mechanism and preserve favorable upstream activities of complement activation the current application reveals the development of a novel therapeutic monoclonal antibody that binds C5 but uniquely allows processing of the C5 molecule to C5a and C5b but inhibits formation of MAC, Figure 2, thus preventing formation of the key pathogenic component associated with AMD. Through blocking MAC formation, while preserving key supportive ocular tissues i.e., choroicapilars and RPE, function and survival of the neural retina, which is vital to maintaining vision will be retained.

SUMMARY OF THE INVENTION

[0008] The invention encompasses methods and compositions of a pharmaceutical formulation comprising an anti-complement C5 antibody or anti-C5 antibody. In one aspect, the anti-C5 antibody does not bind to C5a and inhibits complement dependent hemolysis. In another aspect, the anti-C5 antibody binds to C5b and inhibits the formation of membrane attack complex (MAC) in a patient. In one embodiment, the anti-C5 antibody blocks C5 binding to human complement component 6. In another embodiment, the anti-C5 antibody blocks C5 binding to human complement component 7. In another aspect, the anti-C5 antibody is characterized by the feature that it no longer binds or has reduced binding to C5 (or a subunit thereof) once it is incorporated into the membrane attack complex.

[0008a] In another aspect, there is provided an anti-C5 antibody, wherein the antibody binds to C5 and inhibits complement dependent hemolysis, but does not block C5a formation, wherein the antibody comprises a light chain variable domain and a heavy chain variable domain and selected from the group consisting of:

(i) an antibody in which the light chain variable domain comprises a CDR1 of SEQ ID NO: 25, a CDR2 of SEQ ID NO: 26 and a CDR3 of SEQ ID NO: 27 and in which the heavy chain variable domain comprises a CDR1 of SEQ ID NO: 28, a CDR2 of SEQ ID NO: 29 and a CDR3 of SEQ ID NO: 30,

(ii) an antibody in which the light chain variable domain comprises a CDR1 of SEQ ID NO: 31, a CDR2 of SEQ ID NO: 32 and a CDR3 of SEQ ID NO: 33 and in which the heavy chain variable domain comprises a CDR1 of SEQ ID NO: 34, a CDR2 of SEQ ID NO: 35 and a CDR3 of SEQ ID NO: 36,

(iii) an antibody in which the light chain variable domain comprises a CDR1 of SEQ ID NO: 37, a CDR2 of SEQ ID NO: 38 and a CDR3 of SEQ ID NO: 39 and in which the heavy chain variable domain comprises a CDR1 of SEQ ID NO: 40, a CDR2 of SEQ ID NO: 41 and a

CDR3 of SEQ ID NO: 42, and

(iv) an antibody in which the light chain variable domain comprises a CDR1 of SEQ ID NO: 43, a CDR2 of SEQ ID NO: 44 and a CDR3 of SEQ ID NO: 45 and in which the heavy chain variable domain comprises a CDR1 of SEQ ID NO: 46, a CDR2 of SEQ ID NO: 47 and a CDR3 of SEQ ID NO: 48.

[0009] In another aspect, the anti-complement C5 antibody or anti-C5 antibody binds to C5 with a Kd of less than about 10 pM. In another aspect, the anti-C5 antibody is a monoclonal antibody. In another embodiment, the anti-C5 antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody, a chimeric antibody, a multispecific antibody and an antibody fragment. In one embodiment, the anti-C5 antibody is an antibody fragment and that 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. In another embodiment, the anti-C5 antibody is an IgG1, IgG2, IgG3, or IgG4. In another embodiment, the anti-C5 antibody is an IgG1.

[0010] In another aspect, the anti-C5 antibody is coupled to a labelling group. In another embodiment, the anti-C5 antibody is coupled to a labelling group and that labelling group is an optical label, radioisotope, radionuclide, an enzymatic group, and a biotinyl group.

[0011] In another aspect, the invention comprises a process for preparing an isolated antibody that binds to complement C5 comprising isolating said antibody from a host cell that secretes the antibody.

[0011a] In another aspect, there is provided a process for preparing an isolated antibody as disclosed herein, comprising preparing said antibody from a host cell that secretes said antibody.

[0012] In another aspect, the invention is an anti-complement C5 antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 13, 18, 23, 28, 33, and 38. In another aspect, the anti-C5 antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 19, 24, 29, 34 and 39. In another aspect, the anti-C5 antibody comprises an amino acid sequence selected from the group consisting of GTS, SGS, RTS, YTS, and WAS. In another aspect, the anti-C5 antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 20, 25, 30, 35 and 40. In another aspect, the anti-C5 antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 21, 26, 31, 36, and 41. In another aspect, the anti-C5 antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 17, 22, 27, 32, 37 and 42. In another aspect, the invention is an antibody comprising a first and second amino acid

sequence, the first amino acid sequence comprising a CDR1 selected from the group consisting of SEQ ID NOs: 13, 18, 23, 28, 33, and 38; a CDR2 selected from the group consisting of amino acid sequence GTS, SGS, YTS, and WAS; a CDR3 selected from the group consisting of SEQ ID NOs: 14, 19, 24, 29, 34 and 39; and a second amino acid sequence comprising a CDR1 selected from the group consisting of SEQ ID NOs: 15, 20, 25, 30, 35 and 40; a CDR2 selected from the group consisting of SEQ ID NOs: 16, 21, 26, 31, 36 and 41; and a CDR3 selected from the group consisting of SEQ ID NOs: 17, 22, 27, 32, 37 and 42. In other embodiment, the invention is an antibody comprising the amino acid sequence of SEQ ID NO: 10 and SEQ ID NO: 2.

[0013] In another aspect, the invention comprises a nucleic acid molecule encoding an isolated antibody that binds to complement C5. In one embodiment, the nucleic acid molecule encoding the antibody that binds to complement C5 is operably linked to a control sequence.

[0013a] In another aspect, the invention comprises a nucleic acid molecule encoding an isolated antibody as described herein.

[0014] In another aspect, the invention comprises an anti-complement C5 antibody and a pharmaceutically acceptable carrier. In one embodiment, the anti-complement C5 antibody further comprises an additional active agent. In another embodiment, the anti-complement C5 antibody and additional active agent also include a pharmaceutically acceptable carrier.

[0014a] In another aspect, there is provided a pharmaceutical composition comprising at least one antibody as disclosed herein and pharmaceutically acceptable carrier.

[0015] In another aspect, the invention comprises a method for treating or preventing an indication in a patient in need of treatment or prevention, the method comprising administering to the patient, an effective amount of at least one anti-complement C5 antibody. In one embodiment, the indication is age-related macular degeneration (AMD). In another embodiment, the disease or disorder in a patient in need of treatment or prevention is an ocular condition.

[0015a] In another aspect, there is provided the use of an effective amount of the antibody as disclosed herein in the manufacture of a medicament for treating or preventing an indication in a patient in need of treatment or prevention.

[0015b] In another aspect, there is provided the use of the antibody as described herein, or the pharmaceutical composition as described herein , in the manufacture of a medicament for treating or preventing an indication associated with complement activation in a patient in need of treatment or prevention, wherein the indication is selected from a group consisting of Glomerulonephritis, Systemic Lupus Erythematosus, Paroxysmal Nocturnal Hemoglobinuria,

Alzheimer's, Hereditary Angioedema, Myasthenia Gravis and Age-related Macular Degeneration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 shows a schematic of the Complement Pathway.

[0017] Figure 2 shows a schematic of MAC formation and shows the mechanism of a monoclonal antibody therapeutic in blocking MAC but not C5a generation

[0018] Figure 3 shows percent inhibition of MAC by anti-C5 antibody sub-clones.

[0019] Figures 4A and 4B show percent inhibition of MAC by anti-C5 antibody sub-clones.

[0020] Figures 5A, 5B, and 5C show percent inhibition of MAC by anti-C5 antibody sub-clones.

[0021] Figures 6A, 6B and 6C show the generation of C5a inhibition by examining single point determinations or by titration of the antibody.

[0022] Figure 7 shows dose dependent interaction of monoclonal antibodies with C5 directly coated on to an ELISA plates.

[0023] Figure 8 shows binding affinities of anti-C5 monoclonal antibodies to C5.

[0024] Figure 9 shows the binding of the monoclonal antibodies to C5 protein in solution using Bio-Layer Interferometry (BLI).

[0025] Figure 10 shows ability to recognize C5 with in the C5b-9 complex when deposited into the bottom of ELISA plates after complement activation with IgM.

[0026] Figures 11a and 11b show the ability of the monoclonal antibodies to bind soluble C5b-9 using Bio-Layer Interferometry (BLI) technology.

[0027] Figures 12A, 12B and 12C show inhibition of MAC for full-length antibodies with humanized heavy and light chains of 10C9.

[0028] Figure 13A, 13B, and 13C show activity of Fab fragments with humanized heavy and light chains of 10C9.

Example 14 – Use of C5 Antibody for Prevention of C5b-9 Deposition in Retinal and Choroidal Tissues

[00305] Additionally, the therapeutic potential of a compound by intravitreal delivery in blocking C5b-9 formation in retinal and choroidal tissues can be assessed by use of standard models leading to complement activation in tissues of interest as provided in , AL-78898A Inhibits Complement Deposition in a Primate Light Damage Model, ARVO Ab A387 2012,. Humanized H5L2 (SEQ ID NO:10 and SEQ ID NO: 3, respectively) antibody was humanized from the mouse monoclonal antibody subclone 10C9. H5L2 was tested in a non-human primate light injury model. Intravitreal dosing of the H5L2 antibody provided efficacy in blocking complement deposition in the retina that was comparable to the negative control (PBS, no light injury, labeled "PBS No BL"). Positive control of PBS with light injury (labeled "PBS") was also used. Graphical representation of the results is shown in Figures 14A (retina) and 14B (choroid). These data indicate that local delivery of the H5L2 antibody is efficacious in an *in vivo* model relevant to the treatment of macular degeneration and other ocular indications.

WE CLAIM:

1. An anti-C5 antibody, wherein the antibody binds to C5 and inhibits complement dependent hemolysis, but does not block C5a formation, wherein the antibody comprises a light chain variable domain and a heavy chain variable domain and selected from the group consisting of:

(i) an antibody in which the light chain variable domain comprises a CDR1 of SEQ ID NO: 25, a CDR2 of SEQ ID NO: 26 and a CDR3 of SEQ ID NO: 27 and in which the heavy chain variable domain comprises a CDR1 of SEQ ID NO: 28, a CDR2 of SEQ ID NO: 29 and a CDR3 of SEQ ID NO: 30,

(ii) an antibody in which the light chain variable domain comprises a CDR1 of SEQ ID NO: 31, a CDR2 of SEQ ID NO: 32 and a CDR3 of SEQ ID NO: 33 and in which the heavy chain variable domain comprises a CDR1 of SEQ ID NO: 34, a CDR2 of SEQ ID NO: 35 and a CDR3 of SEQ ID NO: 36 ,

(iii) an antibody in which the light chain variable domain comprises a CDR1 of SEQ ID NO: 37, a CDR2 of SEQ ID NO: 38 and a CDR3 of SEQ ID NO: 39 and in which the heavy chain variable domain comprises a CDR1 of SEQ ID NO: 40, a CDR2 of SEQ ID NO: 41 and a CDR3 of SEQ ID NO: 42, and

(iv) an antibody in which the light chain variable domain comprises a CDR1 of SEQ ID NO: 43, a CDR2 of SEQ ID NO: 44 and a CDR3 of SEQ ID NO: 45 and in which the heavy chain variable domain comprises a CDR1 of SEQ ID NO: 46, a CDR2 of SEQ ID NO: 47 and a CDR3 of SEQ ID NO: 48.

2. The antibody of claim 1, wherein the antibody blocks C5 binding to human Complement Component 6 and/or 7; and/or wherein the antibody inhibits formation of membrane attack complex (MAC).

3. The antibody of any one of claims 1 or 2, further comprising a heavy chain and a light chain wherein the light chain comprises an amino acid sequence identical to a sequence selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, and 11; and the heavy chain

comprises an amino acid sequence identical to a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, and 12.

4. The antibody of any one or more or the preceding claims, wherein the antibody is selected from the group consisting of

(i) an antibody in which the light chain variable domain comprises SEQ ID NO: 1 and the heavy chain variable domain comprises SEQ ID NO: 2,

(ii) an antibody in which the light chain variable domain comprises SEQ ID NO: 1 and the heavy chain variable domain comprises SEQ ID NO: 4,

(iii) an antibody in which the light chain variable domain comprises SEQ ID NO: 1 and the heavy chain variable domain comprises SEQ ID NO: 6,

(iv) an antibody in which the light chain variable domain comprises SEQ ID NO: 1 and the heavy chain variable domain comprises SEQ ID NO: 8,

(v) an antibody in which the light chain variable domain comprises SEQ ID NO: 1 and the heavy chain variable domain comprises SEQ ID NO: 10,

(vi) an antibody in which the light chain variable domain comprises SEQ ID NO: 3 and the heavy chain variable domain comprises SEQ ID NO: 2,

(vii) an antibody in which the light chain variable domain comprises SEQ ID NO: 3 and the heavy chain variable domain comprises SEQ ID NO: 4,

(viii) an antibody in which the light chain variable domain comprises SEQ ID NO: 3 and the heavy chain variable domain comprises SEQ ID NO: 6,

(ix) an antibody in which the light chain variable domain comprises SEQ ID NO: 3 and the heavy chain variable domain comprises SEQ ID NO: 8,

(x) an antibody in which the light chain variable domain comprises SEQ ID NO: 3 and the heavy chain variable domain comprises SEQ ID NO: 10,

(xi) an antibody in which the light chain variable domain comprises SEQ ID NO: 5 and the heavy chain variable domain comprises SEQ ID NO: 2,

(xii) an antibody in which the light chain variable domain comprises SEQ ID NO: 5 and the heavy chain variable domain comprises SEQ ID NO: 4,

(xiii) an antibody in which the light chain variable domain comprises SEQ ID NO: 5 and the heavy chain variable domain comprises SEQ ID NO: 6,

(xiv) an antibody in which the light chain variable domain comprises SEQ ID NO: 5 and the heavy chain variable domain comprises SEQ ID NO: 8,

(xv) an antibody in which the light chain variable domain comprises SEQ ID NO: 5 and the heavy chain variable domain comprises SEQ ID NO: 10,

(xvi) an antibody in which the light chain variable domain comprises SEQ ID NO: 7 and the heavy chain variable domain comprises SEQ ID NO: 2,

(xvii) an antibody in which the light chain variable domain comprises SEQ ID NO: 7 and the heavy chain variable domain comprises SEQ ID NO: 4,

(xviii) an antibody in which the light chain variable domain comprises SEQ ID NO: 7 and the heavy chain variable domain comprises SEQ ID NO: 6,

(xix) an antibody in which the light chain variable domain comprises SEQ ID NO: 7 and the heavy chain variable domain comprises SEQ ID NO: 8, and

(xx) an antibody in which the light chain variable domain comprises SEQ ID NO: 7 and the heavy chain variable domain comprises SEQ ID NO: 10.

5. The antibody of any one or more of the preceding claims, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof, or 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, and/or wherein said antibody is of the lgG1-, lgG2-, lgG3- or lgG4-type, preferably an lgG1-type.

6. The antibody of any one or more of the preceding claims, wherein the antibody is coupled to a labelling group, preferably wherein the labelling group is selected from an optical label, radioisotope, radionuclide, an enzymatic group, and a biotinyl group.

7. A process for preparing an isolated antibody according to any one or more of the preceding claims, comprising preparing said antibody from a host cell that secretes said antibody.

8. A nucleic acid molecule encoding an isolated antibody according to any one or more of the preceding claims.

9. The nucleic acid molecule according to claim 8, wherein the nucleic acid molecule is operably linked to a control sequence.

10. A pharmaceutical composition comprising at least one antibody according to any one or more of the preceding claims 1-6, and pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, further comprising an additional active agent.

12. Use of the antibody of any one or more of the preceding claims 1-6, or the pharmaceutical composition according to claim 10 or 11 , in the manufacture of a medicament for treating or preventing an indication associated with complement activation in a patient in need of treatment or prevention, wherein the indication is selected from a group consisting of Glomerulonephritis, Systemic Lupus Erythematosus, Paroxysmal Nocturnal Hemoglobinuria, Alzheimer's, Hereditary Angioedema, Myasthenia Gravis and Age-related Macular Degeneration.

13. The use of claim 12, wherein the indication is an ocular condition.

14. The use of claim 13, wherein the indication is age-related macular degeneration.