mouse C1s-AP (LSBio, 1:5000) as capture and detection antibody, respectively. C3d assay was performed using anti-human C3d (Dako, 1 μ g/ml) and anti-mouse C3 (11H9 clone, Abcam, 1:1000) as capture and detection antibody, respectively. Albumin assay was performed with a kit (Abcam, ab108792). Standards were fit using a 4PL logistic fit and unknowns converted to concentration, corrected for dilution, and then plotted using GraphPad Prism.

Immunohistochemistry

Animals were transcardially perfused with saline, followed by 4% PFA (min. 10 min/ min. 50 ml). After saline/PFA perfusion, eyes were collected. Posterior eye cups were drop fixed in 4% PFA for 2hs, transferred through serial sucrose gradient (10%, 20% 30%), embedded in optimal cutting temperature compound (OCT) and frozen.

Following embedding, 10 μ m-thick sections were cut using a cryostat, serial collected onto microscope slides (Superfrost plus; VWR) and stored at -80°C until further use. For histological staining, retina sections were washed in PBS, blocked in blocking buffer (PBS containing 4% donkey serum, 0.3% Triton X-100) for 1 h and incubated with primary antibodies overnight at 4°C . The following day, sections were washed, incubated with appropriate Alexa-fluorophore-conjugated secondary antibodies (ThermoFisher Scientific) for 2h, washed and coverslipped with Fluoromount G (Southern Biotech). All wash steps were 3 x 10 min in PBS. Nuclei were counterstained with Dapi. The following antibodies were used: in-house rabbit anti-C1q (clone 4.8, ATUM, 1:500), mouse anti-bassoon (Abcam, 1:500), guinea pig anti-vGlut1 (Millipore Sigma, 1:500), chicken anti-homer1 (Synaptic System, 1: 500), goat anti-Iba1 (Novus, 1:500), rat anti-CD68 (BioRad, 1:200). Rabbit IgG isotype antibody (ThermoFisher) was used as negative control for the C1q staining. Images were captured at 10x or 20x magnification using epifluorescence microscopy (Leica) and at 63x magnification using confocal microscopy (Leica, Stellaris 5). Images were processed using ImageJ.

C1q synaptic co-localization and engulfment analysis

Two z-stack images (Z stack size: 0.7 μ m, 12 planes) were taken per section and at least three sections per animal were analyzed. 3D volume surface renderings of each z-stack were created (Imaris Software). Retinal OPL was selected as the region of interest. Surface-rendered images were used to identify microglia surface and volume, as well synaptic and C1q elements. C1q tagged synapses were quantified based on proximity (C1q and bassoon elements at a distance $\leq 400 \mu\text{m}$). Engulfed synapses were quantified based on overlap (bassoon - Iba1 overlap ratio $\geq 70\%$) and calculated as number of engulfed C1q tagged-synapses/total number of synapses.

Phosphatidylserine (PS) – C1q binding assay

Phosphatidylserine (PS) and phosphatidylcholine (PC) lipid microparticles were purchased from Echelon Biosciences (# P-B1PS and P-B1PC). Purified human C1q was

purchased from Complement Technology (#A099). Ninety-six (96) well clear round bottom plates were used for the assay (VWR # 353227). Microparticle suspension was prepared according to manufacturer's instructions. Briefly, microparticles were first vortexed thoroughly to ensure uniform bead suspension. Wash, dilution, titration, and incubation steps were done in Annexin V binding buffer (Thermo Fisher # BMS500BB). All washes steps were done at a centrifugation speed of 10,000 g for 10 min. Beads were diluted 20 times prior use. For each test point, 150 μ L of bead suspension (~100,000 beads) was used. Microparticles were washed twice and resuspended in binding buffer. Fifty microliters per well were considered as reaction volume. C1q titration (1:10 dilution, 100-0.1 μ g/mL) was prepared in binding buffer. C1q and lipid microparticles were added to the wells at 1:1 ratio and incubated for 30 min at 37 °C. After incubation, microparticles were washed twice with 1 volume of flow buffer (PBS, 1% BSA, 2mM EDTA). Supernatant was decanted, microparticles were resuspended in flow buffer (100ul per well) containing anti C1q-APC (Dako, 1:1000), and incubated at 4 °C for 30 min. After incubation, microparticles were washed twice, resuspended in flow buffer (150 μ l) and analyzed via flow cytometry utilizing the green channel (FITC) for the microparticles and far-red channel (APC) for C1q binding.

Complement deposition assay

Wash, dilution, titration, and incubation steps were done in GVB++ buffer (Complement Technology #B100). PS and PC lipid microparticles were washed twice and resuspended in appropriate volume considering ~100,000 beads for each test point. Human serum titrations were prepared in GVB++. Ninety-six (96) well clear round bottom plates were used for the assay (VWR 353227). GVB EDTA (Complement Technologies #B105) was used as negative control buffer. Reaction mixture included buffer (GVB++ or GVB EDTA, +/- titrated anti C1q antibody): lipid microparticles: human serum at a 1:1:1 ratio for a final volume of 33.3 μ l. Following 30 min incubation at 37 °C, the plate was washed twice with GVB++ (150 μ l). Microparticles were resuspended in flow buffer (PBS, 1% BSA, 2mM EDTA) containing anti C1q-APC (Dako, 1:2000) or anti C4-APC (Dako, 1:500), and incubated at 4 °C for 30 min. After incubation, microparticles were washed twice, resuspended in flow buffer (150 μ l) and analyzed via flow cytometry utilizing the green channel (FITC) for the microparticles and far-red channel (APC) for C1q or C4 deposition.

Human GA donor tissue procurement and Immunohistochemistry

Human donor eyes were obtained within 24 hours postmortem from the San Diego Eye Bank, California, USA. Clinical records and a family questionnaire were obtained for all donors. Human eyes were fixed in 4% for 2 hours than transferred to PBS overnight.

5 The next day, the posterior eye cup was cryoprotected in sucrose 30% for 24-48 hours. The macula was then isolated using a 6 mm diameter dissecting trephine (Biomedical Research Instruments, MD, USA). Temporal, nasal, superior and inferior regions were sampled using the same trephine. Retinal samples were embedded in OCT and frozen. Following embedding, 10 μ m-thick sections were cut using a cryostat, serial collected
10 onto microscope slides (Superfrost plus; VWR) and stored at -80°C until further use. Histological staining of human donor retinal sections was performed as described above for mouse samples. The following antibodies were used: rabbit anti-human C1q (Dako, 1:500), guinea pig anti-vGlut1 (Millipore Sigma, 1:500), chicken anti-homer1 (Synaptic System, 1: 500). Rabbit IgG isotype antibody (ThermoFisher) was used as negative
15 control for the C1q staining. Images were captured at 10x magnification using epifluorescence microscopy (Leica) and at 63x magnification using confocal microscopy (Leica, Stellaris 5). Images were processed using ImageJ.

Statistical Analysis

All data are shown as means $\pm$ standard deviation (SD). Statistical analysis was
20 performed with GraphPad Prism using the unpaired Student's *t* test, or one-way analysis of variance (ANOVA) or two-way ANOVA, followed by Bonferroni or Dunnet's or Sidak's or Tukey's post hoc test. Data are shown as Mean $\pm$ SD. All *p* values are indicated in figure legends and were considered statistically significant when less than 0.05.

Example 2: Photoreceptor synapse loss and increased microgliosis in the photo-oxidative light damage model

The pre-synaptic marker Bassoon was used to identify synapses and measure synapse density using epifluorescence. The number of rows of photoreceptor nuclei was
30 used as a measure of photoreceptor survival. Iba1 (calcium binding protein specifically express in microglia) was used as a pan microglia/macrophage marker. CD68 (lysosomal protein) was used to identify reactive phagocytic microglia. Progressive photoreceptor

synaptic and cell body loss (Figures 1A-1C), as well as increased microglia reactivity (Figures 1D-1F) were observed following photo-oxidative damage. Notably, distribution of phagocytic microglia in the synaptic layer peaked at day 1, the same time point when significant synapse loss was first observed (Figure 1E).

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Example 3: Increased C1q levels on photoreceptor synapses correlates with photoreceptor synapse loss in the photo-oxidative light damage model of photoreceptor degeneration

Increased levels of the initiating classical complement components C1q and C1s, as well as the downstream activation product C3d, were observed in retina lysate from light exposed animals by standard ELISA (Figures 2A-2C). Retinal C1q distribution was next investigated by immunofluorescence. As shown in Figure 2D, C1q (i) co-localized with Iba1 (iii) and Bassoon (iv), confirming C1q expression in microglia/macrophage and expression/deposition on synapses. A significant negative correlation was observed between C1q expression and photoreceptor synaptic density (Figure 2G, Pearson's $r = -0.72$, $p = 0.00003$), suggesting causal relationship (Figure 2E).

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Example 4: Microglia engulfment of photoreceptor C1q tagged pre-synaptic elements following photo-oxidative damage

To assess microglia engulfment of C1q tagged synapses, we triple labelled retinal sections from naïve and light exposed mice for C1q, Bassoon and Iba1 (Figure 3A). High resolution imaging was performed using confocal microscopy. Engulfment analysis was performed using a 3D reconstruction and surface rendering software (Figure 3B). Significant reduction in synapse density (Figure 3C) was associated with a significant increase in the percentage of C1q tagged synapses (Figure 3D) and a significant increase in microglia engulfed C1q tagged synapses in light damaged retina compared to naïve (Figure 3E).

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Example 5: Phosphatidylserine binds to C1q and is externalized on photoreceptor synapses following photo-oxidative light damage

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To test whether PS exposure occurs at photoreceptor synapses during disease, we performed IVT administration of the PS-binding probe PSVue (PSVue 550) in the light damaged model (Scott-Hewitt N et al, The EMBO Journal, 2020). Retinal tissue was

processed and analyzed using IHC on day 3 days post light exposure. Increased PSVue labelling was detectable in the OPL and ONL of light damaged retina compared to naïve (Figure 4A). High resolution confocal imaging and 3D reconstruction/surface rendering confirmed co-localization of PSVue labelling with C1q and Bassoon (Figure 4A).

- 5 Notably, PSVue-positive surfaces appear in close proximity to both Bassoon and C1q positive surfaces in a sandwich-like fashion (Figure 4A iii), indicating PS externalization on synapses and C1q interaction.

To assess whether PS directly binds to C1q and activates the complement cascade, C1q binding and complement deposition assays were performed using PS-lipid-green-fluorescent-microparticles. Phosphatidylcholine (PC)-lipid-green-fluorescent microparticles were used as negative control. Direct binding of C1q to PS lipid microparticles, but not PC, was observed following incubation with C1q at a concentration of 10 ng/mL (Figure 4B). Deposition of both C1q and C4 was observed on PS lipid microparticles, but not on PC lipid microparticles. Little to no deposition was observed in negative control groups (Fig. 4C and D). Titration of anti-C1q neutralizing antibody (Mab1-Fab) within the serum, resulted in reduced C1q and C4 deposition on PS lipid microparticles (Figures 4E and 4F), suggesting that anti-C1q antibody competitive binding reduced PS mediated complement activation.

20 *Example 6: Anti C1q intravitreal treatment reduced retinal complement component level following photo-oxidative light damage*

Intravitreal administration of neutralizing optimized murine anti-C1q antibody (Mab3, optimized from Mab1) was performed one day prior exposure to light damage. Detectable drug level and selected complement component levels were assessed at day 3 post light damage by standard ELISA. Measurable drug levels were found in retina lysates from animals receiving anti-C1q treatment, but not in IgG1 treated or untreated groups (Figure 5A). Increased levels of classical complement component C1q and C1s, as well as downstream activated component C3d, were confirmed in retina lysates from both untreated and IgG treated light exposed animals, compared to naïve (Figures 5B-5D). Significant decrease in C1q, C1s and C3d was observed following anti-C1q treatment, compared to IgG antibody (Figures 5B-5D). Validation studies confirms target engagement and assessing neuroprotection following treatment.

Example 7: C1q expression and deposition on photoreceptor synapses in human GA donor retina

GA donor eyes were procured and histological assessment of C1q distribution across retinal layers was performed. Synaptic integrity was assessed by immunofluorescence in the macula region of GA donor versus healthy donor retina. Reduced immunoreactivity for the pre-synaptic marker Vglut1 and increased labelling for C1q in the photoreceptor synaptic layer confirmed synaptic loss and C1q accumulation occurring in GA retina, compared to healthy donors (Figures 6A-6B). Finally, triple immunolabelling for C1q (grey), presynaptic marker Vglut1 and postsynaptic marker (Homer1) confirmed co-localization of C1q with photoreceptor synapses in human GA donor retina (Figure 6C).

Example 8: Evaluating FabA in nonclinical studies

FabA Drug Product is a sterile, isotonic liquid for IVT injection.

FabA is provided as sterile, single-use vials for IVT injection.

An extensive series of *in vitro* and *in vivo* pharmacology studies have been conducted with FabA.

The antibody Mab1, Mab1-Fab, and Mab2, were active in an acute mouse model of glaucoma, protecting against retinal ganglion cell and/or nerve fiber loss. In a photo-oxidative light-induced damage model in mouse, Mab1 administered intravitreally protected against photoreceptor cell loss and retinal functional connectivity in the eye.

The FabA GLP studies consist of a single-dose rat ocular toxicology study, and three repeat-dose cynomolgus monkey ocular toxicology studies. The route of administration for the toxicology studies was IVT injection. In the single dose and two dose (once monthly) IVT GLP studies, FabA has shown no evidence of adverse ocular toxicity with a No-Observed-Adverse-Effect-Level (NOAEL) of 5 mg/eye (equivalent to 10 mg human dose) once monthly in cynomolgus monkeys, and 0.05 mg/eye (equivalent to 10 mg human dose) in the single dose rat study. In the 26-week chronic ocular toxicology study in cynomolgus monkeys, adverse ocular changes were associated with the double injection procedure and/or determined to be anti-drug antibody (ADA)-mediated and not a direct effect of FabA IVT administration.

Pharmacokinetic evaluations of FabA in rat and cynomolgus monkey serum and vitreous were conducted. C1q levels were measured in the vitreous as a PD marker for FabA inhibition of C1q in monkeys. The PK/PD and TK/PD studies in monkeys demonstrated a robust ocular PD effect consistent with the level of FabA drug exposure in the vitreous.

Binding and Affinity of FabA and Precursor Molecules for Human C1q

C1q binding affinity of FabA and precursor molecules was also examined by ELISA. All molecules (Mab2-Fab, FabA, and Mab2, Mab1, and Mab1-Fab) showed affinity for human C1q with half maximal effective concentration (EC₅₀) in the range of 2.2–4.9 ng/mL (20–95 pM). The EC₅₀ for FabA binding to C1q is 2.5 ng/mL.

Effect on IgM-mediated Red Blood Cell hemolysis

The activity of FabA, Mab2, and Mab2-Fab to functionally-inhibit classical complement-dependent hemolysis of IgM opsonized-RBCs in human serum was measured (Figure 9). The three molecules exhibit nearly identical potency, consistent with their equivalent binding affinities. The half maximal inhibitory concentration (IC₅₀) of FabA inhibition of IgM-coated RBC hemolysis is 0.62 µg/mL (~12 nM).

In vivo Pharmacology Studies

Anti-C1q antibody treatment prevents optic nerve damage in an acute mouse model of glaucoma

In mice, injection of polystyrene beads into the anterior chamber of the eye results in acute elevation of IOP, loss of the retinal ganglion cells, and optic nerve damage over a period of 2 weeks. Mab1, Mab1-Fab and Mab2 were administered intravitreally into mice on the day before and 7 days after IOP elevation. 2 µL of 10 mg/mL antibody or saline was administered at each time point. Based on a vitreal volume of 5-10 µL in mouse eye, the concentration of antibody was 2000-4000 µg/mL. Optic nerves were collected 2 weeks following the injury and the number of intact and damaged axons was quantified. Anti-C1q antibody treatment led to protection against RGC loss and/or retinal nerve fiber damage in this induced mouse model of glaucoma (Figure 10).

Anti-C1q antibody treatment protects against photoreceptor cell damage in a photo-oxidative light-induced damage model

Photo-oxidative damage resulted in retinal photoreceptor loss when mice were exposed to 100 Klux of natural white LED for 1-7 days. In this model, there was time dependent increase in C1qa gene expression over 3-7 days which correlated with photoreceptor cell death and microglia/macrophage recruitment. C1qa^{-/-} mice displayed less photoreceptor cell death, reduced microglia/macrophage recruitment to the photoreceptor lesion, and higher visual function at 14 days after induction of photodamage but not at 7 days. IVT administration of Mab1 antibody on Day 7 after photodamage reduced photoreceptor cell loss and maintained retinal function as measured by electroretinogram (Figure 11). Mice were administered 1 μ L of 7.5 mg/mL antibody, which is equivalent to 750-1500 ug/mL concentration in the vitreous. In contrast, systemic delivery of Mab1 at 100 mg/kg on Day 0, 4, and 8 had no effect of photoreceptor loss or function. Retinal C1q was mainly expressed by subretinal microglia / macrophages located in the outer retina in early AMD and in mouse retinas. Thus, protection with anti-C1q antibody suggests a clear role of C1q in initiation of photoreceptor damage and the classical complement cascade in the pathogenesis of GA in human disease.

Safety Pharmacology

Systemic exposure following chronic IVT dosing in the 26-week cynomolgus monkeys did not exceed 86.3 ng/mL, while systemic exposure of Mab2 with the same CDR with once weekly IV dosing in a 26-week cynomolgus monkey study exceeded 1 mg/mL at the NOAEL of 200 mg/kg.

Thus, the safety pharmacology endpoints for the full-length antibody, Mab2, following IV administration up to 200 mg/kg weekly in a 4-week repeat-dose GLP toxicity study in monkeys and up to 200 mg/kg weekly in a 26-week repeat-dose toxicity study in monkeys, in which there was no evidence of a treatment-related effect on cardiovascular, respiratory, or neurologic endpoints support the systemic safety of FabA administered IVT.

Additionally, the safety pharmacology endpoints for FabA, following SC administration up to 20 mg/kg daily in a 4-week repeat-dose GLP toxicity study in monkeys where there was no evidence of a treatment-related effect on cardiovascular,

respiratory, or neurologic endpoints support the systemic safety of FabA administered IVT.

Pharmacokinetics in Animals

Nonclinical studies designed to characterize the PK, TK, and PD of FabA were conducted in rats and in cynomolgus monkeys. These studies include single dose IVT PK studies in rats and cynomolgus monkeys, and repeat-dose TK/PD studies in the cynomolgus monkey with FabA. More extensive TK/PD studies were performed in the monkey, and there was no ocular toxicity in either the rat or monkey single dose studies.

Pharmacokinetic/Toxicokinetic/Pharmacodynamic Analyses

10 Pharmacokinetics of FabA in the Vitreous

Following single bilateral IVT administration of FabA at a dose of 0.01 mg/eye (equivalent to 2 mg human dose) or 0.05 mg/eye (equivalent to 10 mg human dose) to rats, the drug was eliminated from the vitreous relatively quickly, consistent with a half-life of approximately 12 hours at both dose levels. In cynomolgus monkeys, also receiving bilateral IVT FabA, the drug was distributed from the vitreous more slowly, when compared to rats, with a half-life of approximately 3 days for both the 1 mg/eye (equivalent to 2 mg human dose) and the 5 mg/eye (equivalent to 10 mg human dose) dose groups.

In both species, FabA IVT PK was dose linear. Data from the ocular toxicology studies in cynomolgus monkeys, where FabA was given twice over a 28-day period at doses of 1.0 mg/eye (equivalent to 2 mg human dose), 2.5 mg/eye (equivalent to 5 mg human dose), or 5.0 mg/eye (equivalent to 10 mg human dose), indicate that vitreous concentrations at the time of sacrifice (i.e., 15 and 30 days after the second dose), were generally consistent with data from the single dose IVT administration.

In the 26-week chronic ocular toxicology study in cynomolgus monkeys, where FabA was dosed IVT 2.5 mg/eye monthly (equivalent to 5 mg human dose), 5 mg/eye monthly (equivalent to 10 mg human dose), or 5 mg/eye biweekly (both 5 mg/eye doses were subsequently reduced to 2.5 mg/eye and are referred to as 5/2.5 mg/eye) vitreous humor FabA concentrations were quantifiable on Day 184 in all animals that received FabA through Day 169, and were below the quantification limit (BQL) in all animals on Day 242/243 after the 10-week dose-free recovery period. Vitreous humor FabA

concentrations showed high variability with no clear differences or trends between dose groups or sexes.

Pharmacokinetics of FabA in the Serum

Following single IVT administration, serum concentrations were much lower than in the vitreous with a $C_{\max}$ serum/ $C_{\max}$ vitreous of ~ 0.003 in rats and 0.000001 in cynomolgus monkeys. In cynomolgus monkeys who received bilateral FabA IVT twice over a 28-day period, the serum concentrations were low and the highest mean peak concentration ($C_{\max}$) was 10.1 ng/mL, which was observed after administration of the second IVT dose of 5 mg/eye (equivalent to 10 mg human dose). As FabA distributes from the vitreous into the serum compartment, FabA can either bind to C1q, or remain in its free form and be quantifiable with the assay, resulting in low FabA serum concentrations which were not quantifiable (i.e., < 1.25 ng/mL) in the 1 mg/eye group, and a mean $C_{\max}$ of 3.3 and 10.1 ng/mL for the 2.5 and 5.0 mg/eye, respectively.

In contrast, following IV administration of FabA at a dose of 10 mg/kg, FabA maximum concentrations were 13800 and 17000 ng/mL in the 2 cynomolgus monkeys tested and the concentrations declined very rapidly afterwards, consistent with a half-life of approximately 2 hours, as expected for a Fab fragment.

When comparing the serum FabA concentrations after bilateral IVT administration (5 mg/eye) twice over a 28-day period to those obtained after systemic IV administration of Mab2 at a dose of 200 mg/kg once weekly for 4 weeks, the FabA serum exposure were considerably lower (FabA /Mab2 $C_{\max}$ ratio of 0.00000701).

In the 26-week chronic ocular toxicology study in cynomolgus monkeys, where FabA was dosed IVT 2.5 mg/eye monthly, $5/2.5$ mg/eye monthly, or $5/2.5$ mg/eye biweekly systemic exposure to FabA in serum was low, consistent with the local route of administration. Serum concentrations of FabA on Day 85 did not exceed 86.3 ng/mL and on Day 169 after the last dose was administered, FabA serum concentrations did not exceed 60.8 ng/mL. Maximum serum FabA concentrations were observed at 24 to 48 hour postdose across dose levels/regimens and evaluation days. The half-life ($T_{1/2}$) values for FabA in serum were calculable/reportable only in a few instances in animals in the $5/2.5$ mg/eye biweekly group and ranged from 49.9 to 143 hours across all evaluation days, likely representing distribution from the ocular space into the serum. There was little accumulation of FabA in serum with repeated monthly IVT dosing at 2.5 mg/eye.

However, there were increasingly more calculable FabA serum concentrations in this group on each subsequent evaluation day after Day 1. Accumulation could not be determined from Day 1 in any other groups due to the changes in dose levels after Day 57. Day 169/Day 85 area under the curve to time “t” (AUC[0-t]) ratios ranged from 0.0407 to 0.664 in 5/2.5 mg/eye once monthly males and females, and ranged from 0.132 to 7.15 in 5/2.5 mg/eye biweekly males and females. When comparing FabA and Mab2 mean sex combined systemic exposures after chronic 26-week dosing in cynomolgus monkeys, FabA exposure AUC0-t (1,230 hr*ng/mL or 1.23 hr*μg/mL) after bilateral IVT administration at 5/2.5 mg/eye biweekly compared to the 200 mg/kg AUC0-t (3,150,000 hr*μg/mL) obtained after once weekly systemic IV administration of Mab2, the FabA serum exposures were considerably lower (FabA /Mab2 C_{max} ratio of 0.000000073, AUC0-t ratio of 0.00000039).

Pharmacodynamics of Ocular C1q

In control animals, mean vitreous free C1q concentration was 40.3 ng/mL while in the vitreous of cynomolgus monkeys receiving a single FabA IVT dose of either 1 mg/eye (equivalent to 2 mg human dose) or 5 mg/eye (equivalent to 10 mg human dose), free C1q levels were below the detection limit (<1.953 ng/mL) for the study duration (30 days), indicating complete C1q suppression. In the monkeys who had received FabA every 28 days for a total of 2 doses, C1q remained suppressed for 15 days after administration of the second dose at all 3 dose levels (i.e., 1, 2.5 and 5 mg/eye q 28 days x 2 doses). Thirty days after administration of the second FabA dose, C1q remained below the detection limit in some, but not all eyes.

Fifteen days after administration of the second 5 mg/eye IVT, >80% of C1q was bound to FabA in the retina, choroid and optic nerve head. Thirty days after the second administration of 5 mg/eye, C1q remained suppressed in the retina and choroid only.

In the 26-week chronic ocular toxicology study in cynomolgus monkeys, where FabA was dosed IVT 2.5 mg/eye monthly, 5/2.5 mg/eye monthly, or 5/2.5 mg/eye biweekly, at the terminal necropsy, there was a reduction of vitreous humor C1q levels in all groups that received FabA; and at the terminal and recovery necropsies, animals with dose holidays and/or after the 10-week dose-free recovery period, respectively, vitreous humor C1q levels recovered and were comparable to the control group.

Serum C1q and Serum Hemolysis Inhibition

Following bilateral IVT administration of 5 mg/eye (equivalent to 10 mg human dose) to cynomolgus monkeys, C1q-dependent serum hemolysis was inhibited by ~50–80%, which lasted approximately 24–48 hours after administration of the first IVT dose, and up to 96 hours following administration of the second FabA dose, returning towards baseline afterwards.

After a single IV administration of 10 mg/kg to cynomolgus monkeys, maximum C1q-dependent serum hemolysis inhibition was reached at 1 hour. Maximum inhibition was maintained for ~24 hours and returned to baseline 120 hours after FabA administration. Serum free C1q also declined rapidly but had not returned to baseline value by 120 hours, which suggests that some FabA remained bound to circulating C1q over this time frame.

Toxicology

The safety of FabA is supported by a comprehensive nonclinical ocular toxicology program designed to support the use of FabA for IVT administration in clinical trials. Initial single dose studies were performed in the rat and cynomolgus monkey with FabA and no ocular toxicity was observed in either of these species. Based on the similar findings in rats and monkeys, and the in vitro pharmacology data and sequence homology data that indicated the monkey was more relevant than rat, the cynomolgus monkey was selected for repeat-dose ocular toxicology studies of FabA.

The repeat dose ocular toxicology studies included ophthalmic examinations (OE), IOP, electroretinogram (ERG), ocular histopathology, and the measurement of FabA in serum and vitreous for TK analyses. Additionally, FabA PD properties were characterized by measurement of C1q in vitreous (for all repeat dose studies) and ocular tissues (in two dose studies), and the inhibition of C1q-dependent hemolysis in serum (in two dose studies).

Single-Dose Toxicity

IVT administration of FabA was well tolerated in the single-dose (rat and cynomolgus monkey) ocular toxicology studies. In these studies, the NOAELs for rat and cynomolgus monkey were considered to be 0.05 mg/eye (equivalent to 10 mg human dose) and 5 mg/eye (equivalent to 10 mg human dose), respectively, which were the

highest doses evaluated in each study and are equivalent (2.5 mg/mL) when corrected for vitreous volume (rat 0.02 mL, monkey 2 mL).

GLP Single-Dose Ocular Toxicity Study of FabA by Intravitreal Injection in Sprague Dawley Rats

5 In this single dose GLP rat ocular toxicology study, vehicle or FabA was administered at doses of 0.01 mg/eye (equivalent to 2 mg human dose) and 0.05 mg/eye (equivalent to 10 mg human dose) by IVT injection once bilaterally to young adult male rats. FabA treated animals were terminated at Day 1 (6 hours post dose), Day 3, Day 7, Day 10, Day 20, Day 30 and all vehicle control animals were terminated on Day 30. All
10 animals survived until scheduled necropsy.

Standard safety parameters were included in this study. Blood samples were collected at termination and terminal vitreous samples were obtained for TK analysis. Additionally, ophthalmic examinations (OEs), including IOP, and ocular histopathology were evaluated.

15 No FabA-related changes were noted in any safety parameter evaluated, including OEs, IOPs, and ocular histopathology.

Vitreous exposure to FabA was confirmed by TK in treated animals for 6 hours (first collection) to 144 hours post dose at both 0.01 mg/eye (equivalent to 2 mg human dose) and 0.05 mg/eye (equivalent to 10 mg human dose). Serum exposure to FabA was
20 confirmed on TK in treated animals (2 to 48 hours post dose only) at 0.01 and 0.05 mg/eye.

No adverse effects considered related to FabA were observed at any dose level, including 0.05 mg/eye, the highest dose evaluated, were observed in this study. Based on these results, the NOAEL was 0.05 mg/eye (2.5 mg/mL in vitreous).

25 Non-GLP Single-Dose Ocular Toxicity Study of FabA by Intravitreal Injection in Cynomolgus Monkeys

In this single dose non-GLP cynomolgus monkey ocular toxicology study, vehicle or FabA was administered bilaterally by IVT injection at doses of 1 mg/eye (equivalent to 2 mg human dose) and 5 mg/eye (equivalent to 10 mg human dose) to young adult female
30 cynomolgus monkeys. FabA treated animals were terminated at Day 1 (6 hours post dose), Day 3, Day 7, Day 10, Day 20, Day 30. All vehicle control animals were terminated on Day 30 and all animals survived until scheduled necropsy.

Standard safety parameters including OE, IOP, and ocular histopathology were assessed in this study. Additionally, blood samples were collected throughout the study, and terminal vitreous samples for TK and PD were analyzed.

FabA-related changes were limited to non-adverse findings that were not associated with inflammation. These findings included histiocytic infiltrates in the uvea and mild basophilia in the 1 mg/eye dose group. Findings in the 5 mg/eye dose consisted of histiocytic infiltrates in the uvea, and minimal to mild basophilia.

No FabA-related changes were observed in OEs and IOPs. No adverse effects considered related to FabA at any dose level, including 5 mg/eye (the highest dose evaluated) were observed in this study. Based on these results, the NOAEL was considered to be 5 mg/eye (2.5 mg/mL in vitreous).

Exposure to FabA in the vitreous was confirmed on TK in all treated animals for the duration of the study (through Day 30). Serum exposure to FabA was absent at 1 mg/eye, was low and transient at 5 mg/eye, and did not exceed 6 ng/mL (LLOQ 1.25 ng/mL). Clq was absent in all FabA treated animals in the vitreous through Day 30.

Repeated-Dose Toxicity Studies

In the repeat-dose ocular toxicity studies, FabA was administered at least once every 4 weeks by IVT injection. Repeat-dose administration of FabA was well tolerated in the cynomolgus monkey. In the initial repeat-dose GLP ocular toxicology studies, the NOAEL for the cynomolgus monkey was 5 mg/eye (equivalent to 10 mg human dose) once monthly for two doses, the highest dose evaluated. In the 26-week chronic ocular toxicology study in cynomolgus monkeys, adverse ocular changes were associated with the double injection procedure and/or determined to be ADA-mediated and not a direct effect of FabA IVT administration, thus the NOAEL was determined to be 2.5 mg/eye (equivalent to 5 mg human dose) biweekly or once monthly in cynomolgus monkeys for 13 or 7 doses, respectively.

6-Week GLP Repeated-Dose Ocular Toxicity Study of FabA by Intravitreal Injection in Cynomolgus Monkeys

Standard safety parameters were included in this study, and blood samples were collected throughout the study. Terminal vitreous samples for TK and PD analysis and terminal optic nerve sections for TK and PD analysis were collected as well. Additionally, OEs, IOPs, ERGs, and ocular histopathology were evaluated.

FabA findings determined to not be adverse were limited to one high dose (2.5 mg/eye) (equivalent to 5 mg human dose) female, which had minimal basophilic / blue-staining of the vitreous with no associated inflammation (referred to as basophilia).

Importantly, there were no FabA-related changes noted in OEs, IOPs, and ERGs. TK
5 confirmed exposure to FabA in all treated animals in the vitreous for the duration of the study and through recovery (30 days post the last dose).

Serum exposure was not measurable at 1 mg/eye (equivalent to 2 mg human dose), was low and transient (12 to 48 hours post the first dose, 6 to 168 hours post the last dose) at 2.5 mg/eye (equivalent to 5 mg human dose) and did not exceed 8 ng/mL
10 (LLOQ 1.25 ng/mL). PD confirmed the absence of C1q in all treated animals in the vitreous, when FabA levels were ~100 ng/mL. FabA ADAs were detected in animals at the 1 mg/eye (equivalent to 2 mg human dose) (6 of 12 animals) and 2.5 mg/eye (equivalent to 5 mg human dose) (7 of 12 animals), but there was no clear impact of ADA on FabA exposure in serum or vitreous.

15 6-Week GLP Repeated-Dose Ocular Toxicity Study of FabA by Intravitreal Injection in Cynomolgus Monkeys

In this 6-week GLP cynomolgus monkey ocular toxicology study, vehicle or FabA was administered bilaterally via IVT injection at a dose of 5 mg/eye (equivalent to 10 mg human dose) every four weeks (on Days 1 and 29) to young adult male and female
20 cynomolgus monkeys, followed by a 4-week recovery period. All main study animals were terminated on Day 44 and all recovery animals were terminated on Day 59/60. All main study and recovery animals survived until scheduled necropsy.

Standard safety parameters were included in this study (with the exception of systemic histopathology), and blood samples were collected throughout the study, as well
25 as terminal vitreous samples for TK and PD analysis. ADA and aqueous humor samples were collected and archived. Additionally, OEs, IOPs, ERGs, and ocular histopathology were evaluated.

No FabA-related changes were noted in any safety parameter evaluated including OEs, IOPs, ERGs, and ocular histopathology. Minimal-mild basophilic / blue-staining of
30 the vitreous with no associated inflammation (referred to as basophilia) was observed in both treated and control animals and thus was not considered related to FabA.

TK confirmed exposure to FabA in all treated animals in the vitreous for the duration of the study and through recovery (30 days post the last dose). The absence of FabA was confirmed in the serum and vitreous of control animals. PD confirmed the absence of C1q in all treated main study animals in the vitreous on Day 44. On Day 59, 2/4 recovery animals had measurable C1q in the vitreous. FabA ADAs were detected in animals at the 5 mg/eye (equivalent to 10 mg human dose) (9 of 10 animals) group, but there was no clear impact of ADA on FabA exposure in serum or vitreous.

Inhibition of C1q-dependent hemolysis of >80% was achieved 24–48 hours after FabA administration and returned towards baseline thereafter.

C1q levels were also significantly decreased in the retina, choroid and optic nerve head on Day 44, and continued to be reduced in the retina and choroid, but not the optic nerve head on Day 59.

No adverse effects considered related to FabA at any dose level, including 5 mg/eye (equivalent to 10 mg human dose) (the highest dose evaluated) were observed in this study. Based on these results, NOAEL was 5 mg/eye (equivalent to 10 mg human dose) (2.5 mg/mL in vitreous).

26-Week GLP Repeated-Dose Ocular Toxicity Study of FabA by Intravitreal Injection in Cynomolgus Monkeys with 10-Week Recovery

In this 26-week GLP cynomolgus monkey ocular toxicology study, vehicle or FabA was administered bilaterally via IVT injection at a dose of 2.5 mg/eye (equivalent to 5 mg human dose) once monthly, 5 mg/eye (equivalent to 10 mg human dose) once monthly, and 5 mg/eye once every other week (biweekly) to young adult male and female cynomolgus monkeys, followed by a 10-week recovery period. Single injection of 50 µL corresponded to 2.5 mg/eye, or double injections totaling 100 µL (two 50 µL injections separated by 10 min corresponded to 5 mg/eye) every 2 weeks (13 dosing periods) or every 4 weeks (7 dosing periods). All main study animals were terminated on Day 184 and all recovery animals were terminated on Day 242/243. All main study and recovery animals survived until scheduled necropsy.

Dose holidays or cessation of dosing occurred in animals in the control, 5 mg/eye (equivalent to 10 mg human dose) once monthly, and 5 mg/eye biweekly dose groups. Double injections in these groups were discontinued due to adverse findings detected by OEs and were considered related to the procedure and high dose volume. Beginning on

Day 71 of the study the 5 mg/eye once monthly group was dosed 2.5 mg/eye (equivalent to 5 mg human dose) once monthly (referred to as 5/2.5 mg/eye once monthly), and 5 mg/eye biweekly was dose 2.5 mg/eye biweekly (referred to as 5/2.5 mg/eye biweekly). Dose holidays continued in these dose groups (including control) after the double
5 injections were discontinued, which were procedural and/or ADA-related as described below. There were no dose holidays in the 2.5 mg/eye once monthly group (low dose group).

Standard safety parameters were included in this study (with the exception of systemic histopathology), and blood samples were collected throughout the study, as well
10 as terminal vitreous samples for TK and PD analysis. ADA and aqueous humor samples were collected and archived. Additionally, OEs, IOPs, ERGs, ocular histopathology, and immunohistochemistry (IHC) for the detection of deposited immune complexes in globes were evaluated.

No FabA-related changes were noted in body weights, food consumption,
15 electroretinography, tonometry, and clinical pathology.

Ocular clinical signs and ophthalmic examination findings considered related to FabA were limited to eyeball opacity (likely due to opacity in the anterior chamber, lens capsule, and/or posterior chamber) and the presence of cells and/or pigment. The presence of these findings in animals that did not have ADA detected in serum (4 of 12
20 Group 2 animals, 2 of 12 Group 3 animals, and 2 of 12 Group 4 animals) indicates a relationship to FabA. Findings considered related to ADA and potentially to immune complex deposition tended to be more severe and included aqueous flare and the presence of vitreal haze, altered pupillary light reflex, and retinal vessel attenuation.

Following IVT administration of FabA to male and female monkeys systemic
25 exposures as measured by serum FabA concentrations were transient, low, and did not exceed 86.3 ng/mL after dosing on Day 85, or 60.81 ng/mL after the last dose on Day 169. TK confirmed exposure to FabA in nearly all treated animals that received FabA through Day 169, which corresponded with vitreous C1q not being detectable, with the exception of some animals with dose holidays. On Day 242/243 after the 10-week dose-
30 free recovery period FabA vitreous concentrations were not measurable, and C1q concentrations were detectable in all treated dose groups. The absence of FabA was confirmed in the serum and vitreous of control animals.

The presence of anti-FabA antibodies in serum samples was confirmed in 4 of 12 Group 1 (Control) animals, 8 of 12 Group 2 animals, 10 of 12 Group 3 animals, and 10 of 12 Group 4 animals. Two Group 1 animals confirmed positive at a single time point per animal after Day 1, whereas FabA-treated ADA-positive animals were identified at 3 or 4
5 or more time points (a total of 4 or 5 samples were collected for main study and recovery animals, respectively). There was no clear impact of ADA on FabA exposure in serum or vitreous.

At the terminal euthanasia on Day 184, microscopic changes consistent with an ADA-mediated immune response to FabA were observed in the right eye at 5/2.5 mg/eye
10 monthly and biweekly (mid and high dose groups, respectively). Intraocular changes related to inflammation included mild mixed cell infiltration of the ciliary body and vitreous chamber, minimal to moderate fibrosis (severity proportional to dose frequency) within the vitreous chamber, and minimal to mild posterior lens degeneration (severity proportional to dose frequency). Minimal perivascular mononuclear cell infiltrates were
15 also observed within the posterior retina in one female each at 5/2.5 mg/eye biweekly and monthly treatment groups. Minimal to mild, mononuclear cell infiltration was observed within the periocular limbus of animals administered 5/2.5 mg/eye biweekly and monthly, with severity proportional to dose frequency.

At the recovery euthanasia on Day 242/243, microscopic changes in the right eye
20 related to the ADA-mediated immune response to FabA were limited and minor at 5/2.5 mg/eye monthly, while additional changes persisted or developed at 5/2.5 mg/eye biweekly. Minimal histiocytic infiltration of the vitreous chamber and uvea and increased basophilia of the vitreous chamber were exclusive to animals administered FabA 5/2.5 mg/eye biweekly and/or monthly at recovery. These changes were similar to those
25 observed in control animals at the terminal necropsy where they were considered related to minor inflammation/disruption of the anterior vitreous associated with the IVT injection procedure. However, the persistence of these changes after the recovery period, the resolution of these changes in control animals at recovery, and the presence of more severe inflammatory changes at the terminal necropsy in animals administered FabA
30 5/2.5 mg/eye biweekly and monthly indicated that these changes at recovery more likely represented resolving inflammation related to an ADA-mediated immune response to

FabA rather than lingering effects of the injection procedure. Minimal mononuclear cell infiltration of the periocular limbus persisted at both 5/2.5 mg/eye biweekly and monthly.

Minimal mixed cell infiltration and fibrosis of the vitreous chamber persisted at 5/2.5 mg/eye biweekly, while moderate decreased cellularity and hemosiderin pigment of the retina developed. Minimal perivascular mononuclear cell infiltration of the retina at the optic disk was also observed at 5/2.5 mg/eye biweekly. These changes were also considered secondary to an ADA-mediated response to FabA.

Pathologically adverse microscopic changes were considered secondary to ADA-mediated inflammation and included fibrosis within the vitreous chamber, lenticular degeneration, and decreased cellularity of the retina at 5/2.5 mg/eye biweekly and monthly.

There were no microscopic changes related to FabA 2.5 mg/eye monthly at either the terminal or recovery euthanasia.

Immunohistochemistry was conducted for 2 of 12, 4 of 12, and 6 of 12 animals from Groups 1, 3, and 4, respectively. Evaluation revealed the presence of immunohistochemically detected granular deposits containing FabA, monkey IgG, IgM, and/or C3 within the left eye of 4 of 10 treated animals in the mid dose 5/2.5 mg/eye monthly (2 of 4 animals) and high dose 5/2.5 mg/eye biweekly (2 of 6 animals) selected for IHC. These intramural vascular deposits were present in association with perivascular inflammatory cellular infiltrates similar to those observed with hematoxylin and eosin evaluation of the right eye. Other microscopic changes observed within the right eye were consistent with secondary changes associated with this immune response to FabA in the monkey. Although ocular immune complex deposits were not observed in all animals selected for immunohistochemistry, including some with negative serum ADA as well, this was not unexpected as deposit identification may vary with tissue sectioning and serum ADAs are not always present in animals with microscopic evidence consistent with immune complex pathology. Additionally, in some animals with multiple dose holidays, ADA and/or immune complexes may have cleared prior to analyses. The presence of immunohistochemically confirmed deposits even in a subset of animals was considered the most convincing weight of evidence that similar and pathogenetically consistent pathology observed in the right eye was likely related to an immune response to FabA.

In this 26-week chronic ocular toxicology study in cynomolgus monkeys, adverse ocular changes were determined to be related to the double injection procedure and/or ADA-mediated and not a direct effect of FabA IVT administration, thus the NOAEL was determined to be 2.5 mg/eye (equivalent to 5 mg human dose) biweekly or once monthly in cynomolgus monkeys for 13 or 7 doses, respectively.

Example 9: Evaluating FabA in clinical studies

FabA Drug Product is a sterile, isotonic liquid for IVT injection. A Phase 1 first-in-human, open-label, dose-escalation study (FabA-GLA-01) was conducted to evaluate the initial safety and tolerability of a single IVT injection of FabA in patients with primary open-angle glaucoma.

A Phase 1b, randomized, double-masked study (FabA-GLA-02) was conducted to evaluate the safety and tolerability of repeat IVT injections of FabA in patients with primary open-angle glaucoma.

Results of both studies found that single (1 to 5 mg/eye) (equivalent to 2-10 mg human dose) and repeat doses (2.5 and 5 mg/eye, 2 doses separated by 4 weeks) of FabA IVT were well tolerated in glaucoma patients; no serious or significant adverse events (AEs) were reported. Ocular AEs in patients treated with FabA in these studies included conjunctival hyperemia, conjunctival hemorrhage, and eye irritation and only occurred in the treated eye. In the Phase 1b study, ocular AEs in patients in the Sham group included eye pain, foreign body sensation in eyes, ocular hyperemia, and vision blurred. No systemic AEs occurred that were considered related to FabA IVT treatment.

Single IVT injections of 2.5 mg (equivalent to 5 mg human dose) and 5 mg (equivalent to 10 mg human dose) FabA inhibited free C1q for at least 29 days in aqueous humor (Study FabA-GLA-02).

Pharmacokinetics and Pharmacodynamics in Humans

Ocular Pharmacokinetics and Pharmacodynamics

FabA-GLA-02 is a Phase 1b study in which aqueous humor was sampled to assess PK and PD. Subjects were administered two IVT injections of sham, 2.5 mg/eye FabA (equivalent to 5 mg human dose), or 5 mg/eye (equivalent to 10 mg human dose) FabA separated by 29 days. In this study, aqueous humor was sampled predose and 29 days following the first FabA dose, prior to the second dose. Free FabA was detected in the aqueous humor of all treated patients on Day 29 (D29). In parallel, both dose levels of 2.5

mg/eye and 5 mg/eye FabA inhibited free C1q for at least 29 days in aqueous humor (Figure 12).

Systemic Pharmacokinetics and Pharmacodynamics

FabA-GLA-01 is a single dose Phase 1 study in which serum FabA and C1q were sampled predose and at 3 hours postdose. FabA-GLA-02 is a multidose Phase 1b study in which serum and FabA and C1q were sampled predose and at 3 hours postdose for each of 2 doses separated by 29 days. FabA was generally not detectable in systemic circulation after single or repeat IVT injections at any dose level studied in either the Phase 1 or Phase 1b clinical studies. Similarly, no changes in circulating free C1q were detected in either study.

As described below, the 5 mg/eye (equivalent to 10 mg human dose) dose level was well tolerated as single or two doses separated by 29 days in FabA clinical studies. As described above, in the Phase 1b study, single doses of FabA at 2.5 mg (equivalent to 5 mg human dose) and 5 mg (equivalent to 10 mg human dose) inhibited free C1q in aqueous humor for at least 29 days (Figure 12).

Safety and Efficacy

Phase 1 Dose Escalation (FabA-GLA-01)

This was a Phase 1, open-label, dose-escalation study evaluating the safety/tolerability and PK of a single IVT injection of FabA in patients with primary open-angle glaucoma. Eligible patients were adults with mean deviation of 3 to 18 dB on a reliable visual field test who were able to perform a reliable visual field test in the study eye with a cutoff of 33% for fixation losses and 33% for false-positive response rates using the Humphrey Field Analyzer-Swedish Interactive Threshold Algorithm (HFA-SITA) 24-2 fast algorithm, and had IOP < 21 mmHg on a stable IOP treatment regimen in the study eye for ≥ 4 weeks prior to dosing. Nine patients were assigned to 3 cohorts, with 3 patients enrolled per cohort as follows:

- Cohort 1 = 1.0 mg/eye, single dose (0.02 mL) $\times$ 1 dose
- Cohort 2 = 2.5 mg/eye, single dose (0.05 mL) $\times$ 1 dose
- Cohort 3 = 5.0 mg/eye, single dose (0.10 mL) $\times$ 1 dose

After screening, 3 eligible patients were enrolled into the lowest open cohort, with enrollment in the next cohort initiated only after tolerability and short-term safety had been demonstrated at the preceding lower dose. All patients within each cohort were

required to complete a minimum of a 15-day, safety observation period before patients in the next cohort could be injected. No dose-limiting toxicities (DLTs) were reported during the study.

Nine patients were enrolled, treated, and completed the study.

5 Safety

Ocular treatment-emergent adverse event (TEAEs) included conjunctival hyperemia (all dose levels), conjunctival hemorrhage (2.5 mg/eye only), and eye irritation (1 mg/eye only) and only occurred in the study eye.

The only systemic TEAE experienced in the study was sinusitis.

- 10 • All TEAEs were mild in severity.
- There were no serious or significant TEAEs.
- No patients discontinued treatment or withdrew from the study due to a TEAE.
- IOP returned to normal (within 5 mmHg of immediate pre-injection IOP or < 21 mm Hg) within 30 minutes in 9 of 9 patients.
- 15 • No patient showed any evidence of anti-FabA antibodies.

Overall Summary/Conclusions:

In this study in patients with stable glaucoma, single IVT doses of FabA were well tolerated up to 5 mg/eye. The ocular AEs reported were similar to those reported with IVT administration of approved drugs. No safety signals with FabA were observed.

- 20 FabA was generally not detectable in the systemic circulation and no changes in circulating free C1q were detected after single IVT administration.

Phase 1b (FabA-GLA-02)

- 25 This was a double-masked, randomized, sham-controlled study to evaluate two dose levels of FabA vs. sham injection, administered as repeat IVT injections in patients with primary open-angle glaucoma. Eligible patients were adults with a mean deviation of -3 to -24 dB on a reliable visual field test in the study eye who were able to perform a reliable visual field test in the study eye with a cutoff of 33% for fixation losses and 33% for false-positive response rates using the HFA-SITA fast algorithm, had IOP < 21 mmHg at screening and on Day 1, and were on a stable IOP treatment regimen for $\geq$ 4
- 30 weeks prior to injection, with no anticipated change in IOP treatment regimen during the study. Patients received two injections, 4 weeks apart, and were followed for a total of 12 weeks for evaluation of the safety, tolerability, PK, PD, immunogenicity, and ongoing

exploratory evaluations. Patients were randomly assigned (1:1:1) to one of 3 cohorts (5 patients per cohort were planned), as follows:

- Dose Level 1 = 2.5 mg/eye, single dose (0.05 mL) × 2 doses
- Dose level 2 = 5.0 mg/eye, single dose (0.10 mL) × 2 doses
- 5 • Sham = 0 mg/eye × 2 doses

Eighteen patients were randomized (7 to the 2.5 FabA group, 5 to the 5.0 mg FabA group, and 6 to the sham group) and 17 patients were treated. One patient in the 2.5 mg dose group was randomized, but was not treated. Sixteen patients completed the study.

10 Safety

Ocular TEAEs experienced by patients treated with FabA included conjunctival hyperemia (2.5 and 5 mg/eye), conjunctival hemorrhage (5 mg/eye only), and eye irritation (5 mg/eye only); none of these TEAEs were experienced by patients in the Sham group. Ocular TEAEs in the Sham group included eye pain, foreign body sensation
15 in eyes, ocular hyperemia, and vision blurred and occurred in 1 patient each.

Systemic TEAEs were experienced in the study; none were considered related to study treatment by the investigator.

- All TEAEs were mild in severity.
- All but one of the TEAEs reported occurred after the first dose but prior to the
20 second administration of study treatment.
- There were no serious or significant TEAEs.
- No patient discontinued treatment or withdrew from the study due to a TEAE.
- IOP returned to normal (< 21 mm Hg) for 16/17 patients within 30 minutes of the IVT injection and within 45 minutes for the remaining patient.
- 25 • Of the 11 patients dosed intravitreally with FabA, 6 patients tested positive during at least one time point. One patient was ADA positive with modest increase in titer over time, and the remaining 5 patients were positive at all time points, including predose, without any change in titer over time. One Sham patient was positive for ADA at all time points, including predose, without any change in titer over time. Together, these
30 data suggest an unclear relationship between ADA measurement and FabA dosing.

Overall Summary/Conclusions:

In patients with stable glaucoma, 2 IVT doses of FabA separated by 4 weeks were well tolerated up to 5 mg/eye. The ocular AEs reported were similar to those reported with IVT administration of approved drugs. In this study, no safety signals with FabA were observed.

- 5 Single doses of FabA IVT (2.5 and 5 mg/eye) inhibited free C1q in aqueous humor for at least 29 days.

Example 10: A Phase 2, Multicenter, Randomized, Parallel-Group, Double-Masked, 4-Arm, Sham-Controlled Study of the Efficacy, Safety, and Tolerability of FabA Administered by Intravitreal Injection in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

Rationale:

Brief Summary:

- 15 This study is being conducted in patients with GA secondary to AMD. The purpose of the study is to determine if intravitreal (IVT) injections of FabA once every month (EM) or once every other month (EOM) for 12 months reduces GA lesion growth rate. The study consists of a 30-day screening period and a 12-month treatment period, followed by a 6-month (off treatment) follow-up period. The total duration of patient participation is 19 months. Patients visit the clinic each month during the 12-month treatment period for treatment and/or safety assessments.

20 Approximately 240 patients are enrolled and randomly assigned to one of 4 treatment arms so that approximately 204 patients are evaluable at Month 12 for the primary analysis (primary analysis is based on modified intent-to-treat [ITT]).

Intervention Groups and Duration:

- 25 Study intervention assignment is based on randomization (2:2:1:1). Patients are assigned to one of the following treatment arms. Dose level is fixed and are not modified.
- Arm 1 = FabA 5.0 mg/eye (0.10 mL) once every month (EM) for 12 months (12 doses)
 - Arm 2 = FabA 5.0 mg/eye (0.10 mL) once every other month (EOM) for 12 months (6 doses)
 - Arm 3 = Sham injection EM for 12 months (12 Sham injections)
 - Arm 4 = Sham injection EOM for 12 months (6 Sham injections)
- 30

Injection

FabA/Sham administration is completed by the injecting physician using aseptic technique.

5 All patients randomized to FabA receive 5.0 mg/eye IVT (at a fixed volume of 0.10 mL) once every month or once every other month for 12 months.

Post-Injection

10 Immediately following drug administration, the injecting physician assesses hand motion vision or central retinal artery perfusion visualization. If necessary, rule out other causes of vision loss such as vitreous hemorrhage. If needed, perform digital massage, and administer topical/oral IOP lowering medications, until hand motion vision or central retinal artery perfusion is observed.

IOP (tonometry) is evaluated in the study eye only, 30 minutes after drug administration and, if elevated, every 15 minutes thereafter until IOP < 25 mmHg.

Pharmacokinetics, Pharmacodynamics, and Immunogenicity

15 Blood samples for PK (FabA serum concentrations) and PD evaluations (serum C1q concentrations and plasma concentrations of other biomarkers) are collected within 30 minutes before dosing and 3 hours (± 15 min) after dosing at the visits.

20 Samples for immunogenicity testing (ADA) are collected pre-injection during the site visits. Additionally, a sample for ADA is collected at Week 2 at the site or a home health visit.

Pharmacokinetics: This test requires serum. Blood samples are collected for measurement of serum concentrations of FabA.

Pharmacodynamics: This test requires serum and plasma. Serum concentrations of C1q and plasma concentrations of exploratory complement biomarkers are analyzed.

25 Immunogenicity: This test requires serum. Immunogenicity is assessed by analysis of serum anti-drug (FabA) antibodies (ADA).

PROCEDURE FOR INTRAVITREAL INJECTION

Preparation of FabA

30 Withdraw the entire volume of FabA (approximately 0.3 mL) from the sterile vial of FabA, using a sterile 1.0 cc syringe with a 19-gauge $\times$ 1-1/2 inch, 5 micron, filter needle.

Replace the filter needle with a 30-gauge $\times$ 1/2 inch injection needle. Expel the excess volume of FabA from the syringe just prior to injection, leaving only the required injection volume in the syringe.

The dose volume of FabA is fixed at 0.10 mL once every month (EM) for 12 months (12 doses) or once every other month (EOM) for 12 months (6 doses).

Preparation for Intravitreal Injection

1. Verify the study eye.

2. Measure and record the pre-op intraocular pressure (IOP) in the study eye before injection. Perform tonometry on study eye only. The IOP must be $\leq$ 21 mmHg to proceed. If $>$ 21 mmHg, reschedule the injection of FabA and manage the IOP at the Investigator's discretion.

3. Apply 1 drop of topical phenylephrine hydrochloride ophthalmic solution 2.5% to the study eye 30 minutes before the injection to allow visualization of the posterior pole after the injection, if necessary.

4. Immediately before injection:

- Have the patient lie back in the examination chair with the neck well supported.

Intravitreal Injection

1. Hand-washing, sterile gloves, and surgical mask are required for the injection.

2. Apply topical proparacaine 0.5% to the study eye.

3. Apply povidone-iodine 10% to the eyelashes and eyelid margins. Avoid extensive massage of the eyelids either pre- or post-injection to avoid meibomian gland expression.

4. Retract the eyelids away from the intended injection site for the duration of the procedure. Use of a speculum is recommended.

5. Apply povidone-iodine 5% to the conjunctival surface, including the intended injection site.

6. For injection with FabA: Insert the needle perpendicular to the sclera, 3.5 to 4 mm posterior to the limbus, between the vertical and horizontal rectus muscles. Apply a sterile cotton-tip applicator over the injection site immediately following removal of the needle to reduce vitreous reflux.

7. Sham injection: The preparation and post-injection care for the sham injection is identical to injection with FabA. The sham injection is performed by applying pressure to the eye at the location of a typical intravitreal injection using the blunt end of an empty syringe without a needle.

5 Post-Intravitreal Injection

1. Patients are to remain in the clinic after injection for ocular evaluations and safety follow-up.

2. Assess hand motion vision or central retinal artery perfusion immediately and rule out other causes of vision loss such as vitreous hemorrhage. Perform digital massage and administer topical/oral IOP lowering medications until hand motion vision or central retinal artery perfusion is observed, if no other cause is found.

3. Obtain IOP measurement in the study eye only at 30 minutes post-injection and, if elevated, every 15 minutes until IOP < 25 mmHg. Intraocular pressure in excess of 30 mmHg for more than 15 minutes should be treated at the physician's discretion.

15 4. Topical antibiotics are not required.

Example 11: C1q Mediates Microglial Pruning of Photoreceptor Synapses in a Light Damage Model of Photoreceptor Degeneration

Anti-C1q treatment (e.g., Mab3) reduces retinal complement levels (Figures 5A-5D), decreases inflammation (Figures 13A and 13B) and reduces neurodegeneration (Figures 13A and 13C-13D) in the light damage model. Figures 13A-13D show immunofluorescence (IF) data. Figure 13B shows reduced microgliosis in the outer plexiform layer (OPL) (aka outer synaptic layer) of the Retina at day 3 post-treatment. A reduction in microgliosis is associated with decreased inflammation. Figure 13C shows the significant preservation of photoreceptor synapses and Figure 13D shows the significant preservation of cell bodies at day 5 post-treatment. The measurement of preserved photoreceptor synapses and cell bodies post-treatment demonstrates that treatment with the anti-C1q treatment reduces neurodegeneration in this light damage model.

30

Example 12: Anti C1q intravitreal treatment reduced retinal complement component level in the rd10 mouse model

Measurable treatment (e.g., Mab3) levels were found in retina lysates from animals receiving anti-C1q treatment, but not in IgG1-treated or untreated groups (Figure 14A). Increased levels of classical complement component C1q were confirmed in retina lysates from both untreated and IgG d10 animals, compared to WT (Figure 14B). Anti-C1q treatment resulted in reduced C1q levels in retina lysates compared to IgG1-treated and untreated rd10 groups (Figure 14B), confirming good measurable PK and C1q engagement in retina (and in plasma, data not shown). Figure 15A is a bar graph representing a quantification of immunofluorescence images, and Figure 15B shows immunofluorescence images demonstrating the preservation of the photoreceptor synapses (BSN marker) upon treatment with a C1q inhibitor. This is evidence of photoreceptor synapse protection.

INCORPORATION BY REFERENCE

Each of the patents, published patent applications, and non-patent references cited herein are hereby incorporated by reference in their entirety.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method of treating an inherited retinal disease in a human patient, comprising administering to the patient a composition comprising about 1 mg to about 10 mg of an anti-C1q antibody via an intravitreal injection,
5 wherein the antibody comprises a light chain variable domain comprising an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7; and a heavy chain variable domain comprising an HVR-H1 having the amino acid sequence of SEQ ID NO: 9, an HVR-H2 having the amino acid of
10 SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11.
2. The method of claim 1, wherein the inherited retinal disease is retinitis pigmentosa.
3. The method of claim 1, wherein the inherited retinal disease is choroideremia.
4. The method of claim 1, wherein the inherited retinal disease is Stargardt disease.
- 15 5. The method of claim 1, wherein the inherited retinal disease is cone-rod dystrophy.
6. The method of claim 1, wherein the inherited retinal disease is leber congenital amaurosis.
7. The method of claim 1, wherein the inherited retinal disease is X-linked RP.
- 20 8. The method of claim 1, wherein the inherited retinal disease is Usher Syndrome.
9. A method of treating retinal detachment in a human patient, comprising administering to the patient a composition comprising about 1 mg to about 10 mg of an anti-C1q antibody via an intravitreal injection,
25 wherein the antibody comprises a light chain variable domain comprising an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7; and a heavy chain variable domain comprising an HVR-H1 having the

amino acid sequence of SEQ ID NO: 9, an HVR-H2 having the amino acid of SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11.

10. The method of claim 9, wherein the anti-C1q antibody is administered before retinal detachment surgery.

5 11. The method of claim 9, wherein the anti-C1q antibody is administered after retinal detachment surgery.

12. The method of claim 9, wherein the anti-C1q antibody is administered simultaneous with retinal detachment surgery.

10 13. The method of any one of claims 1-12, wherein the method restores vision in the human patient.

14. The method of any one of claims 1-12, wherein the method improves vision in the human patient.

15. The method of any one of claims 1-14, wherein the antibody comprises a light chain variable domain comprising an amino acid sequence with at least about 95%
15 homology to the amino acid sequence selected from SEQ ID NO: 4 and 35-38 and wherein the light chain variable domain comprises an HVR-L1 having the amino acid sequence of SEQ ID NO: 5, an HVR-L2 having the amino acid of SEQ ID NO: 6, and an HVR-L3 having the amino acid of SEQ ID NO: 7.

20 16. The method of claim 15, wherein the light chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 4 and 35-38.

17. The method of any one of claims 1-16, wherein the antibody comprises a heavy chain variable domain comprising an amino acid sequence with at least about 95% homology to the amino acid sequence selected from SEQ ID NO: 8 and 31-34 and wherein the heavy chain variable domain comprises an HVR-H1 having the amino acid
25 sequence of SEQ ID NO: 9, an HVR-H2 having the amino acid of SEQ ID NO: 10, and an HVR-H3 having the amino acid of SEQ ID NO: 11.

18. The method of claim 17, wherein the heavy chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 8 and 31-34.

19. The method of any one of claims 1-18, wherein the antibody is a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody, an antibody
5 fragment, or antibody derivative thereof.

20. The method of claim 19, wherein the antibody is an antibody fragment and the antibody fragment is a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a diabody, or a single chain antibody molecule.

21. The method of claim 20, wherein the Fab fragment comprises a heavy chain Fab
10 fragment of SEQ ID NO: 39 and a light chain Fab fragment of SEQ ID NO: 40.

22. The method of any one of claims 1-21, wherein the antibody is administered once a week.

23. The method of any one of claims 1-21, wherein the antibody is administered once every other week.

15 24. The method of any one of claims 1-21, wherein the antibody is administered once every three weeks.

25. The method of any one of claims 1-21, wherein the antibody is administered once a month.

26. The method of any one of claims 1-21, wherein the antibody is administered once
20 every four weeks.

27. The method of any one of claims 1-21, wherein the antibody is administered once every six weeks.

28. The method of any one of claims 1-21, wherein the antibody is administered once every 8 weeks.

25 29. The method of any one of claims 1-21, wherein the antibody is administered once every other month.

30. The method of any one of claims 1-21, wherein the antibody is administered once every 10 weeks.
31. The method of any one of claims 1-21, wherein the antibody is administered once every 12 weeks.
- 5 32. The method of any one of claims 1-21, wherein the antibody is administered once every three months.
33. The method of any one of claims 1-21, wherein the antibody is administered once every 4 months.
34. The method of any one of claims 22-33, wherein the antibody is administered for
10 at least 3 months, at least 4 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, or at least 12 months.
35. The method of any one of claims 22-34, wherein the antibody is administered for 12 months.
36. The method of any one of claims 1-35, wherein the administered composition
15 comprises about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 6.5 mg, about 7 mg, about 7.5 mg, about 8 mg, about 8.5 mg, about 9 mg, about 9.5 mg, or about 10 mg of the anti-C1q antibody.
37. The method of any one of claims 1-36, wherein the composition comprises
20 administering about 1 mg of the anti-C1q antibody.
38. The method of any one of claims 1-36, wherein the composition comprises administering about 2.5 mg of the anti-C1q antibody.
39. The method of any one of claims 1-36, wherein the composition comprises administering about 5 mg of the anti-C1q antibody.
- 25 40. The method of any one of claims 1-36, wherein the composition comprises administering about 2 mg of the anti-C1q antibody.

41. The method of any one of claims 1-36, wherein the composition comprises administering about 5 mg of the anti-C1q antibody.
42. The method of any one of claims 1-36, wherein the composition comprises administering about 10 mg of the anti-C1q antibody.
- 5 43. The method of any one of claims 1-36, wherein the composition comprises administering about 1 mg to about 2.5 mg, about 2.5 mg to about 5 mg, about 5 mg to about 7.5 mg, or about 7.5 mg to about 10 mg of the anti-C1q antibody.

FIGURES

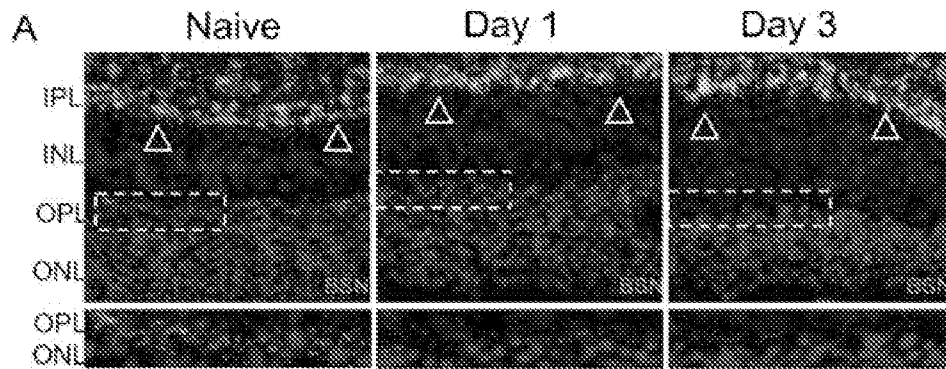


Figure 1A

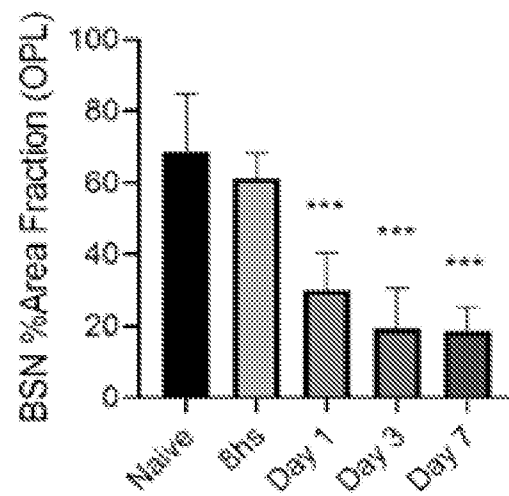


Figure 1B

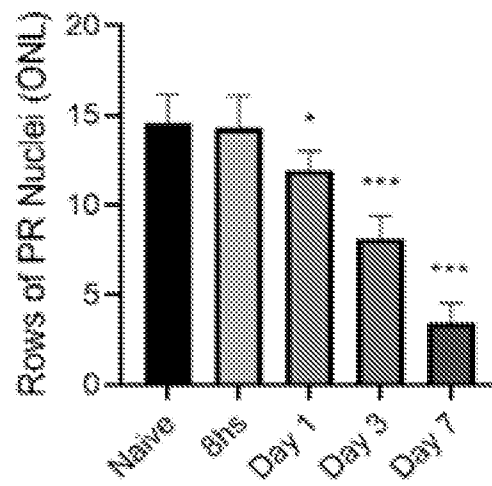


Figure 1C

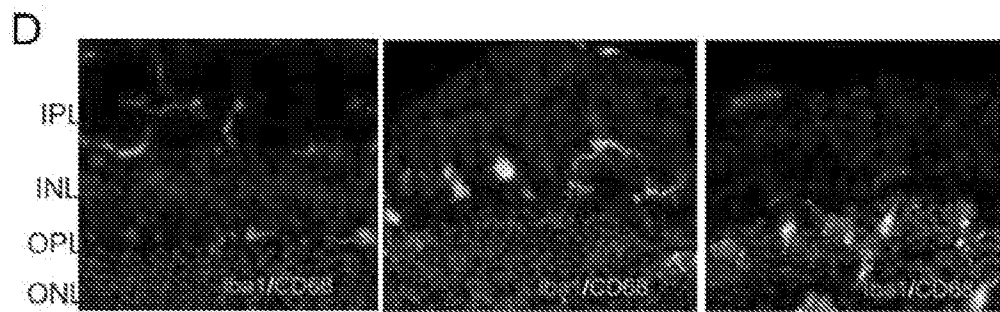


Figure 1D

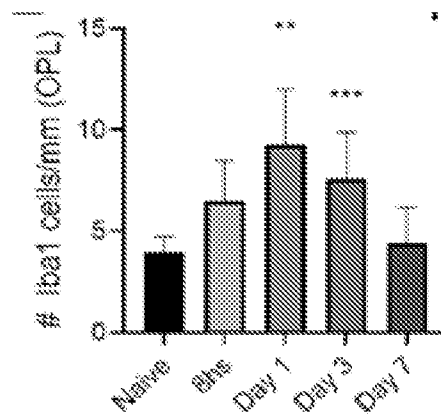


Figure 1E

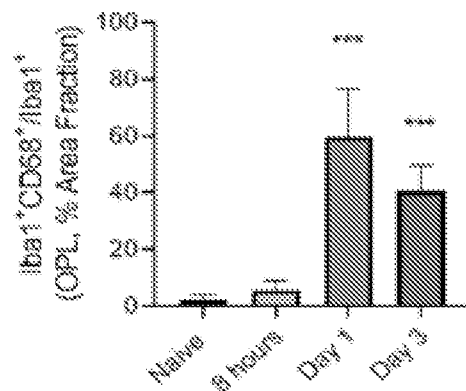


Figure 1F

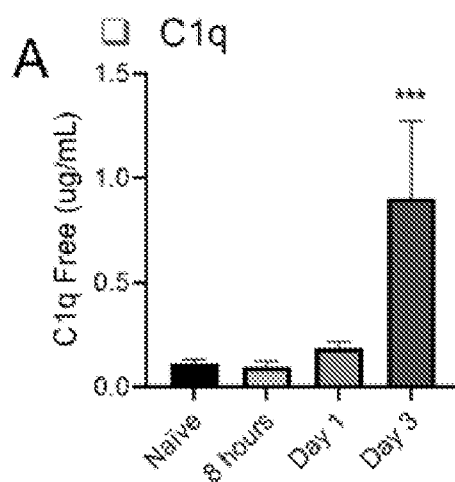


Figure 2A

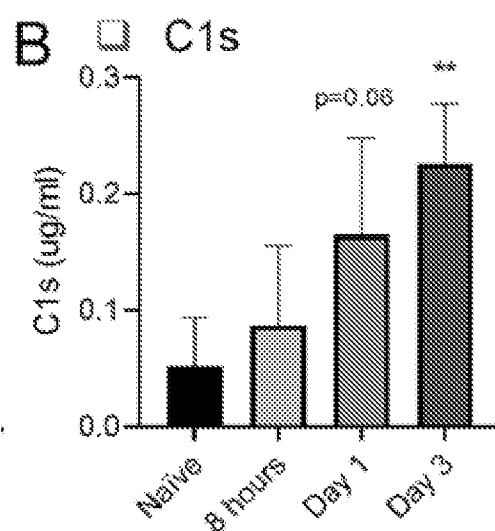


Figure 2B

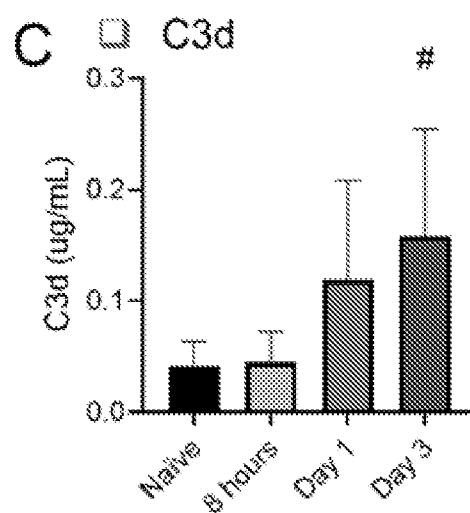


Figure 2C

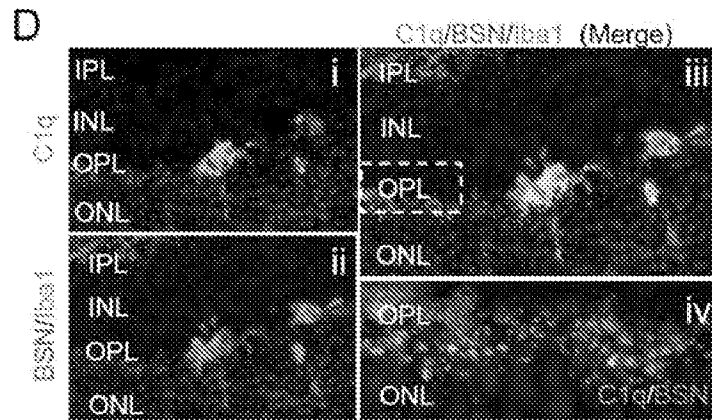


Figure 2D

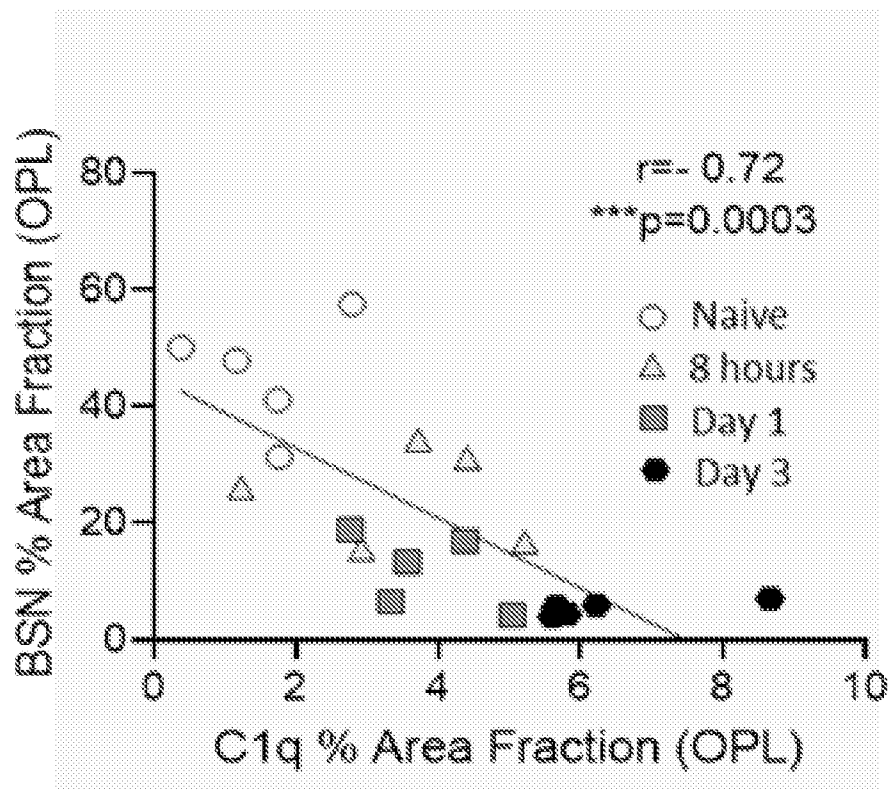


Figure 2E

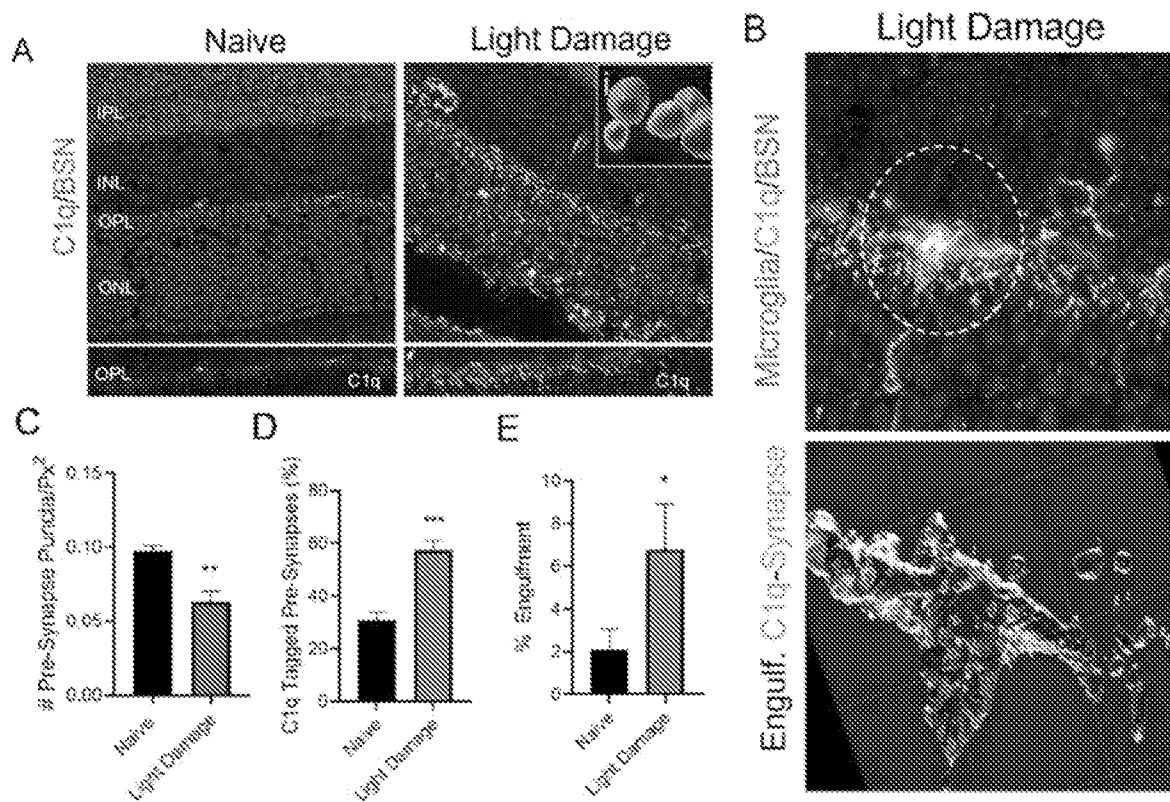


Figure 3

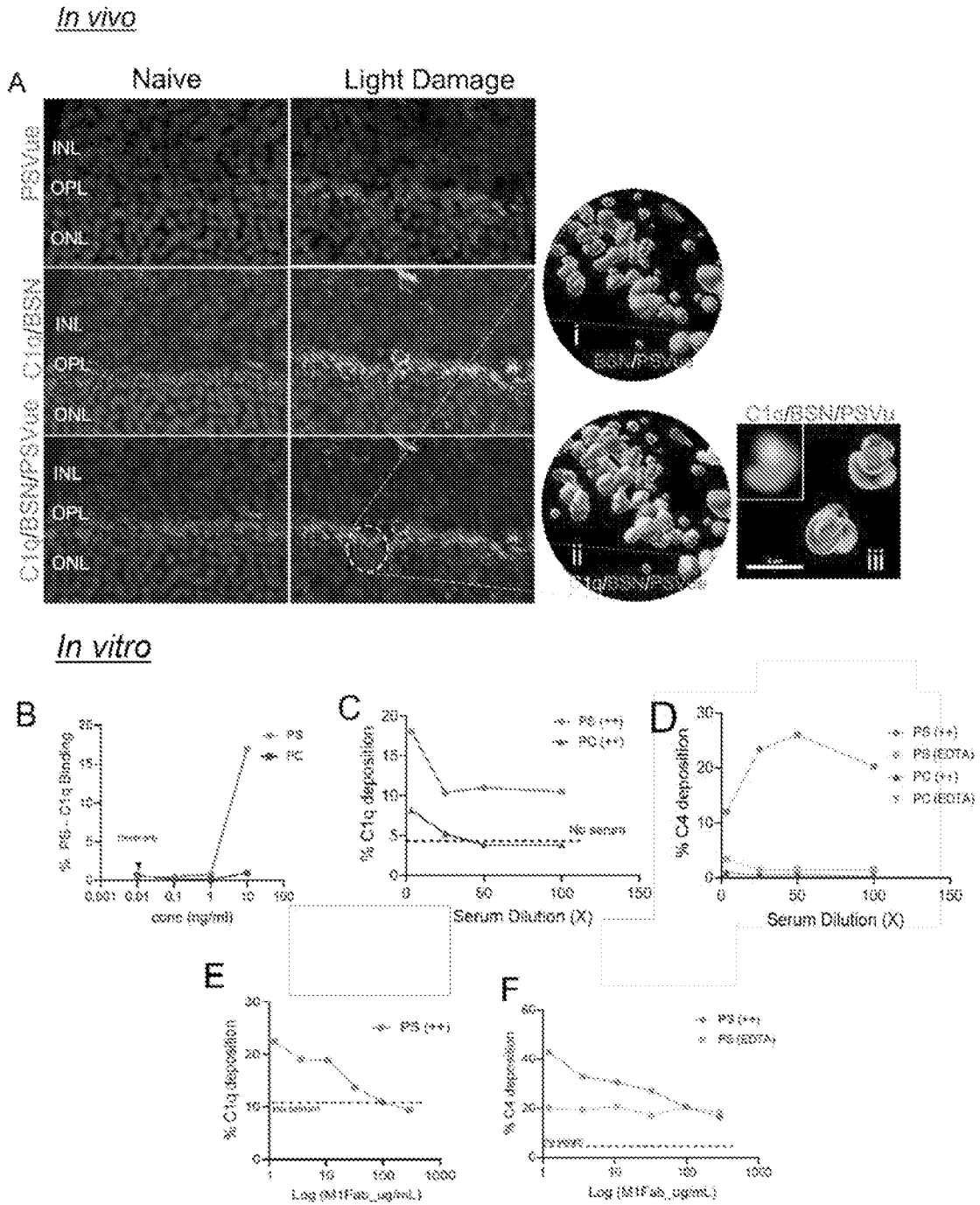


Figure 4

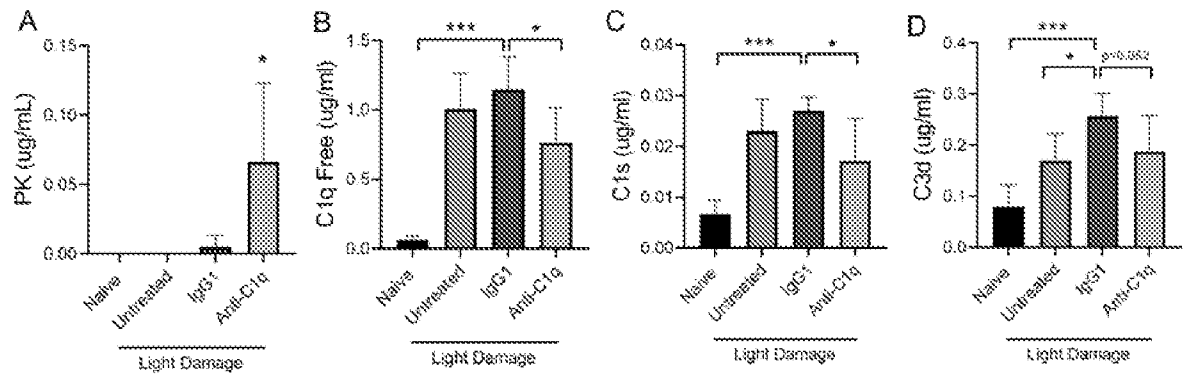


Figure 5

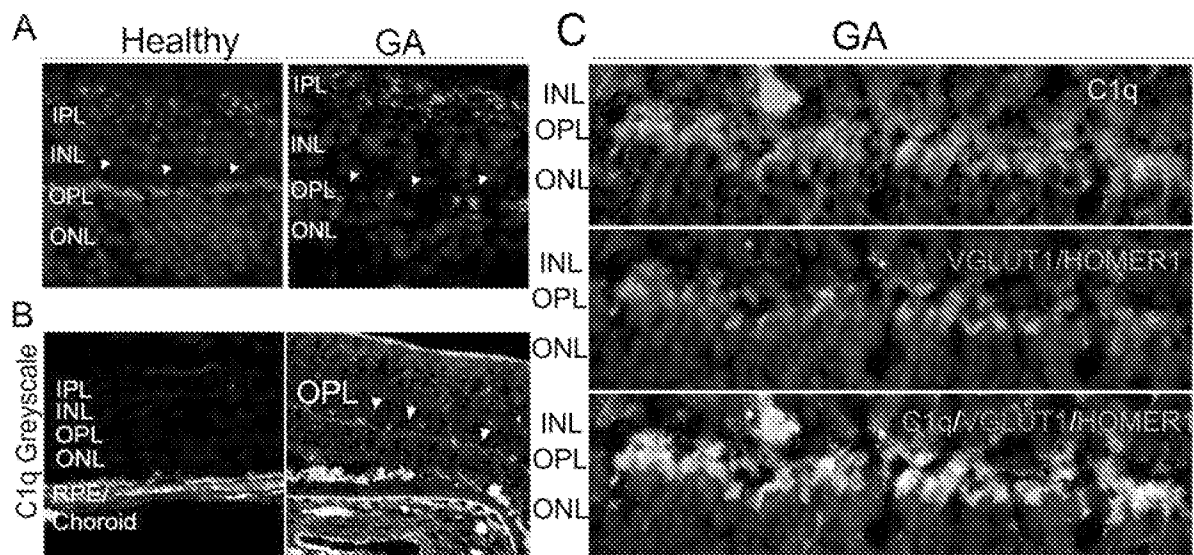


Figure 6

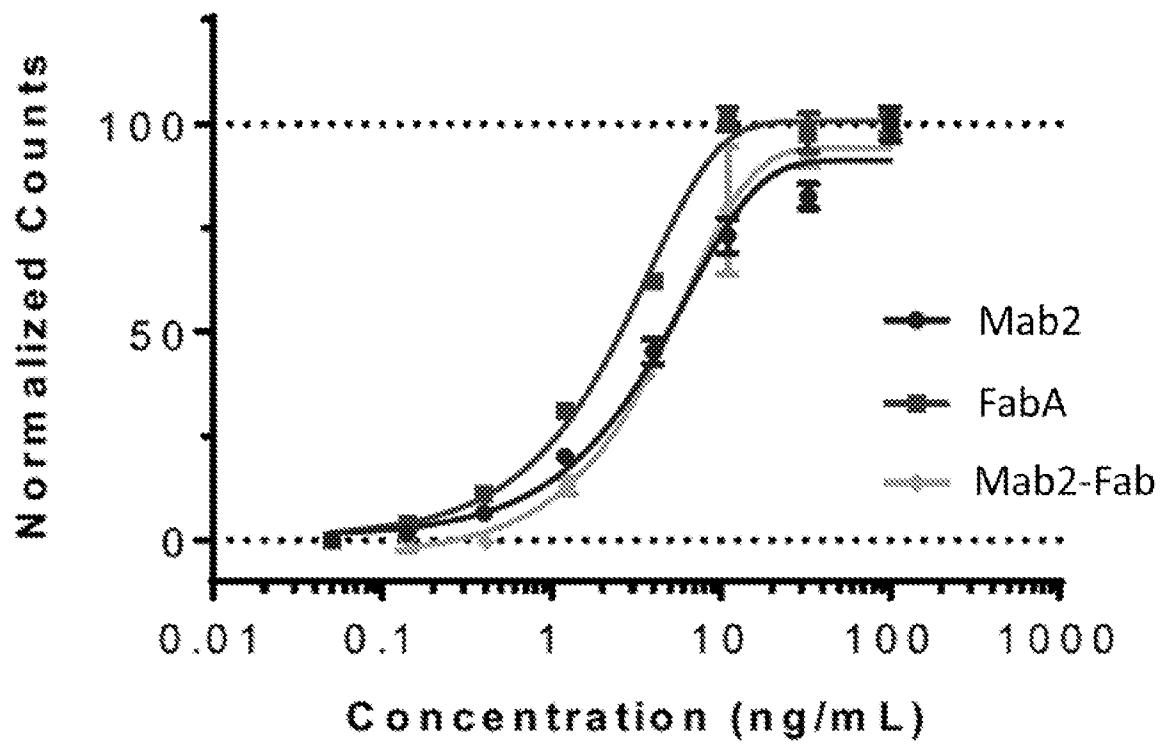


Figure 7

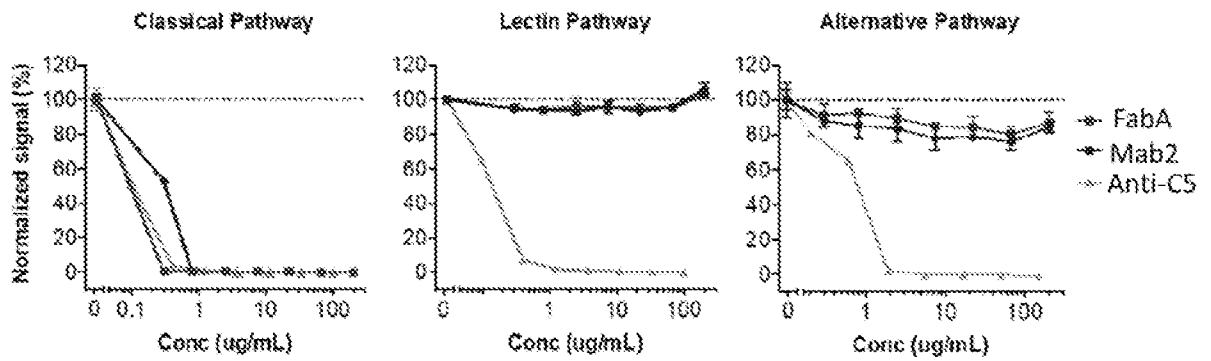


Figure 8

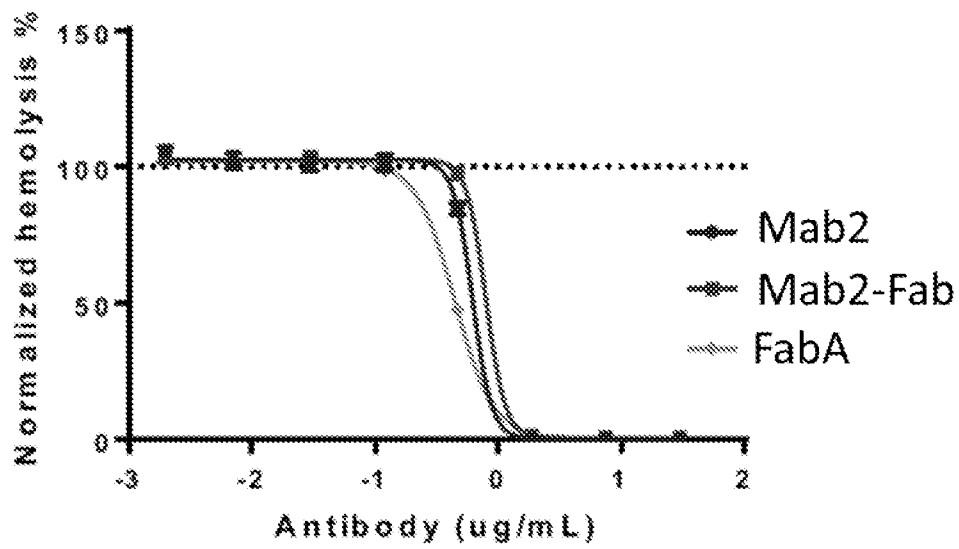


Figure 9

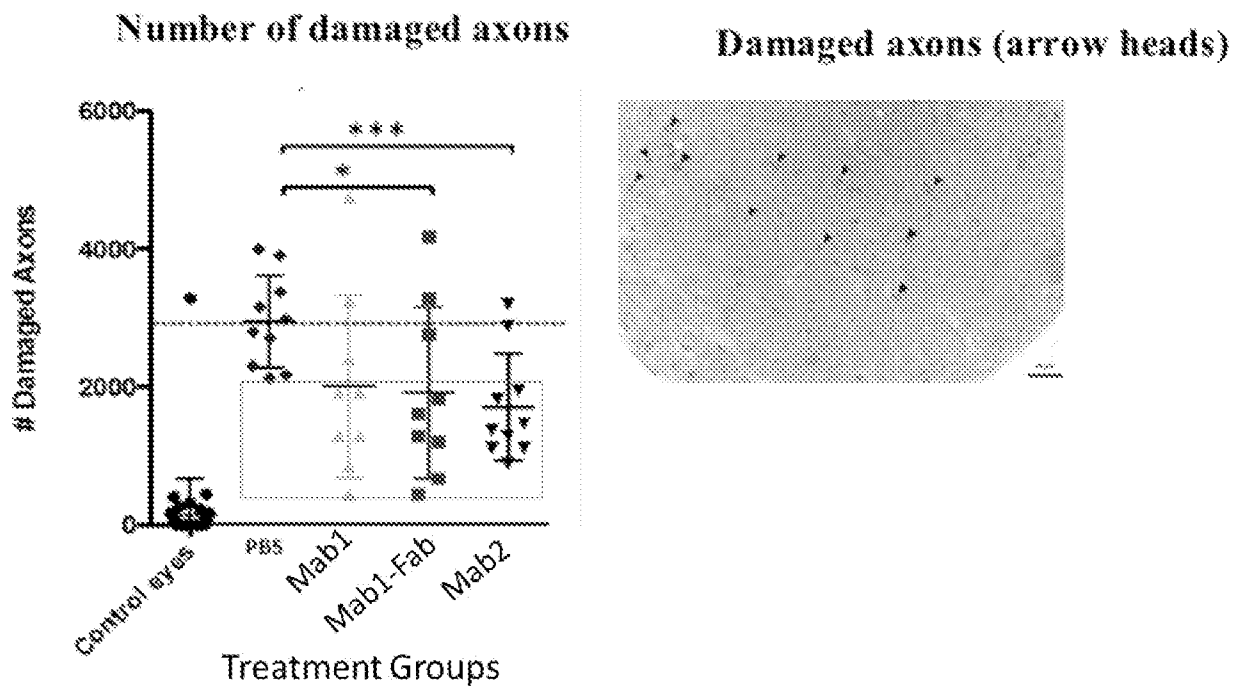


Figure 10

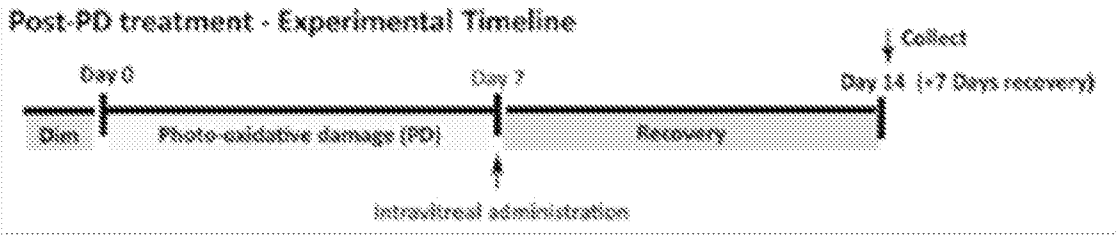


Figure 11A

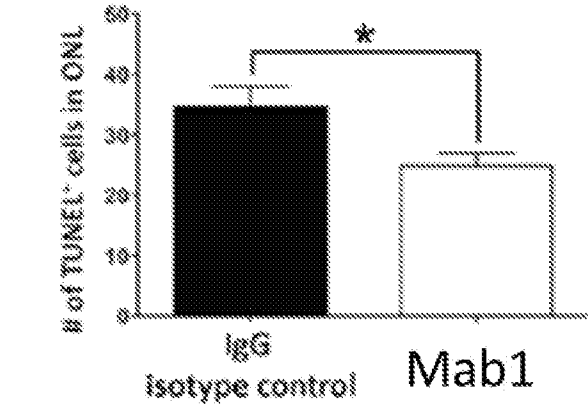


Figure 11B

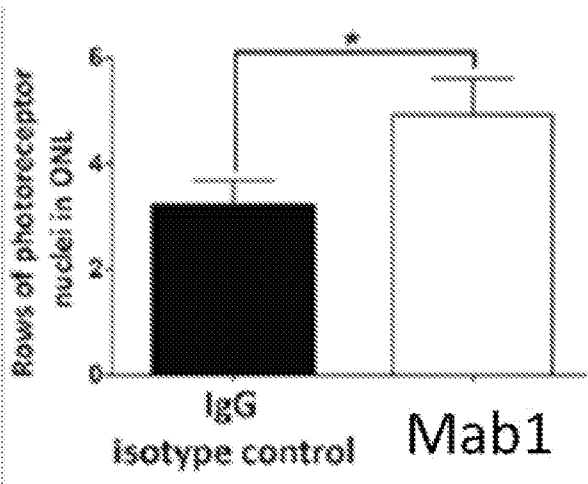


Figure 11C

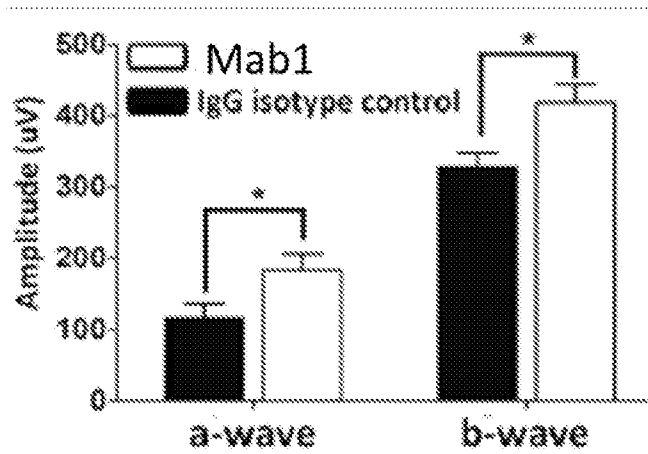


Figure 11D

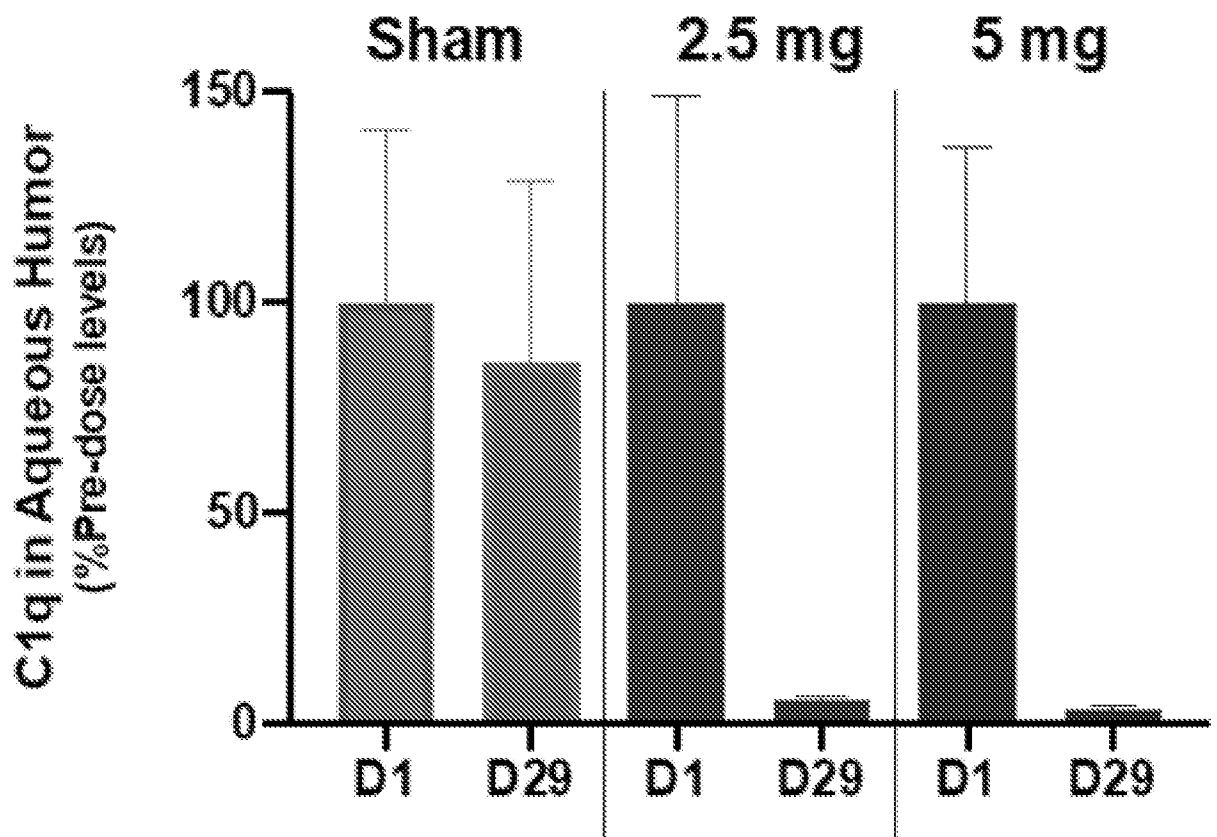


Figure 12

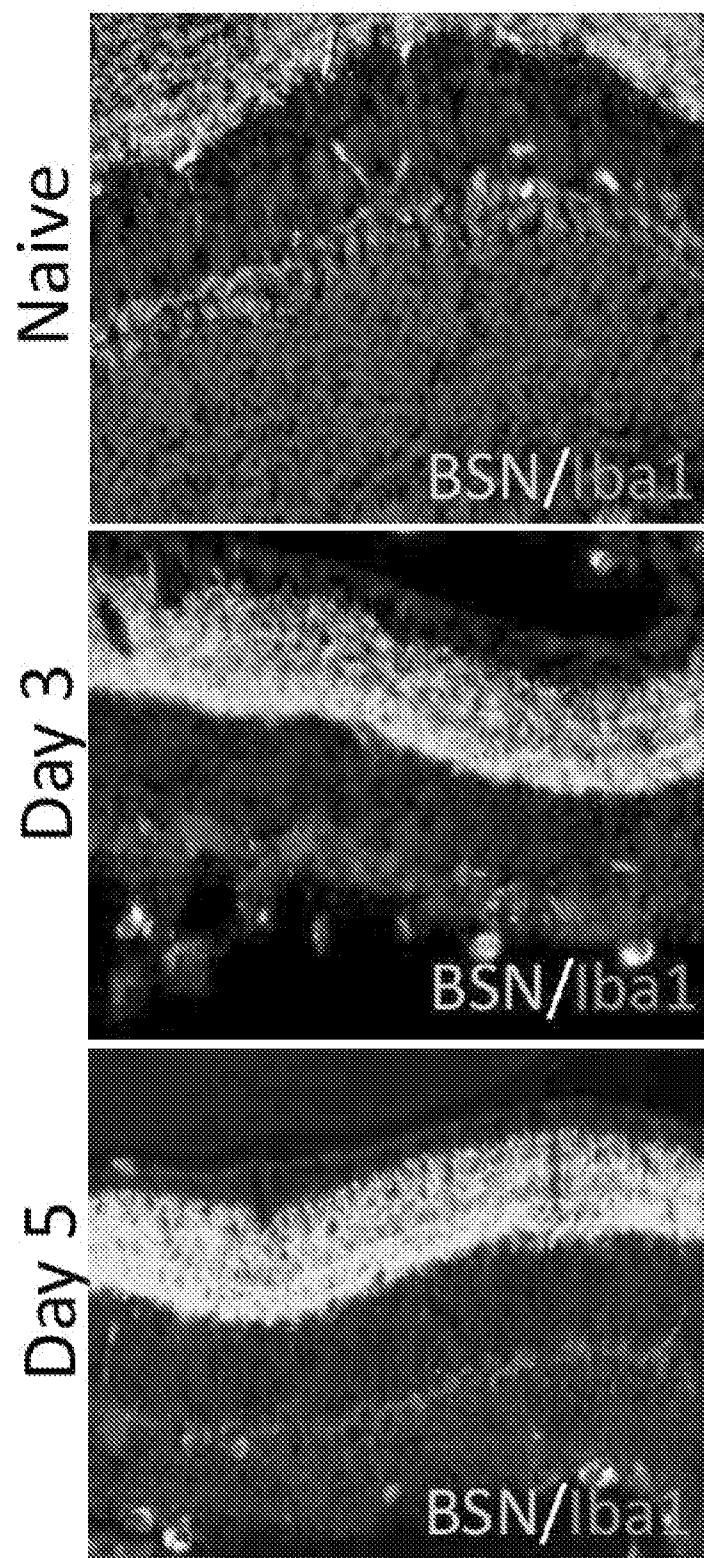


Figure 13A

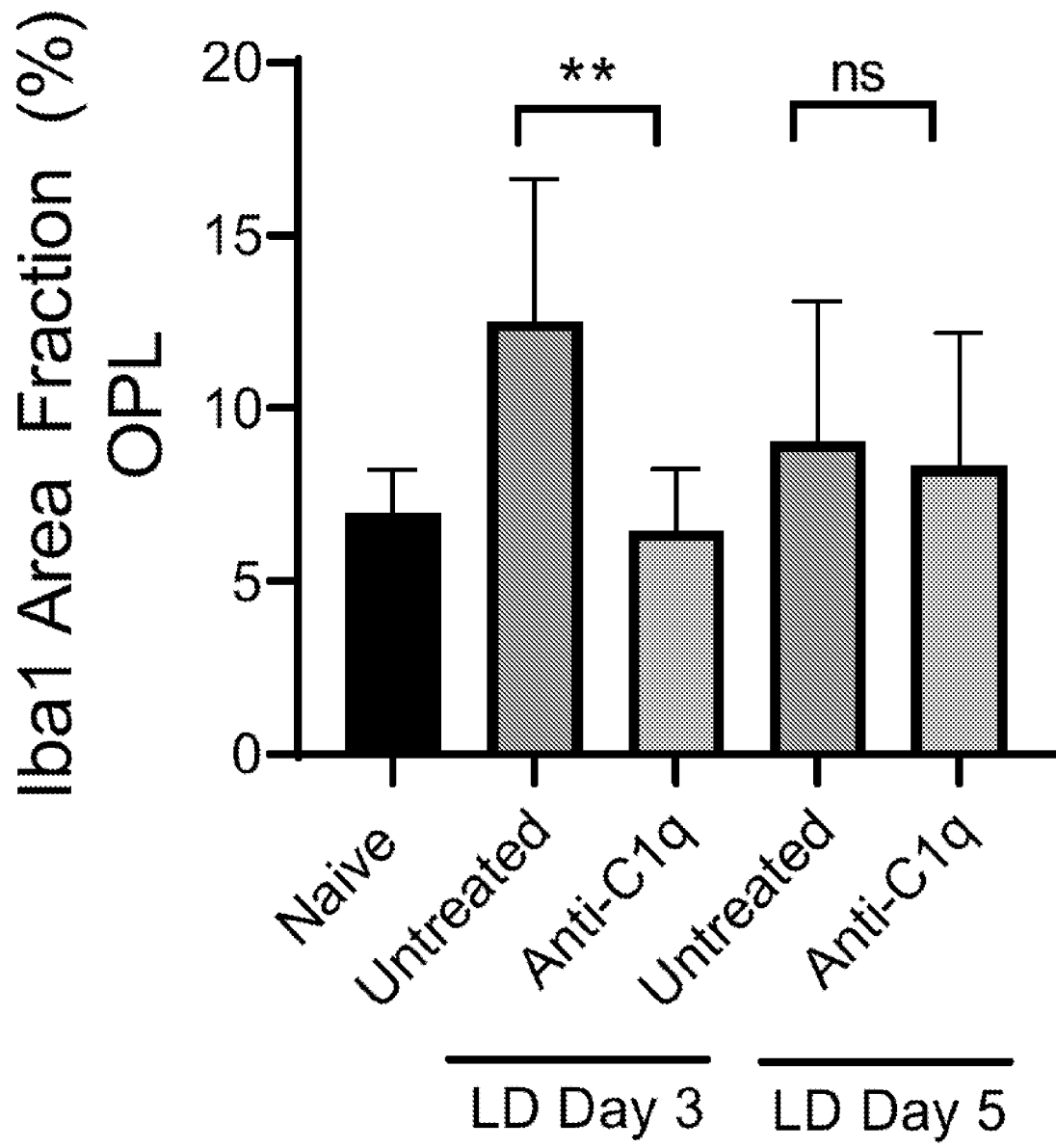


Figure 13B

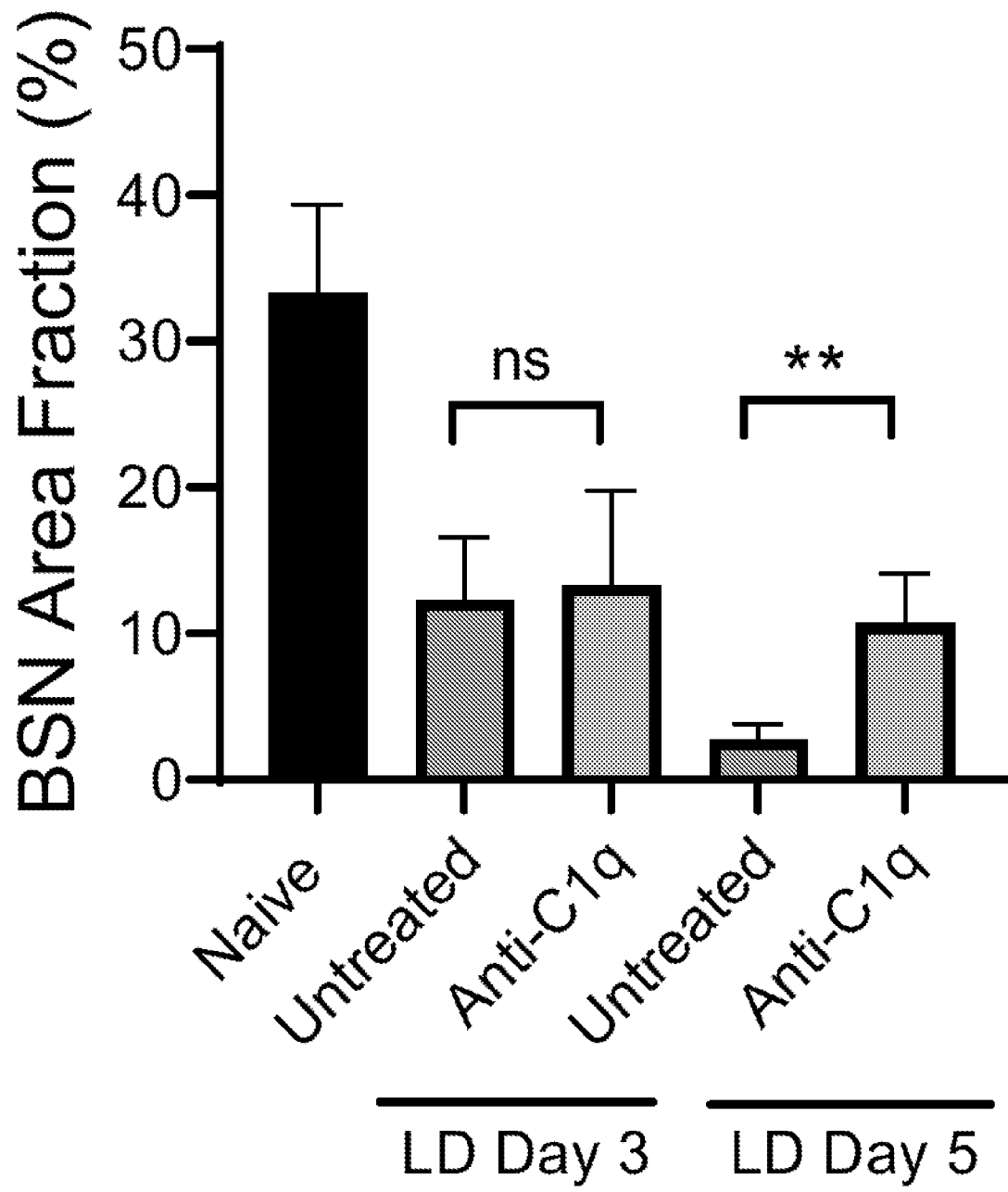


Figure 13C

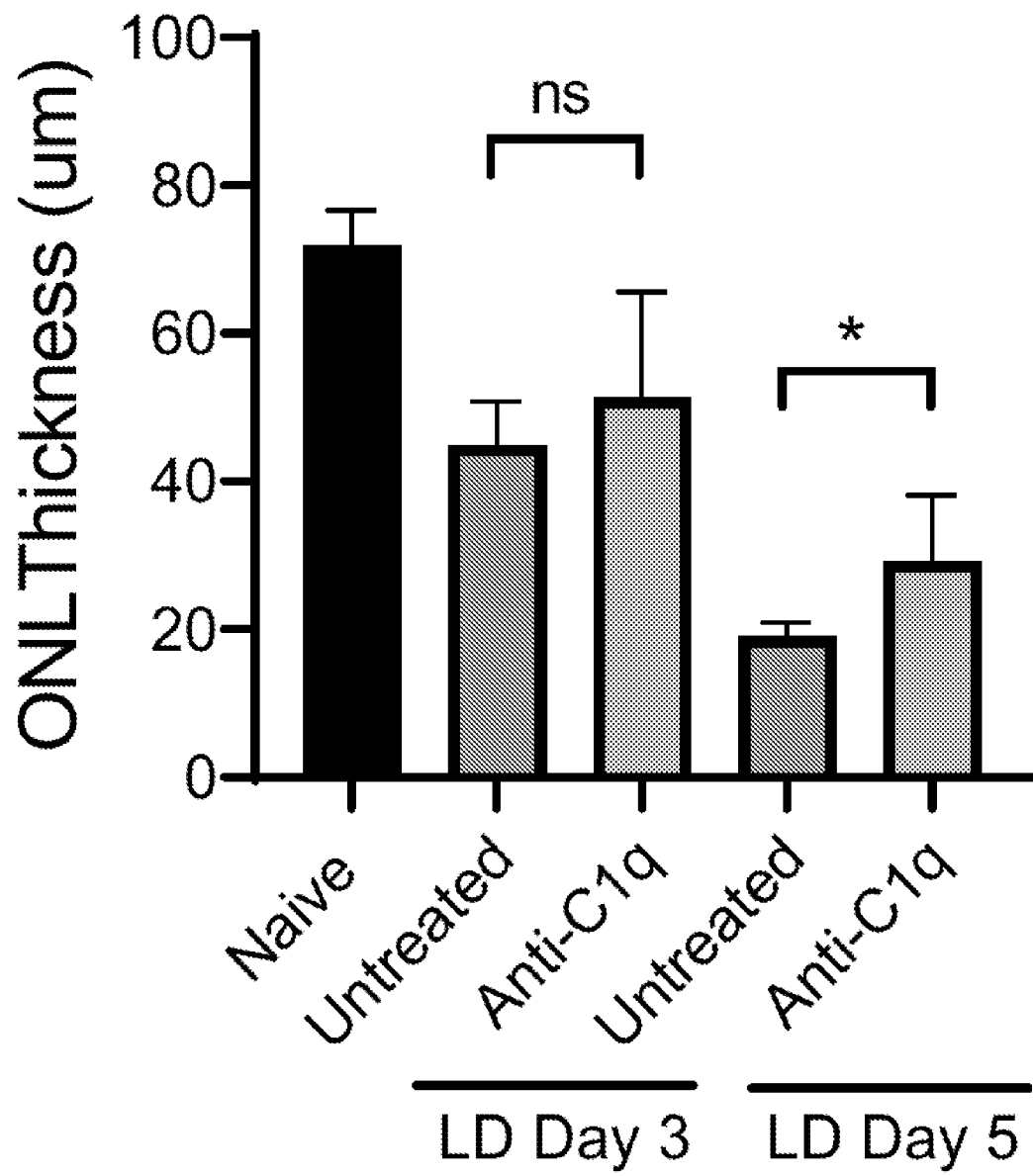


Figure 13D

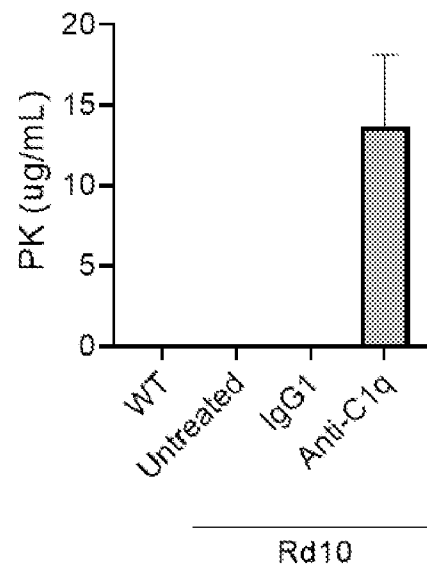


Figure 14A

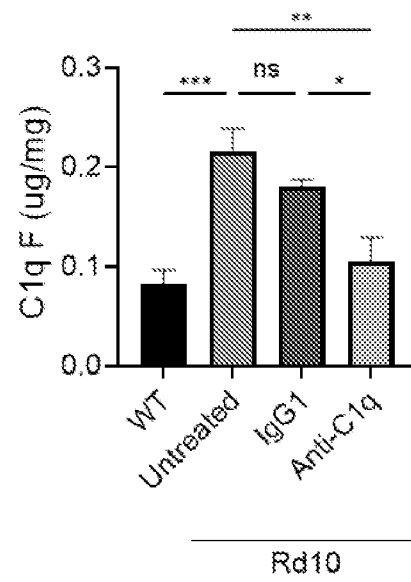


Figure 14B

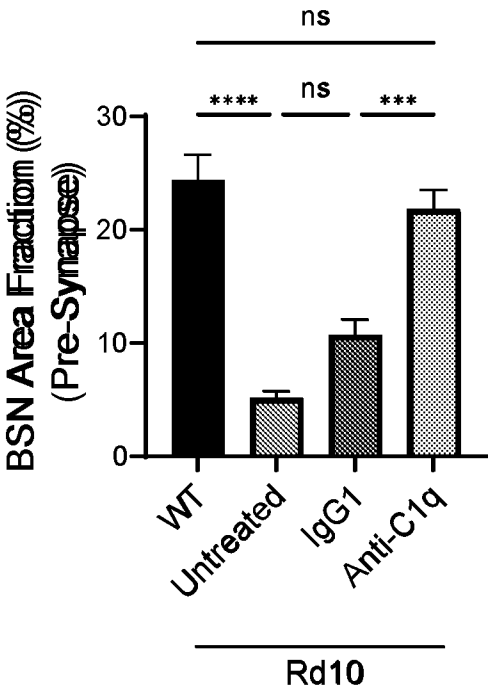


Figure 15A

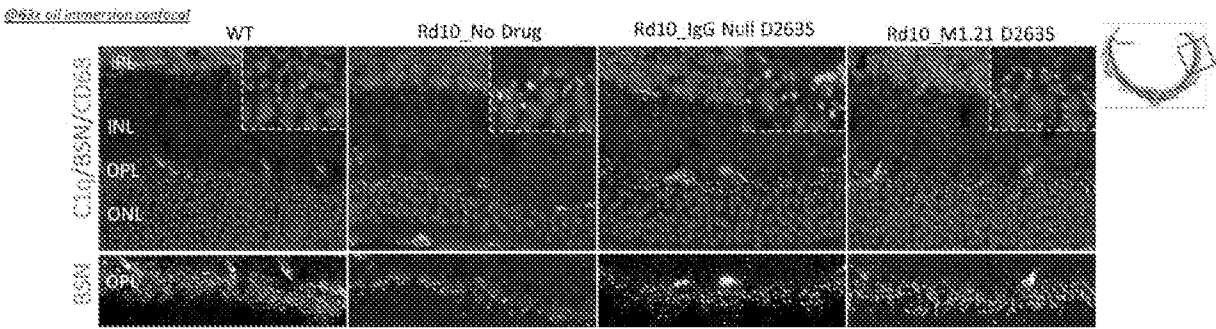


Figure 15B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/066393

A. CLASSIFICATION OF SUBJECT MATTER A61K 39/395 (2023.01)i; A61P 27/02 (2023.01)i CPC:A61K 39/395; A61P 27/02 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K 39/395; A61P 27/02 CPC:A61K 39/395; A61P 27/02 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Databases consulted: CAPLUS, BIOSIS, EMBASE, MEDLINE, PubMed, Derwent Innovation Search terms used: retinal, retinitis pigmentosa, rod-cone dystrophy, choroideremia, Stargardt, cone-rod dystrophy, leber congenital amaurosis, X-linked RP, Usher Syndrome, c1q, complement		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Jiao, Haihan, et al. "Subretinal macrophages produce classical complement activator C1q leading to the progression of focal retinal degeneration." Molecular neurodegeneration 13.1 (2018): 1-18.# https://doi.org/10.1186/s13024-018-0278-0 (2018/08/20) page 5 left column third para. , page 7 right column –page 9 right column, figures 1 and 4	1-8,13-43
Y	WO 2007103549 A2 (ARCHEMIX CORP[US]; EPSTEIN DAVID[US]; KURZ JEFF C[US]) 13 September 2007 (2007-09-13) examples, claims	1-8,13-43
Y	WO 2017091719 A1 (ANNEXON INC[US]) 01 June 2017 (2017-06-01) example, claims	20,21
P,Y	WO 2022120137 A1 (ANNEXON INC[US]) 09 June 2022 (2022-06-09) example, claims	1-8,13-43
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents: “A” document defining the general state of the art which is not considered to be of particular relevance “D” document cited by the applicant in the international application “E” earlier application or patent but published on or after the international filing date “L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) “O” document referring to an oral disclosure, use, exhibition or other means “P” document published prior to the international filing date but later than the priority date claimed “T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention “X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone “Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art “&” document member of the same patent family		
Date of the actual completion of the international search 20 August 2023		Date of mailing of the international search report 21 August 2023
Name and mailing address of the ISA/IL Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Israel Telephone No. 972-73-3927172 Email: pctoffice@justice.gov.il		Authorized officer HOROWITZ Anat Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/066393

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- [0001] Invention/s 1 : Claim/s 1-8,13-43 : A method of treating an inherited retinal disease in a human patient, comprising administering to the patient a composition comprising about 1 mg to a about 10 mg of an anti-C1q antibody via an intravitreal injection, wherein the antibody comprises a light and heavy chain variable domains comprising HVR as specified in claim 1.
- [0002] Invention/s 2 : Claim/s 9-43 : A method of treating retinal detachment in a human patient, comprising administering to the patient a composition comprising about 1 mg to a about 10 mg of an anti-C1q antibody via an intravitreal injection, wherein the antibody comprises a light and heavy chain variable domains comprising HVR as specified in claim 9.
- [0003] The International Preliminary Examining Authority is of the opinion that the present application does not comply with the requirements of unity as set forth in Article. 3(4)iii and Rule 13 PCT. An international application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions, involving one or more of the same special technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The following 2 separate inventions have been identified: Invention 1: Claims Nos. 1-8 (all) 13-43 (partially). A method of treating an inherited retinal disease in a human patient, comprising administering to the patient a composition comprising about 1 mg to a about 10 mg of an anti-C1q antibody via an intravitreal injection, wherein the antibody comprises a light and heavy chain variable domains comprising HVR as specified in claim 1. Invention 2: Claims Nos. 9-12 (all) 13-43 (partially). A method of treating retinal detachment in a human patient, comprising administering to the patient a composition comprising about 1 mg to a about 10 mg of an anti-C1q antibody via an intravitreal injection, wherein the antibody comprises a light and heavy chain variable domains comprising HVR as specified in claim 9. The said Inventions are not linked so as to form a single general inventive concept for the following reasons: The feature that links Invention 1, Invention 2 as defined above is method of treatment of diseases associated to the retina, via an intravitreal injection of the antibody specified in the claims. However, such method had already been documented in the prior art (see D1). Therefore, this feature cannot be accepted to constitute a common special technical feature for the whole scope of the present application that would define an appreciable contribution over the prior art. Consequently, the present application does not meet the requirement of unity of invention, as there is no single inventive concept underlying the plurality of the claimed inventions in the present application, in the sense of Rule 13.1 PCT. Consequently, search and examination of the present application has been restricted to the first mentioned group of inventions (vide supra Invention 1).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/066393

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-8,13-43**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US2023/066393

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2007103549	A2	13 September 2007	WO	2007103549	A2	13 September 2007
				WO	2007103549	A3	27 December 2007
				AU	2007223796	A1	13 September 2007
				AU	2007223796	B2	24 January 2013
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				CN	101443050	A	27 May 2009
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				DK	1991275	T3	08 December 2014
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				EP	1991275	A2	19 November 2008
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				HK	1181308	A1	08 November 2013
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				JP	2013067661	A	18 April 2013
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				KR	20080100388	A	17 November 2008
				KR	101513308	B1	28 April 2015
				KR	20140072219	A	12 June 2014
				KR	101584468	B1	13 January 2016
				KR	20150017388	A	16 February 2015
				MX	2008011323	A	18 November 2008
				NZ	571791	A	30 March 2012
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				PL	2596807	T3	30 June 2016
				PT	1991275	E	03 February 2015
				PT	2596807	E	18 March 2016
				RU	2008139901	A	20 April 2010
				RU	2477137	C2	10 March 2013

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US2023/066393

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				SG	10201706440R A	28 September 2017
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				AU	2016361517 A1	14 June 2018
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				EP	3380518 A1	03 October 2018
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				JP	2019501132 A	17 January 2019
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				SG	11201803703U A	28 June 2018
				US	2017152309 A1	01 June 2017
				US	10723788 B2	28 July 2020
				US	2020317765 A1	08 October 2020
WO	2022120137	A1	09 June 2022	WO	2022120137 A1	09 June 2022
				AU	2021391800 A1	22 June 2023