VECTORIZED ANTI-COMPLEMENT ANTIBODIES AND COMPLEMENT AGENTS AND ADMINISTRATION THEREOF

REFERENCE TO ELECTRONIC SEQUENCE LISTING

[0001] The contents of the electronic sequence listing submitted April 8, 2025 as an XML file named "38013_0044P1_SL," created on April 8, 2025, and having a size of 396,601 bytes is hereby incorporated by reference in its entirety.

1. INTRODUCTION

[0002] Compositions and methods are described for the delivery of a fully human post-translationally modified (HuPTM) proteins, including therapeutic monoclonal antibodies ("mAbs") that bind to C5. Also described are HuPTM antigen-binding fragments of a therapeutic mAb that bind to C5—e.g., a fully human-glycosylated (HuGly) Fab of the therapeutic mAb—to a human subject diagnosed with Age-Related Macular Degeneration (AMD).

2. BACKGROUND OF THE INVENTION

[0003] Therapeutic mAbs have been shown to be effective in treating a number of diseases and conditions. However, because these agents are effective for only a short period of time, repeated injections for long durations are often required, thereby creating considerable treatment burden for patients.

[0004] The complement system is a critical element of the immune system that enhances the clearing of microbes and damaged cells, promotes inflammation, and attacks a pathogen's cell membrane. Three biochemical pathways activate the complement system, 1) the classical complement system, 2) the alternative complement pathway and 3) the lectin pathway.

[0005] Age-Related Macular Degeneration (AMD) causes progressive and permanent vision impairment. There are two forms of AMD, dry AMD and wet AMD. Dry AMD accounts for about 85-90% of the 196 million global AMD cases. Overactivation of the complement system is an important driver of AMD. Over one million patients who also present with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) may also benefit from intervention to counteract over-active complement in the eye.

[0006] There is a need for more effective treatments that reduce the treatment burden on patients suffering from AMD. Intravitreal medications have become a promising mode of drug administration in patients as they provide high volume of drug to the target tissues, eliminating the risk of systemic toxicity. Reducing or eliminating the need for periodic ocular administration would reduce patient burden and improve therapy.

3. SUMMARY OF THE INVENTION

[0007] Therapeutic antibodies and other proteins delivered by gene therapy have several advantages over injected or infused therapeutic antibodies that dissipate over time resulting in peak and trough levels. Sustained expression of the transgene product antibody or protein, as opposed to injecting an antibody or protein repeatedly, allows for a more consistent level of antibody or protein to be present at the site of action, and is less risky and more convenient for patients, since fewer injections need to be made. Furthermore, antibodies and other proteins expressed from transgenes are post-translationally modified in a different manner than those that are directly injected because of the different microenvironment present during and after translation. Without being bound by any particular theory, this results in antibodies that have different diffusion, bioactivity, distribution, affinity, pharmacokinetic, and immunogenicity characteristics, such that the antibodies delivered to the site of action are "biobetters" in comparison with directly injected antibodies. In addition, factors such anti-C5 antibodies (*see* Clark et al., 2014, J. Immunol. 193:4962) may inhibit complement activation and drusen deposit in the eye to inhibit, reduce the progression of dry AMD. Accordingly, provided herein are compositions and methods for anti-C5 gene therapy, particularly recombinant AAV gene therapy, designed to target the eye and generate a depot of transgenes for expression of anti-C5 antibodies, including, C5-D-mab scFv mAb (H-L) (amino acid sequence of SEQ ID NO: 195 or 203), C5-D-mab scFv mAb (L-H) (SEQ ID NO: 196), C5-A-mab scFv mAb (H-L) (SEQ ID NO: 197), C5-A-mab scFv mAb (L-H) (SEQ ID NO: 198), C5-C-mab scFv mAb (H-L) (SEQ ID NO: 199), C5-C-mab scFv mAb (L-H) (SEQ ID NO: 200), C5-B-mab scFv mAb (H-L) (SEQ ID NO: 201), and C5-B-mab scFv mAb (L-H) (SEQ ID NO: 202). In embodiments, the administration, including by ocular administration, including, in embodiments, administration to the suprachoroidal space of the eye, results in a therapeutic or prophylactic levels (in ocular tissues and, also, in embodiments, in serum) of the antibody within 20 days, 30 days, 40 days, 50 days, 60 days, or 90 days of administration of the rAAV composition for treatment or reduction in the progression of dry AMD and the geographic

atrophy associated therewith. In embodiments, the rAAV composition is administered to the suprachoroidal space by a microneedle or microinjector device.

[0008] Provided are compositions and methods which comprise AAV gene therapy vectors for the ocular delivery of anti-C5 scFv antibodies, including the C5-D-mab scFv (H-L) having an amino acid sequence of SEQ ID NO: 195 or 203 (with leader sequence), the C5-A-mab scFv (H-L) having an amino acid sequence of SEQ ID NO: 197, the C5-C-mab scFv (H-L) having an amino acid sequence of SEQ ID NO: 199, and the C5-B-mab scFv (H-L) having an amino acid sequence of SEQ ID NO: 201. Methods are described for delivery of the C5-D mab or C5-A mab to a patient (human subject) diagnosed with AMD or other condition indicated for treatment with the therapeutic anti-C5 mAb. Delivery may be advantageously accomplished via gene therapy—*e.g.*, by administering a viral vector or other DNA expression construct encoding a therapeutic anti-C5 mAb, such as C5-D-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 195 or 203), C5-D-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 196), C5-A-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 197), C5-A-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 198), C5-C-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 199), C5-C-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 200), C5-B-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 201), or C5-B-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 202), and wherein the AAV has an engineered VP1 protein of AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249), to a subject diagnosed with a condition indicated for treatment with the therapeutic anti-C5 mAb—to create a permanent depot in the eye, of the patient that continuously supplies the HuPTM mAb or *e.g.*, a human-glycosylated transgene product to one or more ocular tissues where the mAb exerts its therapeutic or prophylactic effect.

[0009] Provided are gene therapy vectors, particularly rAAV gene therapy vectors, which when administered to a human subject result in expression of an anti-C5 antibody, such as C5-D-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 195 or 203) or C5-A-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 197). The sequence encoding the C5-D-mab scFv (H-L) or C5-A-mab scFv (H-L), optionally with a signal sequence at the N-terminus, is provided in an expression cassette where the coding sequence is operably linked to regulatory elements, such as a CAG promoter, and other regulatory elements, such as polyA signal sequences and introns, flanked by AAV ITR sequences. Expression of the transgene can be controlled by constitutive expression elements, such as a CAG

promoter, or tissue-specific expression control elements, particularly elements that are ocular tissue, liver and/or muscle specific control elements, for example one or more elements of **Tables 1** and **1a.** Nucleotide sequences of exemplary constructs, including coding sequences for the transgene products, expression cassettes and artificial genomes are provided in **Table 8** herein and include SEQ ID NO: 225, 226, 227, 228, 229, 233, 234, 235, 236, 237, 238, 239, 240, 242, 276, 277, 278, and 279.

[0010] The construct encoding the C5-D-mab scFv (HL) or C5-A-mab scFv (HL) is packaged in a recombinant AAV (rAAV) which has a tropism for ocular tissues, including, for example, retinal cells, RPE, choroid, Bruch's membrane (BrM) and epithelial cells thereof, choriocapillaris and epithelial cells thereof, photoreceptor cells (rods and cones) and retinal ganglion cells. In embodiments, the AAV has an engineered AAV3B or AAV8 capsid protein which has an ocular tissue homing peptide or 7 to 9 amino acids inserted into either VR-IV or VR-VIII of the capsid protein. The engineered rAAV comprises a capsid protein of AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249) (see Table A).

[0011] Provided are methods of treating ocular indications, including Age-Related Macular Degeneration (AMD), by ocular, including suprachoroidal, administration to a patient suffering therefrom, a pharmaceutical composition comprising the rAAV comprising a transgene encoding the C5-D-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 195 or 203) or C5-A-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 197), including encoded by a polynucleotide comprising the nucleotide sequence of 219-220, or 224-242, packaged in a capsid comprising a capsid protein of AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249) (see Table A). In embodiments, the administration provides a therapeutically effective amount to the target ocular tissues of the subject for treatment of AMD, including to achieve a maximum or steady state concentrations in ocular tissues, such as aqueous humor, vitreous humor, or in serum for example, 20, 30, 40, 50, 60 or 90 days after administration of the vector. In embodiments, the rAAV is administered to the suprachoroidal space by a microneedle or microinjector device.

[0012] In other embodiments, the constructs express an scFv in which the heavy and light chain variable domains are connected via a flexible, non-cleavable linker, such as GGGGSGGGGSGGGGS (SEQ ID NO: 128). In certain embodiments, the construct expresses, from the N-terminus, NH_2-V_L-linker-V_H-COOH or NH_2-V_H-linker-V_L-COOH. In certain embodiments, the construct encodes, from the N-terminus, NH_2-signal or leader sequence-V_L-GGGGSGGGGSGGGGS-V_H-COOH or NH_2-signal or leader sequence-V_H- GGGGSGGGGSGGGGS-V_L-COOH.

[0013] Also provided are methods of manufacturing the viral vectors, particularly the AAV based viral vectors. In specific embodiments, provided are methods of producing recombinant AAVs comprising culturing a host cell containing an artificial genome comprising a cis expression cassette flanked by AAV ITRs, wherein the cis expression cassette comprises a transgene encoding a therapeutic antibody operably linked to expression control elements that will control expression of the transgene in human cells; a trans expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and capsid protein operably linked to expression control elements that drive expression of the AAV rep and capsid proteins in the host cell in culture and supply the rep and cap proteins in trans; sufficient adenovirus helper genes to permit replication and packaging of the artificial genome by the AAV capsid proteins; and recovering recombinant AAV encapsidating the artificial genome from the cell culture.

[0014] Methods of administration and manufacture are also provided.

3.1 Embodiments

1. A recombinant adeno-associated virus (rAAV) vector comprising

   (a) an AAV capsid comprising viral capsid protein; wherein the viral capsid protein comprises a 7 amino acid peptide inserted into a AAV3B or AAV8 capsid protein as a parental capsid protein and is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249); and

   (b) an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene comprising a nucleotide sequence encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197), and wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

wherein the rAAV vector has enhanced tropism to ocular tissue compared to an rAAV vector prepared from the parental capsid protein.

2. The rAAV vector of embodiment 1, wherein said ocular tissue with enhanced tropism is retina, RPE choroid or sclera tissue.
3. The rAAV vector of embodiment 2, wherein the rAAV vector exhibits an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, or 25 fold greater transduction of ocular tissue than an rAAV vector comprising the parental capsid.
4. The rAAV vector of any one of embodiments 1 to 3, wherein the rAAV vector has reduced transduction of liver, heart or astrocytes than an rAAV vector comprising parental capsid protein.
5. The rAAV vector of embodiment 4, wherein the rAAV vector has an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, 25 fold or 40 fold lower transduction of liver than an rAAV vector comprising the parental capsid protein.
6. The rAAV vector any one of embodiments 1 to 5, wherein the viral capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243).
7. The rAAV vector any one of embodiments 1 to 5, wherein the viral capsid protein is AAV3B.455.DVTPLLS (SEQ ID NO: 244).
8. The rAAV vector any one of embodiments 1 to 5, wherein the viral capsid protein is AAV3B.455.LVSVSLP (SEQ ID NO: 245).
9. The rAAV vector of any one of embodiments 6 to 8, wherein the parental capsid is AAV3B (SEQ ID NO: 254).
10. The rAAV vector any one of embodiments 1 to 5, wherein the viral capsid protein is AAV8.456.RIQMGTK (SEQ ID NO: 246).
11. The rAAV vector any one of embodiments 1 to 5, wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247).
12. The rAAV vector any one of embodiments 1 to 5, wherein the viral capsid protein is AAV8.590.GDNTTFRRA (SEQ ID NO: 248).
13. The rAAV vector any one of embodiments 1 to 5, wherein the viral capsid protein is AAV8.590.GRTIRGDLA (SEQ ID NO: 249).
14. The rAAV vector of any one of embodiments 10 to 13, wherein the parental capsid is AAV8 (SEQ ID NO: 260).

15. The rAAV vector any one of embodiments 1 to 14, wherein the transgene encodes a signal sequence at the N-terminus of the scFv that directs secretion and post-translational modification in said human ocular tissue cells.
16. The rAAV vector of embodiment 15, wherein the transgene comprises a signal sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 55) or a signal sequence from Table 2.
17. The rAAV vector of any one of embodiments 1 to 16, wherein the regulatory sequence comprises a regulatory sequence from Table 1 or Table 1a.
18. The rAAV vector of any one of embodiments 1 to 17, wherein the regulatory sequence is a CAG promoter (SEQ ID NO: 2), a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), a CB promoter (SEQ ID NO: 24 or 25), a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS: 5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), a human red opsin (RedO) promoter (SEQ ID NO: 14) or a Best1/GRK1 tandem promoter (SEQ ID NO: 26).
19. The rAAV vector of embodiment 18, wherein the regulatory sequence is a mutated CAG promoter (SEQ ID NO: 29).
20. The rAAV vector of any one of embodiments 1 to 19, wherein the nucleotide sequence encoding C5-D-mab.scFv is the nucleotide sequence of SEQ ID NO:224, SEQ ID NO: 227, or SEQ ID NO: 230.
21. The rAAV vector of any one of embodiments 1 to 19, wherein the expression cassette comprises a nucleotide sequence of SEQ ID NO: 226, 228, 231, 233, 235, 237, 239, 241, 278, or 279.
22. The rAAV vector of any one of embodiments 1 to 21, wherein the rAAV vector comprises a nucleotide sequence of SEQ ID NO: 225, 229, 232, 234, 236, 238, 240, 242, 276, or 277.
23. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a transgene encoding an anti-C5 scFv having an amino acid sequence of SEQ ID NO: 195, or 203 operatively linked to a regulatory sequence which promotes expression in ocular tissue and flanked by ITR sequences.
24. The rAAV vector of embodiment 23, wherein the artificial genome comprises a nucleotide sequence of SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, or SEQ ID NO: 242.

25. A pharmaceutical composition comprising the rAAV vector of any one of embodiments 1 to 24 and a pharmaceutically acceptable carrier.
26. The pharmaceutical composition according to embodiment 25, wherein said composition is formulated for subretinal, intravitreal, intranasal, intracameral, or suprachoroidal administration.
27. The pharmaceutical composition according to embodiment 26, wherein said composition is formulated for suprachoroidal administration.
28. The pharmaceutical composition according to embodiment 26, wherein said composition is formulated for suprachoroidal administration with a microneedle.
29. A method of delivering a transgene to a cell, said method comprising contacting said cell with the rAAV vector of any one of embodiments 1-24.
30. A method of delivering a transgene to a target tissue of a subject in need thereof, said method comprising administering to said subject the rAAV vector of any one of embodiments 1-24.
31. A pharmaceutical composition comprising a recombinant adeno-associated virus (rAAV) vector comprising,

(a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein comprises a 7 amino acid peptide inserted into a AAV3B or AAV8 capsid protein as a parental capsid protein and is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 345), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249); and

(b) an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197), and wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

wherein the rAAV vector has enhanced tropism to ocular tissue compared to an rAAV vector prepared from the parental capsid protein.

32. The composition of embodiment 31, wherein said ocular tissue with enhanced tropism is retina, RPE choroid or sclera tissue.
33. The composition of embodiment 32, wherein the rAAV vector exhibits an at least 2 fold, 5

fold, 10 fold, 15 fold, 20 fold, or 25 fold greater transduction of ocular tissue than an rAAV vector comprising the parental capsid.

34. The composition of any one of embodiments 31 to 33, wherein the rAAV vector has reduced transduction of liver, heart or astrocytes than an rAAV vector comprising parental capsid protein.
35. The composition of embodiment 34, wherein the rAAV vector has an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, 25 fold or 40 fold lower transduction of liver than an rAAV vector comprising the parental capsid protein.
36. The composition any one of embodiments 31 to 35, wherein the viral capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243).
37. The composition any one of embodiments 31 to 35, wherein the viral capsid protein is AAV3B.455.DVTPLLS (SEQ ID NO: 244).
38. The composition any one of embodiments 31 to 35, wherein the viral capsid protein is AAV3B.455.LVSVSLP (SEQ ID NO: 245).
39. The composition of any one of embodiments 33 to 35, wherein the parental capsid is AAV3B (SEQ ID NO: 254).
40. The composition any one of embodiments 31 to 39, wherein the viral capsid protein is AAV8.456.RIQMGTK (SEQ ID NO: 246).
41. The composition any one of embodiments 31 to 39, wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247).
42. The composition any one of embodiments 31 to 39, wherein the viral capsid protein is AAV8.590.GDNTTFRRA (SEQ ID NO: 248).
43. The composition any one of embodiments 31 to 39, wherein the viral capsid protein is AAV8.590.GRTIRGDLA (SEQ ID NO: 249).
44. The composition of any one of embodiments 33 to 35, wherein the parental capsid is AAV8 (SEQ ID NO: 260).
45. The composition any one of embodiments 31 to 44, wherein the transgene encodes a signal sequence at the N-terminus of the scFv that directs secretion and post-translational modification in said human ocular tissue cells.
46. The composition of embodiment 45, wherein the transgene comprises a signal sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 55) or a signal sequence from Table 2.

47. The composition of any one of embodiments 31 to 46, wherein the regulatory sequence comprises a regulatory sequence from Table 1 or Table 1a.
48. The composition of any one of embodiments 31 to 47, wherein the regulatory sequence is a CAG promoter (SEQ ID NO: 2), a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), a CB promoter (SEQ ID NO: 24 or 25), a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS: 5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), a human red opsin (RedO) promoter (SEQ ID NO: 14) or a Best1/GRK1 tandem promoter (SEQ ID NO: 26).
49. The composition of embodiment 44, wherein the regulatory sequence is a mutated CAG promoter (SEQ ID NO: 29).
50. The composition of any one of embodiments 31 to 49, wherein the artificial genome comprises the nucleotide sequence of SEQ ID NO: 225, SEQ ID NO: 229, SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, SEQ ID NO: 242, SEQ ID NO: 276, or SEQ ID NO: 277.
51. A pharmaceutical composition for use in treating Age-Related Macular Degeneration in a subject comprising or a method for treating Age-Related Macular Degeneration (AMD) in a human subject in need thereof comprising administering a therapeutically effective amount of recombinant adeno-associated virus (rAAV) vector comprising,

(a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein comprises a 7 amino acid peptide inserted into a AAV3B or AAV8 capsid protein as a parental capsid protein and is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249); and

(b) an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197), and wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

wherein the rAAV vector has enhanced tropism to ocular tissue compared to an rAAV vector prepared from the parental capsid protein.

52. The pharmaceutical composition or method for treating according to embodiment 51, wherein said ocular tissue with enhanced tropism is retina, RPE choroid or sclera tissue.
53. The pharmaceutical composition or method for treating according to embodiment 52, wherein the rAAV vector exhibits an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, or 25 fold greater transduction of ocular tissue than an rAAV vector comprising the parental capsid.
54. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 53, wherein the rAAV vector has reduced transduction of liver or peripheral than an rAAV vector comprising parental capsid protein.
55. The pharmaceutical composition or method for treating according to embodiment 54, wherein the rAAV vector has an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, 25 fold or 40 fold lower transduction of liver than an rAAV vector comprising the parental capsid protein.
56. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 55, wherein the viral capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243).
57. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 55, wherein the viral capsid protein is AAV3B.455.DVTPLLS (SEQ ID NO: 244).
58. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 55, wherein the viral capsid protein is AAV3B.455.LVSVSLP (SEQ ID NO: 245).
59. The pharmaceutical composition or method for treating according to any one of embodiments 53 to 55, wherein the parental capsid is AAV3B (SEQ ID NO: 254).
60. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 55, wherein the viral capsid protein is AAV8.456.RIQMGTK (SEQ ID NO: 246).
61. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 55, wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247).
62. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 55, wherein the viral capsid protein is AAV8.590.GDNTTFRRA (SEQ ID NO: 248).
63. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 55, wherein the viral capsid protein is AAV8.590.GRTIRGDLA (SEQ ID NO: 249).
64. The pharmaceutical composition or method for treating according to any one of embodiments 53 to 55, wherein the parental capsid is AAV8 (SEQ ID NO: 260).

65. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 64, wherein the transgene encodes a signal sequence at the N-terminus of the heavy chain and the light chain of said antigen-binding fragment that directs secretion and post-translational modification in said human ocular tissue cells.
66. The pharmaceutical composition or method for treating according to embodiment 65, wherein the transgene comprises a signal sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 55) or a signal sequence from Table 2.
67. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 66, wherein the regulatory sequence comprises a regulatory sequence from Table 1 or Table 1a.
68. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 67, wherein the regulatory sequence is a CAG promoter (SEQ ID NO: 2), a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), a CB promoter (SEQ ID NO: 24 or 25), a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS: 5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), a human red opsin (RedO) promoter (SEQ ID NO: 14) or a Best1/GRK1 tandem promoter (SEQ ID NO: 26).
69. The pharmaceutical composition or method for treating according to embodiment 68, wherein the regulatory sequence is a mutated CAG promoter (SEQ ID NO: 29).
70. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 69, wherein the artificial genome comprises the nucleotide sequence of SEQ ID NO: 225, SEQ ID NO: 229, SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, SEQ ID NO: 242, SEQ ID NO: 276, or SEQ ID NO: 277.
71. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 70, wherein the AAV vector is formulated for subretinal, intravitreal, intranasal, intracameral, or suprachoroidal, administration to said human subject.
72. The pharmaceutical composition or method for treating according to embodiment 71, wherein the AAV vector is formulated for suprachoroidal administration to said human subject.
73. The pharmaceutical composition or method for treating according to embodiment 72, wherein the AAV vector is formulated for suprachoroidal administration with a microneedle or microinjector.

74. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 73, wherein the therapeutically effective amount is determined to be sufficient to maintain a concentration of at least 10 ng/ml in RPE, retina, aqueous humor or vitreous humor.
75. The pharmaceutical composition or method for treating according to any one of embodiments 51 to 74, which results in a therapeutic or prophylactic levels in ocular tissues of the antibody within 20 days, 30 days, 40 days, 50 days, 60 days, or 90 days of administration of the rAAV composition.
76. The pharmaceutical composition of method for treating according to any one of embodiments 51 to 74, wherein the AMD is dry AMD with geographic atrophy.
77. The composition of any one of embodiments 51 to 75, wherein the therapeutically effective amount is determined to be sufficient to improve best corrected visual acuity (BCVA) by >= 2 ETDRS lines; to decrease the mean rate of change in geographic atrophy as measured by fundus autofluorescence (FAF); to improve visual function as measured by dark adaptation methodology; to improve contrast sensitivity by the Pelli-Robson test or reduce the drusen area within 10 weeks, 20 weeks, 6 months or 1 year of administration.
78. The pharmaceutical composition of any one of embodiments 25 to 50 or the composition for use in treatment of AMD of any one of embodiments 51 to 77 wherein the pharmaceutical composition or composition or composition for use in the treatment of AMD comprises between about 0.5% to about 1.0% w/v hyaluronic acid.
79. The pharmaceutical composition of any one of embodiments 25 to 50 or the composition for use in treatment of AMD of any one of embodiments 51 to 77 wherein the pharmaceutical composition or composition or composition for use in the treatment of AMD comprises about (2.5% w/v) sucrose and between about 0.5% to about 1.0% w/v hyaluronic acid.
80. The pharmaceutical composition of any one of embodiments 25 to 50 or the composition for use in treatment of AMD of any one of embodiments 51 to 77 wherein the pharmaceutical composition or composition or composition for use in the treatment of AMD comprises about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 0.7% w/v hyaluronic acid.

81. The pharmaceutical composition of any one of embodiments 25-50 or the composition for use in treatment of AMD of any one of embodiments 51-77 wherein the pharmaceutical composition or composition or composition for use in the treatment of AMD comprises about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 40.0 mg/mL (4% w/v) sucrose, about 0.001% (0.01 mg/mL) poloxamer 188, and about 1% carboxymethylcellulose (CMC) high viscosity grade.

82. A method of producing recombinant AAVs comprising:

(a) culturing a host cell containing:

(i) an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197), and wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

(ii) a *trans* expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and an AAV capsid protein operably linked to expression control elements that drive expression of the AAV rep and the AAV capsid protein in the host cell in culture and supply the AAV rep and the AAV capsid protein in *trans,* wherein the capsid has ocular tissue cell tropism, wherein the AAV capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249);

(iii) sufficient adenovirus helper genes to permit replication and packaging of the artificial genome by the AAV capsid protein; and

(b) recovering recombinant AAV encapsidating the artificial genome from the cell culture.

83. A host cell comprising:

a plasmid comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197) operably linked to one or more regulatory sequences that

promote expression of the transgene in human ocular tissue cells.

84. A method for treating a human subject diagnosed with age-related macular degeneration (AMD), comprising delivering to an eye of the human subject a therapeutically effective amount of an anti-C5 scFv antibody produced by the human subject's ocular cells transduced with a recombinant adeno-associated virus (rAAV) vector carrying an artificial genome which comprises an expression cassette comprising a transgene encoding an anti-C5 scFv antibody, by a single dose administration of the rAAV vector via suprachoroidal (SC) injection or subretinal (SR) injection to the eye of the human subject.
85. A pharmaceutical composition for use in treating a human subject diagnosed with age-related macular degeneration (AMD), comprising delivering to an eye of the human subject a therapeutically effective amount of an anti-C5 scFv antibody produced by the human subject's ocular cells transduced with a recombinant adeno-associated virus (rAAV) vector carrying an artificial genome containing an expression cassette comprising a transgene encoding an anti-C5 scFv antibody, by a single dose administration of the rAAV vector via suprachoroidal (SC) injection or subretinal (SR) injection to the eye of the human subject.
86. The method of embodiment 84 or the pharmaceutical composition of embodiment 85, wherein the amount of an anti-C5 scFv antibody in the eye of the human subject is effective to enhance the survival and/or the function of the photoreceptors of the eye.
87. The method or the pharmaceutical composition of embodiments 84 to 86, wherein the human subject is diagnosed with geographic atrophy (GA) secondary to AMD.
88. The method or the pharmaceutical composition of embodiments 84 to 87, wherein the amount of an anti-C5 scFv antibody delivered to the eye of the human subject is effective to slow progression of geographic atrophy.
89. The method or the pharmaceutical composition of embodiments 84 to 88, wherein the rAAV vector comprises an engineered AAV8 capsid protein AAV8.456.RQKNAMV (SEQ ID NO: 247).
90. The method or the pharmaceutical composition of embodiments 84 to 89, wherein the transgene encodes C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197).
91. The method or the pharmaceutical composition of embodiments 84 to 90, wherein the single dose is from about 1×10^{9} genome copies (GC) to about 3×10^{13} GC per eye.

92. A method for enhancing the survival and/or the function of the photoreceptors of an eye, comprising delivering to the eye of a mammal a therapeutically effective amount of an anti-C5 scFv antibody produced by the mammal's ocular cells transduced with a recombinant adeno-associated virus (rAAV) vector carrying an expression cassette encoding the anti-C5 scFv antibody, by a single dose administration of the rAAV vector via suprachoroidal (SC) injection or subretinal (SR) injection to the mammal's eye.
93. The method of embodiment 92, wherein the mammal is a human, non-human primate, mouse or a pig.
94. The method of embodiments 92 or 93, wherein the rAAV vector comprises an engineered AAV8 capsid protein AAV8.456.RQKNAMV (SEQ ID NO: 247).
95. The method of embodiments 92 to 94, wherein the expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197).
96. The method of embodiment 92 to 95, wherein the single dose is from about 1×10^{10} genome copies (GC) to about 3×10^{13} GC per eye.
97. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 225.
98. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 229.
99. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 232.
100. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 234.
101. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID

NO: 236.

102. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 238.

103. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 240.

104. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 242.

105. A pharmaceutical composition for use in treating or a method for treating Age-Related Macular Degeneration in a subject comprising or a method for treating Age-Related Macular Degeneration (AMD) in a human subject in need thereof comprising administering a therapeutically effective amount of recombinant adeno-associated virus (rAAV) vector of any one of embodiments 97-104.

106. The pharmaceutical composition or method for treating according to embodiment 105, wherein the rAAV vector is formulated for suprachoroidal administration to said human subject.

107. The pharmaceutical composition or method for treating according to embodiment 106, wherein the rAAV vector is formulated for suprachoroidal administration with a microneedle or microinjector.

108. The pharmaceutical composition or method for treating according to any one of embodiments 105 to 107, wherein the therapeutically effective amount is determined to be sufficient to maintain a concentration of at least 10 ng/ml in RPE, retina, aqueous humor or vitreous humor.

109. The pharmaceutical composition or method for treating according to any one of embodiments 105 to 108, wherein administration results in a therapeutic or prophylactic levels in ocular tissues of the antibody within 20 days, 30 days, 40 days, 50 days, 60 days,

or 90 days of administration of the rAAV composition.

110. The pharmaceutical composition or method for treating according to any one of embodiments 105 to 109, wherein the AMD is dry AMD with geographic atrophy or wherein geographic atrophy is secondary to AMD.

111. The pharmaceutical composition or method for treating according to any one of embodiments 105 to 110, wherein the therapeutically effective amount is determined to be sufficient to improve best corrected visual acuity (BCVA) by >= 2 ETDRS lines; to decrease the mean rate of change in geographic atrophy as measured by fundus autofluorescence (FAF); to improve visual function as measured by dark adaptation methodology; to improve contrast sensitivity by the Pelli-Robson test or reduce the drusen area within 10 weeks, 20 weeks, 6 months or 1 year of administration.

112. The pharmaceutical composition or method for treating according to any one of embodiments 105 to 111, wherein the pharmaceutical composition comprises between about 0.5% to about 1.0% w/v hyaluronic acid.

113. The pharmaceutical composition or method for treating according to any one of embodiments 105 to 112, wherein the pharmaceutical composition comprises about (2.5% w/v) sucrose and between about 0.5% to about 1.0% w/v hyaluronic acid.

114. The pharmaceutical composition or method for treating according to any one of embodiments 105 to 113, wherein the pharmaceutical composition comprises about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 0.7% w/v hyaluronic acid.

115. The pharmaceutical composition or method for treating according to any one of embodiments 105 to 114, wherein the pharmaceutical composition comprises about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 40.0 mg/mL (4% w/v) sucrose, about 0.001% (0.01 mg/mL) poloxamer 188, and about 1% carboxymethylcellulose (CMC) high viscosity grade.

116. An rAAV vector comprising

(a) an AAV capsid comprising viral capsid protein; wherein the viral capsid protein

comprises a 7 amino acid peptide inserted into a AAV3B or AAV8 capsid protein as a parental capsid protein and is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), or AAV3B.455.LVSVSLP (SEQ ID NO: 245); and

(b) an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a therapeutic transgene, wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

wherein the rAAV vector has enhanced tropism to ocular tissue compared to an rAAV vector prepared from the parental capsid protein.

117. The rAAV vector of embodiment 116, comprising the viral capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243).

118. The rAAV vector of embodiment 116, comprising the viral capsid protein is AAV3B.455.DVTPLLS (SEQ ID NO: 244).

119. The rAAV vector of embodiment 116, comprising the viral capsid protein is AAV3B.455.LVSVSLP (SEQ ID NO: 245).

120. A pharmaceutical composition comprising the rAAV vector of any one of embodiments 116 to 119 and a pharmaceutically acceptable carrier.

121. The pharmaceutical composition according to embodiment 120, wherein said composition is formulated for subretinal, intravitreal, intranasal, intracameral, or suprachoroidal administration.

122. The pharmaceutical composition according to embodiment 120, wherein said composition is formulated for suprachoroidal administration.

123. The pharmaceutical composition according to embodiment 120, wherein said composition is formulated for suprachoroidal administration with a microneedle.

124. A method of delivering a transgene to a cell, said method comprising contacting said cell with the rAAV vector of any one of embodiments 116-119.

125. A method of delivering a transgene to a target tissue of a subject in need thereof, said method comprising administering to said subject the rAAV vector of any one of embodiments 116-119.

126. A method of producing recombinant AAVs comprising:

(a) culturing a host cell containing:

(i) an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a therapeutic transgene, wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

(ii) a *trans* expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and an AAV capsid protein operably linked to expression control elements that drive expression of the AAV rep and the AAV capsid protein in the host cell in culture and supply the AAV rep and the AAV capsid protein in *trans,* wherein the capsid has ocular tissue cell tropism, wherein the AAV capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), or AAV3B.455.LVSVSLP (SEQ ID NO: 245);

(iii) sufficient adenovirus genes to permit replication and packaging of the artificial genome by the AAV capsid protein; and

(b) recovering recombinant AAV encapsidating the artificial genome from the cell culture.

127. A host cell comprising:

a plasmid comprising a *trans* expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and an AAV capsid protein operably linked to expression control elements that drive expression of the AAV rep and the AAV capsid protein in the host cell in culture and supply the AAV rep and the AAV capsid protein in *trans,* wherein the capsid has ocular tissue cell tropism, wherein the AAV capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), or AAV3B.455.LVSVSLP (SEQ ID NO: 245).

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **FIGS. 1A-1C**. Schematics of rAAV vector genome constructs containing an expression cassette encoding the heavy and light chains of a therapeutic mAb separated by a Furin-2A linker, operably linked to a promoter, flanked by the AAV ITRs. The transgene can comprise nucleotide sequences encoding the **A)** full-length heavy and light chains with Fc regions**, B)** the heavy and light

chains of the Fab portion, or **C**) a single chain variable fragment (scFv) connecting the heavy and light chains of the antibody with a linker.

[0016] **FIGS. 2A-2E.** The amino acid sequence of a transgene construct for the Fab region of **A)** C5-D-mab IgG1, **B)** C5-A-mab IgG1, **C)** C5-A-mab IgG2, **D)** C5-C-mab, and **E)** C5-B-mab therapeutic antibodies to C5. Glycosylation sites are boldface. Glutamine glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (italics) are as indicated in the legend. Complementarity-determining regions (CDR) are underscored. The hinge region is highlighted in grey.

[0017] **FIG. 3**. Clustal Multiple Sequence Alignment of various capsids with ocular tissue tropism. Amino acid substitutions (shown in bold in the bottom rows) can be made to AAV8 capsids by "recruiting" amino acid residues from the corresponding position of other aligned AAV capsids. Sequence shown in gray = hypervariable regions. The amino acid sequences of the AAV capsids are assigned sequence ID numbers as indicated in **FIG. 3**.

[0018] **FIG. 4** Glycans that can be attached to HuGlyFab regions of full length mAbs or the antigen-binding domains. (Adapted from Bondt et al., 2014, Mol & Cell Proteomics 13.1: 3029-3039).

[0019] **FIG. 5**. Clustal Multiple Sequence Alignment of constant heavy chain regions (CH2 and CH3) of IgG1 (SEQ ID NO: 192), IgG2 (SEQ ID NO: 193), and IgG4 (SEQ ID NO: 194). The numbering of the amino acids is in EU-format.

[0020] **FIGs. 6A-6B** shows expression of full length C5-D-mab and C5-A-mab levels after transfection of HEK293T cells with pITR-CAG-C5-A-mab and pITR-CAG-C5-D-mab on **A)** non-reducing and **B)** reducing gels.

[0021] **FIGS. 7A and 7B** show the results of the ability of cis plasmid-expressed vectorized antibodies in HEK293 cells to suppress complement in a hemolysis inhibition assay with **A)** 1.5% normal human serum or **B)** 20% normal mouse serum. **A)** human C5 inhibitors, IgG = C5-D-mab full-length mAb, Fab = C5-D-mab Fab, scFv = C5-D-mab scFv mAb, compared to a recombinant C5 inhibitor (C5I) protein and isotype and vehicle controls. **B)** mouse C5 inhibitors, IgG = BB5.1 full-length mAb, Fab = BB5.1 Fab, scFv = BB5.1 scFv mAb, compared to a recombinant C5 inhibitor (C5I) protein and isotype and vehicle controls.

[0022] **FIGS 8A-8F** show that the recombinant purified forms of each C5 inhibitor suppressed classical and alternative complement pathways in hemolysis inhibition assays against **A)** 50% human C5, classical complement pathway conditions, testing anti-hC5 (C5-D-mab formats) and C5 inhibitor,

B) 50% human C5, alternative complement pathway conditions, testing anti-hC5 (C5-D-mab formats) and C5 inhibitor **C**) 50% mouse C5, classical complement pathway conditions, testing anti-hC5 (C5-D-mab formats) and anti-mC5 (BB5.1 mAb formats), **D**) 50% mouse C5, classic complement pathway conditions, comparing anti-hC5 (C5-D-mab full-length mAb) and anti-mC5 (BB5.1 full-length mAb), **E**) 50% mouse C5, classic complement pathway conditions, comparing anti-hC5 (C5-D-mab Fab mAb) and anti-mC5 (BB5.1 Fab mAb), and **F**) 50% mouse C5, classic complement pathway conditions, comparing anti-hC5 (C5-D-mab scFv mAb) and anti-mC5 (BB5.1 scFv mAb).

[0023] **FIGS. 9A-H** measure membrane attack complex (MAC) formation in **A-C)** ARPE-19 cells and **D-F)** iPSC-derived RPE cells, **G)** TP level in apical and basal compartments, and **H)** mRNA/cDNA of AAV.

[0024] **FIGS. 10A-10D** show the results of AAV8-encoding C5 inhibitors injected into wild-type mouse eyes via subretinal (SR) administration at 1E8 and 3E8 vg/eye. AAV8.CAG.anti-hC5 (C5-D-mab) vectors were formatted as IgG (full-length), Fab or scFV vectorized antibodies and administered subretinally (SR) at each dose, and AAV8.CAG.anti-mC5 (BB5.1) vectors were administered SR at each dose, while purified recombinant anti-mC5 IgG (BB5.1) or isotype controls were delivered intraperitoneal (ip). **A**) represents measurement of transgene product (TP) as ng/eye (RNA transcript); **B**) represents measurement of transgene product (TP) as pmol/eye (protein). **C**) represents transgene product (TP) as pmol/eye (protein) in the retina. **D**) represents transgene product (TP) as pmol/eye (protein) in RPE/Choroid/Sclera.

[0025] **FIG. 11** is a diagram of full-length CAG promoter, the CAG-Del5 deletion mutant, the CAG-Delm deletion mutant and the CAG-Del 3 deletion mutant.

[0026] **FIG. 12** is a bar graph showing the relative promoter strength of the CAG-Del5 deletion mutant (25%), the CAG-Delm deletion mutant (61%) and the CAG-Del 3 deletion mutant (11%) compared to the full-length CAG promoter (100%).

[0027] **FIGS. 13A-D** are bar graphs showing the expression of C5-D-mab scFv (in ng) at day 1 (**A**), day 2 (**B**), day 3 (**C**) and day 6 (**D**) after transduction of HEK293T cells with AAV8 ss.CAG. C5-D.scFv (open circles) or AAV8 sc-CAG-Delm. C5-D.scFv (closed circles) at a multiplicity of infection (MOI) of 5e4, 1.6e4 or 5e5.

[0028] **FIGS. 14A-14C** show A) ONL thickness, B) total retinal thickness, C) total retina ONL, as BB5.1 antibody significantly ameliorated ONL and retinal thinning as measured by OCT post NaIO3 induction.

[0029] **FIGS. 15A-15F** show dark-adapted ERG recordings (a-wave amplitudes **A**, **C** and **E**; b-wave amplitudes **B**, **D** and **F**) and b-wave amplitudes of mice cohorts receiving i.p. antibody treatments at baseline, 3 and 7 days after NaIO3 administration.

[0030] **FIGS. 16A-16C** show vector biodistribution (DNA, genome copies per µg of tissue) **A**) and transcript copy (# copies (DNA) per µg RNA) **B**) in bar graphs for various ocular tissues of animals (day 85) following treatment with 3E12 GC per eye by suprachoroidal administration of vector. Vector biodistribution (DNA) detected in peripheral tissues was also measured (**C**).

[0031] **FIGS. 17A-17C** show transgene product (TP) for the scFv antibody levels detected in aqueous humor (AH) following AAV8.CAG.C5-D-mab.scFv SCS dosing at collection intervals (day 15, 29, 57 and 85). **A**) Data set of antibody levels including eyes in the cohort that displayed no or low vector biodistribution; **B**) Data set excluding eyes after day 29 that displayed no or low biodistribution; **C**) Time course of the AH collection antibody levels for all eyes.

[0032] **FIGS. 18A-18B** show TP expression levels in vitreous humor (VH) collected at the end of the study (day 85) following SCS delivery of 3e12 GC/eye AAV8.CAG.C5-D-mab-scFv. **A**) Data set of TP levels including an eye in the cohort that displayed no or low biodistribution; **B**) Data set excluding the eyes that displayed no or low vector biodistribution.

[0033] **FIGS. 19A-19H** shows AAV8-mediated TP production levels (ng/mg tissue) in ocular tissue homogenates: **A**) retina, **B**) RPE-choroid, **C**) sclera, and **D**) Sample 3 only tissues. TP results are illustrated exclusive of the an eye in the cohort that displayed no or low biodistribution; **E**) retina, **F**) RPE-choroid, **G**) sclera , and **H**) Sample 3 only tissues. TP results are illustrated inclusive of the an eye in the cohort that displayed no or low biodistribution.

[0034] **FIGS. 20A-20C** show TP levels in **A**) serum, **B**) peripheral vector genome biodistribution (liver), and **C**) time course following AAV8 vector delivery of CAG.C5-D-mab-scFv.

[0035] **FIGS. 21A-21C** show **A)** vector biodistribution (DNA, genome copies per µg of tissue) and **B**) transcript copy (# copies (DNA) per µg RNA) in bar graphs for various ocular tissues of animals (day 85) following treatment with 3E12 GC per eye by suprachoroidal administration of AAV3B vector. **C**) Vector biodistribution (DNA) detected in peripheral tissues was also measured.

[0036] **FIGS. 22A-22C** show transgene product (TP) for the scFv antibody levels detected in aqueous humor (AH) following AAV3B.CAG.C5-D-mab.scFv SCS dosing at collection intervals (day 15, 29, 57 and 85). **A**) Data set of antibody levels including all data points (including any that displayed

no or low vector biodistribution); **B)** Data set excluding eyes after day 29 that displayed no or low biodistribution or high ATPA; **C)** Time course of the AH collection antibody levels for all eyes.

[0037] **FIGS. 23A-23B** show TP expression levels in vitreous humor (VH) collected at the end of the study (day 85) following SCS delivery of 3e12 GC/eye AAV3B.CAG.C5-D-mab-scFv. **A)** Data set of TP levels including eyes that displayed no or low biodistribution or high ATPA; **B)** Data set excluding the eyes that displayed no or low vector biodistribution or +ATPA.

[0038] **FIGS. 24A-24H** show AAV3B-mediated TP production levels (ng/mg tissue) in ocular tissue homogenates: **A)** retina, **B)** RPE-choroid, **C)** sclera, and **D)** Sample 3 only tissues. TP results are illustrated exclusive of the an eye in the cohort that displayed no or low biodistribution or +ATPA; **E)** retina, **F)** RPE-choroid, **G)** sclera, and **H)** Sample 3 only tissues. TP results are illustrated inclusive of the an eye in the cohort that displayed no or low biodistribution or +ATPA.

[0039] **FIGS. 25A-25C** show TP expression levels in **A)** serum levels, **B)** peripheral vector genome biodistribution (liver), and **C)** time course following AAV3B vector delivery of CAG.C5-D-mab-scFv.

[0040] **FIG. 26** shows vector genome biodistribution (Vector DNA, GC per µg of tissue) were plotted for various ocular tissues of animals (retina, RPE-choroid and sclera) at end of study (day 29) post-injection of AAV8-anti-C5 scFV (AAV8.CAG.C5-D-mab.ScFv.HL) or AAV8-NS-scFv at a dose of 1E10 or 1E11 GC/eye.

[0041] **FIGS. 27A-27B** show AH collected at two and four weeks post-injection of (**A**) AAV8-anti-C5 scFV (AAV8.CAG.C5-D-mab.ScFv.HL) or (**B**) AAV8-NS-scFv at a dose of 1E10 or 1E11 GC/eye.

[0042] **FIGS. 28A-28B** show VH collected at two and four weeks post-injection of (**A**) AAV8-anti-C5 scFV (AAV8.CAG.C5-D-mab.ScFv.HL) or (**B**) AAV8-NS-scFv at a dose of 1E10 or 1E11 GC/eye.

[0043] **FIGS. 29A-29B** show **A)** AH and **B)** VH collected at two and four weeks post-injection of AAV8-anti-C5 scFV (AAV8.CAG.C5-D-mab.ScFv.HL; 1E10 or 1E11 GC/eye), AAV8-NS-scFv (1E10 or 1E11 GC/eye) or AAV8-NS-IgG (full-length Non-specific mab; 3E9 or 1E10 GC/eye) showing greater TP expression levels for vectorized ScFv antibodies.

[0044] **FIGS. 30A-30B** show ocular tissues (retina, RPE-choroid and sclera) collected at two and four weeks post-injection of **A)** AAV8-anti-C5 scFV (AAV8.CAG.C5-D-mab.ScFv.HL) or **B)** AAV8-NS-scFv at a dose of 1E10 or 1E11 GC/eye.

[0045] **FIGS. 31A-31D** show transgene product (TP) levels in **A**) aqueous humor (AH) measured by ELISA following single vector SCS administration in mini-pigs at a dose of $3x10^{11}$ and $3x10^{12}$ vg/eye (AAV vectors carry a CAG.scFv01 transgene). **B**) TP expression level following transduction of iRPE cells at an MOI of $3x10^{5}$ vg/cell. TP levels following single vector SCS administration in NHPs at a dose of $3x10^{12}$ vg/eye in **C**) aqueous humor and in **D**) retina tissue punches.

[0046] **FIGS. 32A-32B** show transgene product **A**) expression and **B**) biodistribution of PEPIN3.1, PEPIN8.1, PEPIN8.2 and PEPIN8.4 in the retina at 3e12 GC/eye (solid) and 3e11 GC/eye (brick).

[0047] **FIGS. 33A-33C** show AAV8 variants PEPIN8.1, PEPIN8.2 and PEPIN8.3 produce greater than 10 times more protein in the **A**) retina, **B**) RPE-C, and **C**) vitreous humor than AAV8 following SCS delivery of scFv01 transgene in NHPs (n=6 eyes at 3e12 GC/eye).

[0048] **FIGS. 34A-34B** show *In vitro* transduction efficiency of rAAV comprising various capsids (AAV8, AAV3B, 3.1, 3.2, 8.1, 8.2, 8.3, and 8.4) in **A**) iRPE cells at day 21 and **B**) ARPE cells at 48 hours .

[0049] **FIGS. 35A-35D** show transgene product expression (scFv01 ng/mg) in **A**) retinal cells and **B**) RPE cells, and biodistribution (GC/µg DNA) in **C**) retinal cells and **D**) RPE cells for AAV3B-3.1 variant vector administered at 3e12 GC/eye (solid) or 3e11 GC/eye (hatched).

[0050] **FIG. 36** shows transgene expression of AAV8 and AAV3B-3.1 in the vitreous humor at day 29.

[0051] **FIGS. 37A-37D** show NHP eyes were harvested at 29 days post-administration with 3e12 GC/eye AAV8.2 and anti-hC5-scFv01 transgene product (TP) levels were measured from **A**) AH, **B**) VH, **C**) retina lysates, and **D**) RPE-Choroid lysates from a macular punch, distal and proximal tissue strips.

[0052] **FIGs. 38A-38B** illustrate the fold-change difference of round 3 engineered capsids with increased transduction of **A**) retina and **B**) RPE-choroid compared to parental AAV8 following an SCS dose of $3x10^{12}$ GC/eye to NHPs. One-way ANOVA Dunnett's test vs AAV8: *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.

5. DETAILED DESCRIPTION OF THE INVENTION

[0053] Compositions and methods are described for the ocular delivery of a fully human post-translationally modified (HuPTM) therapeutic monoclonal antibody (mAb) or a HuPTM antigen-

binding fragment of a therapeutic anti-C5 mAb (for example, a fully human-glycosylated Fab (HuGlyFab) or scFv of a therapeutic mAb) to a patient (human subject) diagnosed with AMD (including dry AMD and dry AMD with geographic atrophy) or other indication indicated for treatment with the therapeutic mAb. Delivery may be advantageously accomplished via gene therapy—*e.g.*, by administering a viral vector or other DNA expression construct encoding a therapeutic mAb or its antigen-binding fragment (or a hyperglycosylated derivative of either) to a patient (human subject) diagnosed with a condition indicated for treatment with the therapeutic mAb—to create a permanent depot in a tissue or organ of the patient, particularly the eye, but, in embodiments, liver or muscle, that continuously supplies the HuPTM mAb or antigen-binding fragment of the therapeutic mAb, *e.g.*, a human-glycosylated transgene product, into ocular tissues of the subject to where the mAb or antigen-binding fragment there of exerts its therapeutic effect.

[0054] Provided are gene therapy vectors, particularly rAAV gene therapy vectors, which when administered to a human subject result in expression of an anti-C5 antibody, such as C5-D-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 195 or 203), C5-D-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 196), C5-A-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 197), C5-A-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 198), C5-C-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 199), C5-C-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 200), C5-B-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 201), or C5-B-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 202). The sequence encoding the C5-D-mab scFv (H-L), optionally with a signal sequence at the N-terminus, is provided in an expression cassette where the coding sequence is operably linked to regulatory elements, such as a CAG promoter, and other regulatory elements, such as polyA signal sequences, or flanked by AAV ITR sequences. Expression of the transgene can be controlled by constitutive expression elements, such as a CAG promoter, or tissue-specific expression control elements, particularly elements that are ocular tissue, liver and/or muscle specific control elements, for example one or more elements of **Tables 1** and **1a.** Nucleotide sequences of exemplary constructs are provided in **Table 8** herein and include SEQ ID NO; 205-242. The construct encoding the C5-D-mab scFv (HL) or C5-A-mab scFv (HL) is packaged in a recombinant AAV (rAAV) which has a tropism for ocular tissues, including, for example, retinal cells, RPE, choroid, Bruch's membrane (BrM) and epithelial cells thereof, choriocapillaris and epithelial cells thereof, photoreceptor cells (rods and cones) and retinal ganglion cells. In embodiments, the AAV has an engineered AAV3B or AAV8 capsid protein which has an ocular tissue homing peptide or 7 to 9 amino acids inserted into either VR-IV or VR-VIII of the capsid

protein. The engineered rAAV comprises a capsid protein of AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249) (see Table A). In an embodiment, the rAAV vector comprises (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 225.

[0055] In an embodiment, the rAAV vector comprises (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 229.

[0056] In an embodiment, the rAAV vector comprises (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 232.

[0057] In an embodiment, the rAAV vector comprises (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 234.

[0058] In an embodiment, the rAAV vector comprises (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 236.

[0059] In an embodiment, the rAAV vector comprises (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 238.

[0060] In an embodiment, the rAAV vector comprises (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 240.

[0061] In an embodiment, the rAAV vector comprises (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 242.

[0062] The compositions and methods provided herein ocularly or systemically deliver anti-C5 antibodies or antigen binding fragments thereof, particularly C5-D-mab scFv or C5-A-mab scFv, from a depot of viral genomes, for example, in the subject's eye (including retinal tissue), or liver/muscle, at a level either in the ocular tissue (e.g., in the vitreous or aqueous humor or retinal tissue, RPE, BrM and/or choroid), or in the serum that is therapeutically or prophylactically effective to treat or ameliorate the symptoms of AMD or other indication that may be treated with an anti-C5 antibody or antigen binding fragment thereof. Identified herein are viral vectors for delivery of transgenes encoding the therapeutic anti-C5 antibodies or antigen-binding fragments thereof, to cells in the human subject, including, in embodiments, one or more ocular tissue cells, and regulatory elements operably linked to the nucleotide sequence encoding the heavy and light chains of the anti-C5 antibody or antigen binding fragment that promote the expression of the antibody or antigen binding fragment in the cells, in embodiments, in the ocular tissue cells. Such regulatory elements, including constitutive promoters, such as CAG, and ocular tissue-specific regulatory elements, are provided in **Table 1** and **Table 1a** and in Example 13 (including certain modified CAG promoters) herein. Accordingly, such viral vectors may be delivered to the human subject at appropriate dosages, such that at least 20, 30, 40, 50 or 60 days after administration, the anti-C5 scFv is present at therapeutically effective levels in the serum or in ocular tissues of said human subject. In embodiments, the therapeutically effective level of the anti-C5 scFv is determined (in human trials, animal models, etc.) to improve best corrected visual acuity (BCVA) by >= 2 ETDRS lines, reduction in geographic atrophy (or slow the progression of geographic atrophy relative to untreated individual either based upon controls or natural history of the disease), reduction in drusen deposits or other metric of dry AMD.

[0063] In certain embodiments, nucleic acids (e.g., polynucleotides) and nucleic acid sequences disclosed herein may be codon-optimized, for example, via any codon-optimization technique known to one of skill in the art (*see*, *e.g.*, review by Quax et al., 2015, Mol Cell 59:149-161) and may also be optimized to reduce CpG dimers. Codon optimized sequences of the C5-D-mab and C5-A-mab heavy and light chains are provided in **Table 8** (SEQ ID NOs: 205 and 206). Useful signal

sequences for the expression of the scFv of the therapeutic antibodies in human cells are disclosed herein, for example in **Tables 2 and 3**. Exemplary recombinant expression constructs are shown in **FIGS. 1A, 1B and 1C**.

[0064] The production of HuPTM mAb or HuPTM Fab (including an HuPTM scFv) should result in a "biobetter" molecule for the treatment of disease accomplished via gene therapy – *e.g.*, by administering a viral vector or other DNA expression construct encoding a full-length HuPTM mAb or HuPTM Fab or other antigen binding fragment, such as an scFv, of a therapeutic mAb, to a patient (human subject) diagnosed with a disease indication for that mAb or protein, to create a permanent depot in the subject that continuously supplies the human-glycosylated, sulfated transgene product produced by the subject's transduced cells. The cDNA construct for the HuPTM mAb or HuPTM Fab or HuPTM scFv should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced human cells.

[0065] Pharmaceutical compositions suitable for administration to human subjects comprise a suspension of the recombinant vector in a formulation buffer comprising a physiologically compatible aqueous buffer, a surfactant and optional excipients. Such formulation buffer can comprise one or more of a polysaccharide, a surfactant, polymer, or oil.

[0066] Combination therapies involving delivery of the full-length HuPTM mAb or HuPTM Fab or HuPTM scFv or antigen binding fragment thereof to the patient accompanied by administration of other available treatments are encompassed by the methods of the invention. The additional treatments may be administered before, concurrently or subsequent to the gene therapy treatment. Such additional treatments can include but are not limited to co-therapy with the therapeutic mAb.

[0067] Also provided are methods of manufacturing the viral vectors, particularly the AAV based viral vectors. In specific embodiments, provided are methods of producing recombinant AAVs comprising culturing a host cell containing an artificial genome comprising a cis expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a transgene encoding a therapeutic antibody operably linked to expression control elements that will control expression of the transgene in human cells; a trans expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and capsid protein operably linked to expression control elements that drive expression of the AAV rep and capsid proteins in the host cell in culture and supply the rep and cap proteins in trans; sufficient adenovirus helper genes to permit replication and packaging of the

artificial genome by the AAV capsid proteins; and recovering recombinant AAV encapsidating the artificial genome from the cell culture.

5.1 CONSTRUCTS

[0068] Viral vectors or other DNA expression constructs encoding an anti-C5 scFv, particularly a HuGlyFab or HuGlyscFv, or a hyperglycosylated derivative of a HuPTM mAb antigen-binding fragment are provided herein. The viral vectors and other DNA expression constructs provided herein include any suitable method for delivery of a transgene to a target cell. The means of delivery of a transgene include viral vectors, liposomes, other lipid-containing complexes, other macromolecular complexes, synthetic modified mRNA, unmodified mRNA, small molecules, non-biologically active molecules (*e.g.*, gold particles), polymerized molecules (*e.g.*, dendrimers), naked DNA, plasmids, phages, transposons, cosmids, or episomes. In some embodiments, the vector is a targeted vector, *e.g.*, a vector targeted ocular tissue cells or a vector that has a tropism for ocular tissue cells.

[0069] In some aspects, the disclosure provides for a nucleic acid for use, wherein the nucleic acid comprises a nucleotide sequence that encodes the C5-D-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 195 or 203) or C5-A-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 197) as a transgene described herein, operatively linked to an ubiquitous promoter, an ocular tissue-specific promoter, or an inducible promoter, wherein the promoter is selected for expression in tissue targeted for expression of the transgene. Promoters may, for example, be a CB7/CAG promoter (SEQ ID NO: 1) and associated upstream regulatory sequences, CAG promoter (CMS early enhancer, Chicken Beta-actin promoter-chicken beta actin intron-rabbit beta-globin splice acceptor) (SEQ ID NO: 2), Chicken Beta-actin promoter-chicken beta actin intron-rabbit beta-globin splice acceptor) with mutations (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), cytomegalovirus (CMV) promoter, EF-1 alpha promoter (SEQ ID NO: 4), mU1a (SEQ ID NO: 3), UB6 promoter, chicken beta-actin (CBA) promoter, and ocular-tissue specific promoters, such as human rhodopsin kinase (GRK1) promoter (SEQ ID NOS: 5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), or a human red opsin (RedO) promoter (SEQ ID NO: 14). See **Tables 1** and **1a** for a list of useful promoters.

[0070] In certain embodiments, the expression cassette (promoter to polyA) comprises the nucleotide sequence of SEQ ID NO: 226, SEQ ID NO: 228, SEQ ID NO: 231, SEQ ID NO: 233, SEQ

ID NO: 235, SEQ ID NO: 237, SEQ ID NO: 239, SEQ ID NO: 241, SEQ ID NO: 278, or SEQ ID NO: 279.

[0071] In certain embodiments, nucleic acids (*e.g.*, polynucleotides) and nucleic acid sequences disclosed herein may be codon-optimized, for example, via any codon-optimization technique known to one of skill in the art (*see, e.g.*, review by Quax et al., 2015, Mol Cell 59:149-161).

[0072] In a specific embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) one or more control elements, b) optionally, a chicken β-actin or other intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for C5-D-mab Vectorized scFv mAb (H-L) (having an amino acid sequence of SEQ ID NO: 195 or 203) or C5-A-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 197). Exemplary constructs are shown in **FIGS. 1A, 1B and 1C** and are provided in **Table 8.**

[0073] In a specific embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) GRK1 promoter (SEQ ID NO: 5), b) optionally, a VH4 intron (SEQ ID NO: 8) or other intron and c) a rabbit β-globin polyA signal (SEQ ID NO: 6); and (3) nucleic acid sequences coding for C5-D-mab Vectorized scFv mAb (H-L) (having an amino acid sequence of SEQ ID NO: 195 or 203).

[0074] In specific embodiments, the artificial genome comprises the nucleotide sequence of SEQ ID NO: 225, SEQ ID NO: 229, SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, SEQ ID NO: 242, SEQ ID NO: 276, or SEQ ID NO: 277.

5.1.2 Viral vectors

[0075] In certain embodiments, the viral vectors provided herein are AAV based viral vectors. In certain embodiments, the AAV-based vectors provided herein do not encode the AAV rep gene (required for replication) and/or the AAV cap gene (required for synthesis of the capsid proteins) (the rep and cap proteins may be provided by the packaging cells in *trans*). Multiple AAV serotypes have been identified. In certain embodiments, AAV-based vectors provided herein comprise components from one or more serotypes of AAV. In preferred embodiments, AAV-based vectors provided herein comprise components from one or more serotypes of AAV with tropism to ocular tissues, liver and/or muscle. In certain embodiments, AAV based vectors provided herein comprise capsid components from one or more of AAV1, AAV2, AAV3, AAV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAV9, AAV9e, AAVrh10, AAVrh20, AAVrh39, AAVhu.37, AAVrh73, AAVrh74, AAV.hu51,

AAV.hu21, AAV.hu12, or AAV.hu26. In certain embodiments, AAV based vectors provided herein are or comprise components from one or more of AAV8, AAV3B, AAV9, AAV10, AAVrh73, or AAVrh10 serotypes. Provided are viral vectors in which the capsid protein is a variant VP1 protein of AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249) (see Table A). Also provided are viral vectors in which the capsid protein is a variant of the AAV8 capsid protein (SEQ ID NO:260), AAV3B capsid protein (SEQ ID NO:254), or AAVrh73 capsid protein (SEQ ID NO:266), and the capsid protein is e.g., at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to the amino acid sequence of the AAV8 capsid protein (SEQ ID NO:260), AAV9 (SEQ ID NO: 261), AAV3B capsid protein (SEQ ID NO:254), or AAVrh73 capsid protein (SEQ ID NO:266), while retaining the biological function of the native capsid. In certain embodiments, the encoded AAV capsid has the sequence of SEQ ID NO: 260 with 1, 2, 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 or 30 amino acid substitutions and retaining the biological function of the AAV8, AAV3B, or AAVrh73 capsid. **FIG. 3** provides a comparative alignment of the amino acid sequences of the capsid proteins of different AAV serotypes with potential amino acids that may be substituted at certain positions in the aligned sequences based upon the comparison in the row labeled SUBS. Accordingly, in specific embodiments, the AAV vector comprises an AAV8, AAV3B, or AAVrh73, capsid variant that has 1, 2, 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 or 30 amino acid substitutions that are not present at that position in the native AAV capsid sequence as identified in the SUBS row of **FIG. 3**. Amino acid sequence for AAV8, AAV9, AAV3B, or AAVrh73 capsids are provided in **FIG. 3**.

[0076] The amino acid sequence of hu37 capsid can be found in international application PCT WO 2005/033321 (SEQ ID NO: 88 thereof) and the amino acid sequence for the rh8 capsid can be found in international application PCT WO 03/042397 (SEQ ID NO:97). The amino acid sequence for the rh64R1 sequence is found in WO2006/110689 (a R697W substitution of the Rh.64 sequence, which is SEQ ID NO: 43 of WO 2006/110689).

[0077] In some embodiments, AAV-based vectors comprise components from one or more serotypes of AAV. In some embodiments, AAV based vectors provided herein comprise capsid components from one or more of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9,

AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, AAV16, AAVS3, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.rh46, AAV.rh73, AAV.Rh74, AAV.RHM4-1, AAV.hu37, AAV.Anc80, AAV.Anc80L65, AAV.7m8, AAV.PHP.B, AAV.PHP.eB, AAV2.5, AAV2tYF, AAV3B, AAV.LK03, AAV.HSC1, AAV.HSC2, AAV.HSC3, AAV.HSC4, AAV.HSC5, AAV.HSC6, AAV.HSC7, AAV.HSC8, AAV.HSC9, AAV.HSC10, AAV.HSC11, AAV.HSC12, AAV.HSC13, AAV.HSC14, AAV.HSC15, or AAV.HSC16 or other rAAV particles, or combinations of two or more thereof. In some embodiments, AAV based vectors provided herein comprise components from one or more of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, AAV16, AAVS3, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.rh46, AAV.rh73, AAV.Rh74, AAV.RHM4-1, AAV.hu37, AAV.Anc80, AAV.Anc80L65, AAV.7m8, AAV.PHP.B, AAV.PHP.eB, AAV2.5, AAV2tYF, AAV3B, AAV.LK03, AAV.HSC1, AAV.HSC2, AAV.HSC3, AAV.HSC4, AAV.HSC5, AAV.HSC6, AAV.HSC7, AAV.HSC8, AAV.HSC9, AAV.HSC10, AAV.HSC11, AAV.HSC12, AAV.HSC13, AAV.HSC14, AAV.HSC15, or AAV.HSC16 or other rAAV particles, or combinations of two or more thereof serotypes. In some embodiments, rAAV particles comprise a capsid protein at least 80% or more identical, e.g., 85%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, etc., i.e. up to 100% identical, to e.g., VP1, VP2 and/or VP3 sequence of an AAV capsid serotype selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, AAV16, AAVS3, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.rh46, AAV.rh73, AAV.Rh74, AAV.RHM4-1, AAV.hu37, AAV.Anc80, rAAV.Anc80L65, AAV.7m8, AAV.PHP.B, AAV.PHP.eB, AAV2.5, AAV2tYF, AAV3B, AAV.LK03, AAV.HSC1, AAV.HSC2, AAV.HSC3, AAV.HSC4, AAV.HSC5, AAV.HSC6, AAV.HSC7, AAV.HSC8, AAV.HSC9, AAV.HSC10, AAV.HSC11, AAV.HSC12, AAV.HSC13, AAV.HSC14, AAV.HSC15, or AAV.HSC16, or a derivative, modification, or pseudotype thereof.

[0078] In particular embodiments, the recombinant AAV for us in compositions and methods herein is AAVS3 (including variants thereof) (*see e.g.*, US Patent Application No. 20200079821, which is incorporated herein by reference in its entirety). In particular embodiments, rAAV particles comprise the capsids of AAV-LK03 or AAV3B, as described in Puzzo et al., 2017, Sci. Transl. Med. 29(9): 418, which is incorporated by reference in its entirety. In particular embodiments, the AAV for use in compositions and methods herein is any AAV disclosed in US 10,301,648, such as AAV.rh46 or AAV.rh73. In some embodiments, the recombinant AAV for use in compositions and methods herein is Anc80 or Anc80L65 (*see, e.g.*, Zinn et al., 2015, Cell Rep. 12(6): 1056-1068, which is incorporated

by reference in its entirety). In particular embodiments, the AAV for use in compositions and methods herein is any AAV disclosed in US 9,585,971, such as AAV-PHP.B. In particular embodiments, the AAV for use in compositions and methods herein is an AAV2/Rec2 or AAV2/Rec3 vector, which has hybrid capsid sequences derived from AAV8 and serotypes cy5, rh20 or rh39 (*see, e.g.*, Issa et al., 2013, PLoS One 8(4): e60361, which is incorporated by reference herein for these vectors). In particular embodiments, the AAV for use in compositions and methods herein is an AAV disclosed in any of the following, each of which is incorporated herein by reference in its entirety: US 7,282,199; US 7,906,111; US 8,524,446; US 8,999,678; US 8,628,966; US 8,927,514; US 8,734,809; US9,284,357; US 9,409,953; US 9,169,299; US 9,193,956; US 9,458,517; US 9,587,282; US 2015/0374803; US 2015/0126588; US 2017/0067908; US 2013/0224836; US 2016/0215024; US 2017/0051257; PCT/US2015/034799; and PCT/EP2015/053335. In some embodiments, rAAV particles have a capsid protein at least 80% or more identical, e.g., 85%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, etc., i.e. up to 100% identical, to the VP1, VP2 and/or VP3 sequence of an AAV capsid disclosed in any of the following patents and patent applications, each of which is incorporated herein by reference in its entirety: United States Patent Nos. 7,282,199; 7,906,111; 8,524,446; 8,999,678; 8,628,966; 8,927,514; 8,734,809; US 9,284,357; 9,409,953; 9,169,299; 9,193,956; 9,458,517; and 9,587,282; US patent application publication nos. 2015/0374803; 2015/0126588; 2017/0067908; 2013/0224836; 2016/0215024; 2017/0051257; and International Patent Application Nos. PCT/US2015/034799; PCT/EP2015/053335.

[0079] In some embodiments, rAAV particles comprise any AAV capsid disclosed in United States Patent No. 9,840,719 and WO 2015/013313, such as AAV.Rh74 and RHM4-1, each of which is incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise any AAV capsid disclosed in WO 2014/172669, such as AAV rh.74, which is incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise the capsid of AAV2/5, as described in Georgiadis et al., 2016, Gene Therapy 23: 857-862 and Georgiadis et al., 2018, Gene Therapy 25: 450, each of which is incorporated by reference in its entirety. In some embodiments, rAAV particles comprise any AAV capsid disclosed in WO 2017/070491, such as AAV2tYF, which is incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise any AAV capsid disclosed in US Pat Nos. 8,628,966; US 8,927,514; US 9,923,120 and WO 2016/049230, such as HSC1, HSC2, HSC3, HSC4, HSC5, HSC6, HSC7, HSC8, HSC9, HSC10, HSC11, HSC12, HSC13, HSC14, HSC15, or HSC16, each of which is incorporated by reference in its entirety.

[0080] In some embodiments, rAAV particles have a capsid protein disclosed in Intl. Appl. Publ. No. WO 2003/052051 (see, e.g., SEQ ID NO: 2 of ´051 publication), WO 2005/033321 (see, e.g., SEQ ID NOs: 123 and 88 of ´321 publication), WO 03/042397 (see, e.g., SEQ ID NOs: 2, 81, 85, and 97 of ´397 publication), WO 2006/068888 (see, e.g., SEQ ID NOs: 1 and 3-6 of ´888 publication), WO 2006/110689, (see, e.g., SEQ ID NOs: 5-38 of ´689 publication) WO2009/104964 (see, e.g., SEQ ID NOs: 1-5, 7, 9, 20, 22, 24 and 31 of ´964 publication), WO 2010/127097 (see, e.g., SEQ ID NOs: 5-38 of ´097 publication), and WO 2015/191508 (see, e.g., SEQ ID NOs: 80-294 of ´508 publication), and U.S. Appl. Publ. No. 20150023924 (see, e.g., SEQ ID NOs: 1, 5-10 of ´924 publication), the contents of each of which is herein incorporated by reference in its entirety. In some embodiments, rAAV particles have a capsid protein at least 80% or more identical, e.g., 85%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, etc., i.e. up to 100% identical, to the VP1, VP2 and/or VP3 sequence of an AAV capsid disclosed in Intl. Appl. Publ. No. WO 2003/052051 (see, e.g., SEQ ID NO: 2 of ´051 publication), WO 2005/033321 (see, e.g., SEQ ID NOs: 123 and 88 of ´321 publication), WO 03/042397 (see, e.g., SEQ ID NOs: 2, 81, 85, and 97 of ´397 publication), WO 2006/068888 (see, e.g., SEQ ID NOs: 1 and 3-6 of ´888 publication), WO 2006/110689 (see, e.g., SEQ ID NOs: 5-38 of ´689 publication) WO2009/104964 (see, e.g., SEQ ID NOs: 1-5, 7, 9, 20, 22, 24 and 31 of 964 publication), W0 2010/127097 (see, e.g., SEQ ID NOs: 5-38 of ´097 publication), and WO 2015/191508 (see, e.g., SEQ ID NOs: 80-294 of ´508 publication), and U.S. Appl. Publ. No. 20150023924 (see, e.g., SEQ ID NOs: 1, 5-10 of ´924 publication).

[0081] In additional embodiments, rAAV particles comprise a pseudotyped AAV capsid. In some embodiments, the pseudotyped AAV capsids are rAAV2/8 or rAAV2/9 pseudotyped AAV capsids. Methods for producing and using pseudotyped rAAV particles are known in the art (see, e.g., Duan et al., J. Virol., 75:7662-7671 (2001); Halbert et al., J. Virol., 74:1524-1532 (2000); Zolotukhin et al., Methods 28:158-167 (2002); and Auricchio et al., Hum. Molec. Genet. 10:3075-3081, (2001).

[0082] AAV8-based, AAV3B-based, and AAVrh73-based viral vectors are used in certain of the methods described herein. Nucleotide sequences of AAV based viral vectors and methods of making recombinant AAV and AAV capsids are taught, for example, in United States Patent No. 7,282,199 B2, United States Patent No. 7,790,449 B2, United States Patent No. 8,318,480 B2, United States Patent No. 8,962,332 B2 and International Patent Application No. PCT/EP2014/076466, each of which is incorporated herein by reference in its entirety. In one aspect, provided herein are AAV (*e.g.*, AAV8, AAV3B, AAVrh73, or AAVrh10)-based viral vectors encoding a transgene (*e.g.*, an

HuPTM Fab or HuPTM scFv or protein). The amino acid sequences of AAV capsids, including AAV8, AAV3B, AAVrh73 and AAVrh10 are provided in **FIG. 3**.

[0083] In embodiments, the AAV vector comprises an engineered capsid protein that comprises a 7 to 9 amino acid peptide that homes to or targets ocular tissue, or enhances transduction and/or integration of the viral genome, and is inserted into an AAV8 or AAV3B capsid protein. The AAV type may be, for example, AAV3B.455.DLMLPGS (capsid protein having an amino acid sequence of SEQ ID NO: 243), AAV3B.455.DVTPLLS (capsid protein having an amino acid sequence of SEQ ID NO: 244), AAV3B.455.LVSVSLP (capsid protein having an amino acid sequence of SEQ ID NO: 245), AAV8.456.RIQMGTK (capsid protein having an amino acid sequence of capsid protein SEQ ID NO: 246), AAV8.456.RQKNAMV (capsid protein having an amino acid sequence of SEQ ID NO: 247), AAV8.590.GDNTTFRRA (capsid protein having an amino acid sequence of SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (capsid protein having an amino acid sequence of SEQ ID NO: 249).

Table A. VP1 Amino Acid Sequences

Name	SEQ ID NO:	Sequences
AAV3B.455.DLMLPGS)	SEQ ID NO: 243	MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKY LGPGNGLDKGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERL QEDTSFGGNLGRAVFQAKKRILEPLGLVEEAAKTAPGKKRPVDQSPQEPDSS SGVGKSGKQPARKRLNFGQTGDSESVPDPQPLGEPPAAPTSLGSNTMASGGG APMADNNEGADGVGNSSGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQI SSQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKKLS FKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGSAHQGCLPP FPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYTFE DVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGDLMLPGSTTNQSRL LFSQAGPQSMSLQARNWLPGPCYRQQRLSKTANDNNNSNFPWTAASKYHLNG RDSLVNPGPAMASHKDDEEKFFPMHGNLIFGKEGTTASNAELDNVMITDEEE IRTTNPVATEQYGTVANNLQSSNTAPTTRTVNDQGALPGMVWQDRDVYLQGP IWAKIPHTDGHFHPSPLMGGFGLKHPPPQIMIKNTPVPANPPTTFSPAKFAS FITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYNKSVNVDFTVDTNGVY SEPRPIGTRYLTRNL
AAV3B.455.DVTPLLS	SEQ ID NO: 244	MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKY LGPGNGLDKGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERL QEDTSFGGNLGRAVFQAKKRILEPLGLVEEAAKTAPGKKRPVDQSPQEPDSS SGVGKSGKQPARKRLNFGQTGDSESVPDPQPLGEPPAAPTSLGSNTMASGGG APMADNNEGADGVGNSSGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQI SSQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKKLS FKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGSAHQGCLPP FPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYTFE DVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGDVTPLLSTTNQSRL LFSQAGPQSMSLQARNWLPGPCYRQQRLSKTANDNNNSNFPWTAASKYHLNG RDSLVNPGPAMASHKDDEEKFFPMHGNLIFGKEGTTASNAELDNVMITDEEE IRTTNPVATEQYGTVANNLQSSNTAPTTRTVNDQGALPGMVWQDRDVYLQGP IWAKIPHTDGHFHPSPLMGGFGLKHPPPQIMIKNTPVPANPPTTFSPAKFAS

Name	SEQ ID NO:	Sequences
		FITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYNKSVNVDFTVDTNGVY SEPRPIGTRYLTRNL
AAV3B.455.LVS VSLP	SEQ ID NO: 245	MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKY LGPGNGLDKGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERL QEDTSFGGNLGRAVFQAKKRILEPLGLVEEAAKTAPGKKRPVDQSPQEPDSS SGVGKSGKQPARKRLNFGQTGDSESVPDPQPLGEPPAAPTSLGSNTMASGGG APMADNNEGADGVGNSSGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQI SSQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKKLS FKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGSAHQGCLPP FPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYTFE DVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGLVSVSLPTTNQSRL LFSQAGPQSMSLQARNWLPGPCYRQQRLSKTANDNNNSNFPWTAASKYHLNG RDSLVNPGPAMASHKDDEEKFFPMHGNLIFGKEGTTASNAELDNVMITDEEE IRTTNPVATEQYGTVANNLQSSNTAPTTRTVNDQGALPGMVWQDRDVYLQGP IWAKIPHTDGHFHPSPLMGGFGLKHPPPQIMIKNTPVPANPPTTFSPAKFAS FITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYNKSVNVDFTVDTNGVY SEPRPIGTRYLTRNL
AAV8.456.RIQM GTK	SEQ ID NO: 246	MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKY LGPFNGLDKGEPVNAADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERL QEDTSFGGNLGRAVFQAKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQRSPDS STGIGKKGQQPARKRLNFGQTGDSESVPDPQPLGEPPAAPSGVGPNTMAAGG GAPMADNNEGADGVGSSSGNWHCDSTWLGDRVITTSTRTWALPTYNNHLYKQ ISNGTSGGATNDNTYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPK RLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGSAHQGC LPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFTY TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTTGRIQMGTKGTANTQ TLGFSQGGPNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHL NGRNSLANPGIAMATHKDDEERFFPSNGILIFGKQNAARDNADYSDVMLTSE EEIKTTNPVATEEYGIVADNLQQQNTAPQIGTVNSQGALPGMVWQNRDVYLQ GPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPADPPTTFNQSKL NSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSTSVDFAVNTEG VYSEPRPIGTRYLTRNL
AAV8.456.RQK NAMV	SEQ ID NO: 247	MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKY LGPFNGLDKGEPVNAADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERL QEDTSFGGNLGRAVFQAKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQRSPDS STGIGKKGQQPARKRLNFGQTGDSESVPDPQPLGEPPAAPSGVGPNTMAAGG GAPMADNNEGADGVGSSSGNWHCDSTWLGDRVITTSTRTWALPTYNNHLYKQ ISNGTSGGATNDNTYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPK RLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGSAHQGC LPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFTY TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTTGRQKNAMVGTANTQ TLGFSQGGPNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHL NGRNSLANPGIAMATHKDDEERFFPSNGILIFGKQNAARDNADYSDVMLTSE EEIKTTNPVATEEYGIVADNLQQQNTAPQIGTVNSQGALPGMVWQNRDVYLQ GPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPADPPTTFNQSKL NSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSTSVDFAVNTEG VYSEPRPIGTRYLTRNL
AAV8.590.GDN TTFRRA	SEQ ID NO: 248	MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKY LGPFNGLDKGEPVNAADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERL QEDTSFGGNLGRAVFQAKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQRSPDS STGIGKKGQQPARKRLNFGQTGDSESVPDPQPLGEPPAAPSGVGPNTMAAGG GAPMADNNEGADGVGSSSGNWHCDSTWLGDRVITTSTRTWALPTYNNHLYKQ ISNGTSGGATNDNTYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPK RLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGSAHQGC

Name	SEQ ID NO:	Sequences
		LPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFTY TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTTGGTANTQTLGFSQG GPNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHLNGRNSLA NPGIAMATHKDDEERFFPSNGILIFGKQNAARDNADYSDVMLTSEEEIKTTN PVATEEYGIVADNLQQQGDNTTFRRANTAPQIGTVNSQGALPGMVWQNRDVY LQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPADPPTTFNQS KLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSTSVDFAVNT EGVYSEPRPIGTRYLTRNL
AAV8.590.GRTI RGDLA	SEQ ID NO: 249	MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKY LGPFNGLDKGEPVNAADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERL QEDTSFGGNLGRAVFQAKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQRSPDS STGIGKKGQQPARKRLNFGQTGDSESVPDPQPLGEPPAAPSGVGPNTMAAGG GAPMADNNEGADGVGSSSGNWHCDSTWLGDRVITTSTRTWALPTYNNHLYKQ ISNGTSGGATNDNTYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPK RLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGSAHQGC LPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFTY TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTTGGTANTQTLGFSQG GPNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHLNGRNSLA NPGIAMATHKDDEERFFPSNGILIFGKQNAARDNADYSDVMLTSEEEIKTTN PVATEEYGIVADNLQQQGRTIRGDLANTAPQIGTVNSQGALPGMVWQNRDVY LQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPADPPTTFNQS KLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSTSVDFAVNT EGVYSEPRPIGTRYLTRNL

[0084] In certain embodiments, a single-stranded AAV (ssAAV) may be used supra. In certain embodiments, a self-complementary vector, *e.g.*, scAAV, may be used (*see, e.g.*, Wu, 2007, Human Gene Therapy, 18(2):171-82, McCarty et al, 2001, Gene Therapy, Vol 8, Number 16, Pages 1248-1254; and U.S. Patent Nos. 6,596,535; 7,125,717; and 7,456,683, each of which is incorporated herein by reference in its entirety).

[0085] In certain embodiments, the viral vectors used in the methods described herein are adenovirus based viral vectors. A recombinant adenovirus vector may be used to transfer in the transgene encoding the scFv. The recombinant adenovirus can be a first-generation vector, with an E1 deletion, with or without an E3 deletion, and with the expression cassette inserted into either deleted region. The recombinant adenovirus can be a second-generation vector, which contains full or partial deletions of the E2 and E4 regions. A helper-dependent adenovirus retains only the adenovirus inverted terminal repeats and the packaging signal (phi). The transgene is inserted between the packaging signal and the 3'ITR, with or without stuffer sequences to keep the genome close to wild-type size of approximately 36 kb. An exemplary protocol for production of adenoviral vectors may be found in Alba et al., 2005, "Gutless adenovirus: last generation adenovirus for gene therapy," Gene Therapy 12:S18-S27, which is incorporated by reference herein in its entirety.

[0086] In a specific embodiment, a vector for use in the methods described herein is one that encodes an HuPTM mAb, such that, upon introduction of the vector into a relevant cell, a glycosylated and/or tyrosine sulfated variant of the HuPTM mAb is expressed by the cell.

5.1.3 Promoters and Modifiers of Gene Expression

[0087] In certain embodiments, the vectors provided herein comprise components that modulate gene delivery or gene expression (*e.g.*, "expression control elements"). In certain embodiments, the vectors provided herein comprise components that modulate gene expression. In certain embodiments, the vectors provided herein comprise components that influence binding or targeting to cells. In certain embodiments, the vectors provided herein comprise components that influence the localization of the polynucleotide (*e.g.*, the transgene) within the cell after uptake. In certain embodiments, the vectors provided herein comprise components that can be used as detectable or selectable markers, *e.g.*, to detect or select for cells that have taken up the polynucleotide.

[0088] In certain embodiments, the viral vectors provided herein comprise one or more promoters that control expression of the transgene. These promoters (and other regulatory elements that control transcription, such as enhancers) may be constitutive (promote ubiquitous expression) or may specifically or selectively express in the eye. In certain embodiments, the promoter is a constitutive promoter.

[0089] In certain embodiments, the promoter is a CAG promoter (SEQ ID NO: 2) (see Dinculescu et al., 2005, Hum Gene Ther 16: 649-663, incorporated by reference herein in its entirety). In some embodiments, the CAG (SEQ ID NO: 2) or CB7 promoter (SEQ ID NO: 1) or a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), includes other expression control elements that enhance expression of the transgene driven by the vector. In certain embodiments, the other expression control elements include chicken β-actin intron and/or rabbit β-globin polyA signal (SEQ ID NO: 6). In certain embodiments, the promoter comprises a TATA box. In certain embodiments, the promoter comprises one or more elements. In certain embodiments, the one or more promoter elements may be inverted or moved relative to one another. In certain embodiments, the elements of the promoter are positioned to function cooperatively. In certain embodiments, the elements of the promoter are positioned to function independently. In certain embodiments, the viral vectors provided herein comprise one or more promoters selected from the group consisting of the human CMV immediate early gene promoter, the SV40 early promoter, the Rous sarcoma virus (RS) long terminal repeat, and rat insulin promoter. In certain embodiments, the vectors provided herein

comprise one or more long terminal repeat (LTR) promoters selected from the group consisting of AAV, MLV, MMTV, SV40, RSV, HIV-1, and HIV-2 LTRs.

[0090] In certain embodiments, the vectors provided herein comprise one or more tissue specific promoters (e.g., a retinal-specific promoter). In particular embodiments, the viral vectors provided herein comprises a ocular tissue cell specific promoter, such as, human rhodopsin kinase (GRK1) promoter (SEQ ID NOS: 5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), or a human red opsin (RedO) promoter (SEQ ID NO: 14).

[0091] Provided are nucleic acid regulatory elements that are chimeric with respect to arrangements of elements in tandem in the expression cassette. Regulatory elements, in general, have multiple functions as recognition sites for transcription initiation or regulation, coordination with cell-specific machinery to drive expression upon signaling, and to enhance expression of the downstream gene.

[0092] In certain embodiments, the promoter is an inducible promoter. In certain embodiments the promoter is a hypoxia-inducible promoter. In certain embodiments, the promoter comprises a hypoxia-inducible factor (HIF) binding site. In certain embodiments, the promoter comprises a HIF-1α binding site. In certain embodiments, the promoter comprises a HIF-2α binding site. In certain embodiments, the HIF binding site comprises an RCGTG (SEQ ID NO: 275) motif. For details regarding the location and sequence of HIF binding sites, *see, e.g.*, Schödel, et al., Blood, 2011, 117(23):e207-e217, which is incorporated by reference herein in its entirety. In certain embodiments, the promoter comprises a binding site for a hypoxia induced transcription factor other than a HIF transcription factor. In certain embodiments, the viral vectors provided herein comprise one or more IRES sites that is preferentially translated in hypoxia. For teachings regarding hypoxia-inducible gene expression and the factors involved therein, *see, e.g.*, Kenneth and Rocha, Biochem J., 2008, 414:19-29, which is incorporated by reference herein in its entirety. In specific embodiments, the hypoxia-inducible promoter is the human N-WASP promoter, *see, e.g.*, Salvi, 2017, Biochemistry and Biophysics Reports 9:13-21 (incorporated by reference for the teaching of the N-WASP promoter) or is the hypoxia-induced promoter of human Epo, *see, e.g.*, Tsuchiya et al., 1993, J. Biochem. 113:395-400 (incorporated by reference for the disclosure of the Epo hypoxia-inducible promoter). In other embodiments, the promoter is a drug inducible promoter, for example, a promoter that is induced by administration of rapamycin or analogs thereof. See, *e.g.*, the disclosure of rapamycin inducible promoters in PCT publications WO94/18317, WO 96/20951, WO 96/41865, WO 99/10508, WO

99/10510, WO 99/36553, and WO 99/41258, and US 7,067,526, which are hereby incorporated by reference in their entireties for the disclosure of drug inducible promoters.

[0093] Provided herein are constructs containing certain ubiquitous and tissue-specific promoters. Such promoters include synthetic and tandem promoters. Examples and nucleotide sequences of promoters are provided in **Tables 1** and **1a** below. **Table 1** also includes the nucleotide sequences of other regulatory elements useful for the expression cassettes provided herein.

Table 1. Promoter and Other Regulatory Element Sequences

Name/ SEQ ID NO.	Sequence
CAG/CB7 SEQ ID NO: 1	gacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcccat atatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacc cccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggactttccatt gacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaagtgtatcata tgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagt acatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctattacca tggtcgaggtgagccccacgttctgcttcactctccccatctccccccccctccccacccccaa ttttgtatttatttatttttttaattattttgtgcagcgatgggggcgggggggggggggggggc gcgcgccaggcggggcggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcgg cagccaatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggcggcggc cctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctgccttcgccccgtgcccc gctccgccgccgcctcgcgccgcccgccccggctctgactgaccgcgttactcccacaggtga gcgggcgggacggcccttctcctccgggctgtaattagcgcttggtttaatgacggcttgttt cttttctgtggctgcgtgaaagccttgaggggctccgggagggccctttgtgcgggggggagcg gctcgggggggtgcgtgcgtgtgtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccg gcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgcgagggga gcgcggccgggggcggtgccccgcggtgcgggggggggctgcgagggggaacaaaggctgcgtgc ggggtgtgtgcgtgggggggtgagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccc tgcaccccccctccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacggggc gtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgccgggcggggcgg ggccgcctcgggccgggggagggctcgggggagggggcgcggcggcccccggagcgccggcggct gtcgaggcgcggcgagccgcagccattgccttttatggtaatcgtgcgagagggcgcagggac ttccttttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcacccccctctagcg ggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgtgcgt cgccgcgccgccgtcccccttctccctctccagcctcggggctgtccgcgggggggacggctgcc ttcgggggggacggggcagggcggggttcggcttctggcgtgtgaccggcggctctagagcct ctgctaaccatgttcatgccttcttcttttttcctacagctcctgggcaacgtgctggttattg tgctgtctcatcattttggcaaag
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3'-ITR	ttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccga cgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcag

Name/ SEQ ID NO.	Sequence
(Deleted D-sequence for self-complimentary AAV) SEQ ID NO: 12	
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Human red opsin (RedO) (photoreceptor-specific) SEQ ID NO: 14	ggaggctgaggggtggggaaagggcatgggtgtttcatgaggacagagcttccgtttcat gcaatgaaaagagtttggagacggatggtggtgactggactatacacttacacacggtag cgatggtacactttgtattatgtatattttaccacgatctttttaaagtgtcaaaggcaa atggccaaatggttccttgtcctatagctgtagcagccatcggctgttagtgacaaagcc cctgagtcaagatgacagcagcccccataactcctaatcggctctcccgcgtggagtcat ttaggagtagtcgcattagagacaagtccaacatctaatcttccaccctggccagggccc cagctggcagcgagggtgggagactccgggcagagcagagggcgctgacattggggcccg gcctggcttgggtccctctggcctttccccaggggccctctttccttggggctttcttgg gccgccactgctcccgctcctctccccccatcccacccccctcacccccctcgttcttcata tccttctctagtgctccctccactttcatccaccccttctgcaagagtgtgggaccacaaa tgagttttcacctggcctggggacacacgtgccccccacaggtgctgagtgactttctagg acagtaatctgctttaggctaaaatgggacttgatcttctgttagccctaatcatcaatt agcagagccggtgaaggtgcagaacctaccgcctttccaggcctcctcccacctctgcca cctccactctccttcctgggatgtgggggctggcacacgtgtggcccagggcattggtgg gattgcactgagctgggtcattagcgtaatcctggacaagggcagacagggcgagcggag ggccagctccgggggctcaggcaaggctgggggcttcccccagacaccccactcctcctct gctggaccccccacttcatagggcacttcgtgttctcaaagggcttccaaatagcatggtg gccttggatgcccagggaagcctcagagttgcttatctccctctagacagaaggggaatc tcggtcaagagggagaggtcgccctgttcaaggccacccagccagctcatggcggtaatg ggacaaggctggccagccatcccaccctcagaagggacccggtggggcaggtgatctcag aggaggctcacttctgggtctcacattcttggatccggttccaggcctcggccctaaata gtctccctgggctttcaagagaaccacatgagaaaggaggattcgggctctgagcagttt caccacccaccccccagtctgcaaatcctgacccgtgggtccacctgccccaaaggcgga cgcaggacagtagaagggaacagagaacacataaacacagagagggccacagcggctccc acagtcaccgccaccttcctggcggggatgggtggggcgtctgagtttggttcccagcaa atccctctgagccgcccttgcgggctcgcctcaggagcaggggagcaagaggtgggagga ggaggtctaagtcccaggcccaattaagagatcaggtagtgtagggtttgggagctttta

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Human rhodopsin (Rho) (photoreceptor-specific) SEQ ID NO:15	Agatcttcccc a cctagccacc tggcaaactg ctccttctct caaaggccca aacatggcct cccagactgc aacccccagg cagtcaggcc ctgtctccac aacctcacag ccaccctgga cggaatctgc ttcttcccac atttgagtcc tcctcagccc ctgagctcct ctgggcaggg ctgtttcttt ccatctttgt attcccaggg gcctgcaaat aaatgtttaa tgaacgaaca agagagtgaa ttccaattcc atgcaacaag gattgggctc ctgggcccta ggctatgtgt ctggcaccag aaacggaagc tgcaggttgc agcccctgcc ctcatggagc tcctcctgtc agaggagtgt ggggactgga tgactccaga ggtaacttgt gggggaacga acaggtaagg ggctgtgtga cgagatgaga gactgggaga ataaaccaga aagtctctag ctgtccagag gacatagcac agaggcccat ggtccctatt tcaaacccag gccaccagac tgagctggga ccttgggaca gacaagtcat gcagaagtta ggggaccttc tcctcccttt tcctggatgg atcctgagta ccttctcctc cctgacctca ggcttcctcc tagtgtcacc ttggcccctc ttagaagcca attaggccct cagtttctgc agcggggatt aatatgatta tgaacacccc caatctccca gatgctgatt cagccaggag cttaggaggg ggaggtcact ttataagggt ctgggggggt cagaacccag agtc (start of exon 1 at 5339; See also Bennett,J., Sun,D. and Kariko,K. Sequence analysis of the 5.34-kb 5' flanking region of the human rhodopsin-encoding gene. Gene 167 (1-2), 317-320 (1995))
Mouse cone arrestin promoter (CAR) *(photoreceptor-specific)* SEQ ID NO: 16	TGGCCCTGGCATTCCCCTATACTGGGACATAGAACCTTCACAGGACCAAGGGCCTCTCCTCCC ATTGATGACTGACTAGGCCATCCTCTAGCTACATAGGTGGTGGAGCCTAGAGTCCCTCCTTGT GTACTCTTTGGTGGTGGTTACTCTGGGGGTACTAGGTTAGTTCGTATTGTTGTTCCTCCTAGG GGACTGCAAACCCCTTCAGCTCCTTGGGTCCTTTCTCTAGTTCCTTCTTTGGGGACCCTGTGC TCAGTTCAATGGATGGCCAATTTCCTTCTTAAATGCCCCTAGCAGTAACTGTTAGGTCTCAAT CCCAAGACAAATGTCTGAGGTGCCTATTTAACAGATCAAAGCGGACCTGTCCTCAGGTTAACC CAGTCACTCCCTGTACCTCAGTCCCTACCCATCACAATTCTCCAGCCCATGAGCTTCGGGCTG TACTTCCCCAACGGGTTCTCCCATTTTGGGTACATGGCCTTTTTTTTTTACCTTTTTGGTTCC TTTGGCCTTTTGGCTTTTGGCTTCCAGGGCTTCTGGATCCCCCCCCAACCCCTCCCATACACA TACACATGTGCACTCGTGCACTCAACCCAGCACAGGATAATGTTCATTCTTGACCTTTCCACA TACATCTGGCTATGTTCTCTCTCTTATCTACAATAAATCTCCTCCACTATACTTAGGAGCAGT TATGTTCTTCTTCTTTCTTTCTTTTTTTTTTTTTTTTTCATTCAGTAACATCATCAGAATCCCC TAGCTCTGGCCTACCTCCTCAGTAACAATCAGC**TGATCCCTGGCCACTAATCTGTACTCACTA ATCTGTTTTCCAAACTCTTGGCCCCTGAGCTAATTATAGCAGTGCTTCATGCCACCCACCCCA ACCCTATCCTTGTTCTCTGACTCCCACTAATCTACACATTCAGAGGATTGTGGATATAAGAGG CTGGGAGGCCAGCTTAGCAACCAGAGCTCGAGGCTGATGCGAGCTTCATCTCTTCCCTC**
Mouse cone arrestin promoter (CAR) *(photoreceptor-specific)* SEQ ID NO: 17	TTTTTTTTTTACCTTTTTGGTTCCTTTGGCCTTTTGGCTTTTGGCTTCCAGGGCTTCTGGATC CCCCCCAACCCCTCCCATACACATACACATGTGCACTCGTGCACTCAACCCAGCACAGGATA ATGTTCATTCTTGACCTTTCCACATACATCTGGCTATGTTCTCTCTCTTATCTACAATAAATC TCCTCCACTATACTTAGGAGCAGTTATGTTCTTCTTCTTTCTTTCTTTTTTTTTTTTTTTCA TTCAGTAACATCATCAGAATCCCCTAGCTCTGGCCTACCTCCTCAGTAACAATCAGC**TGATCC CTGGCCACTAATCTGTACTCACTAATCTGTTTTCCAAACTCTTGGCCCCTGAGCTAATTATAG CAGTGCTTCATGCCACCCACCCCAACCCTATCCTTGTTCTCTGACTCCCACTAATCTACACAT TCAGAGGATTGTGGATATAAGAGGCTGGGAGGCCAGCTTAGCAACCAGAGCTCGAGGCTGATG CGAGCTTCATCTCTTCCCTC**
Mouse cone arrestin promoter (CAR) *(photoreceptor-specific)*	**TGATCCCTGGCCACTAATCTGTACTCACTAATCTGTTTTCCAAACTCTTGGCCCCTGAGCTAA TTATAGCAGTGCTTCATGCCACCCACCCCAACCCTATCCTTGTTCTCTGACTCCCACTAATCT ACACATTCAGAGGATTGTGGATATAAGAGGCTGGGAGGCCAGCTTAGCAACCAGAGCTCGAGG CTGATGCGAGCTTCATCTCTTCCCTC**

Name/ SEQ ID NO.	Sequence
SEQ ID NO: 18	
Human rhodopsin kinase (RK) or GRK1 *(photoreceptor-specific)* SEQ ID NO: 19	gggcccca gaagcctggt ggttgtttgt ccttctcagg ggaaaagtga ggcggccccct tggaggaagg ggccgggcag aatgatctaa tcggattcca agcagctcag gggattgtct ttttctagca ccttcttgcc actcctaagc gtcctccgtg accccggctg ggatttagcc tggtgctgtg tcagccccgg
Human Bestrophin 1 (BEST1) promoter *(a.k.a. hVMD2 promoter)* SEQ ID NO: 20	AAGG ACTCCTTTGT GGAGGTCCTG GCTTAGGGAG TCAAGTGACG GCGGCTCAGC ACTCACGTGG GCAGTGCCAG CCTCTAAGAG TGGGCAGGGG CACTGGCCAC AGAGTCCCAG GGAGTCCCAC CAGCCTAGTC GCCAGACC +38
Human Bestrophin 1 (BEST1) promoter *(a.k.a. hVMD2 promoter)* SEQ ID NO: 21	GTCAAGTGACG GCGGCTCAGC ACTCACGTGG GCAGTGCCAG CCTCTAAGAG TGGGCAGGGG CACTGGCCAC AGAGTCCCAG GGAGTCCCAC CAGCCTAGTC GCCAGACC (transcriptional start site residue underlined at +1)
Human Bestrophin 1 (BEST1) promoter (a.k.a. hVMD2 promoter) SEQ ID NO: 22	CTCAGC ACTCACGTGG GCAGTGCCAG CCTCTAAGAG TGGGCAGGGG CACTGGCCAC AGAGTCCCAG GGAGTCCCAC CAGCCTAGTC GCCAGAC (transcriptional start site residue underlined at +1)
Human Bestrophin 1 (BEST1) promoter *(a.k.a. hVMD2 promoter)* SEQ ID NO: 23	TTAATAAACA TTTGGGCGAT TCTTACGGCC TCTAAAGACC AAGAACCACT GCTGCCTAGA GCTCTGCTCT CTTCATTGAA CAATACAAGA GGAGTGTGTA GGTAGACACC CACCACTTCC AACAGCTTAG GAGAGCCCTT GAGTATGGAT TGATGTATTA AAATTTATTG AATCACATGC TGAGATTTTC ACCAGCTGCC CGTGGGGATC TGGGCATTTA TTCCCATATT GCACTGGCTG GCTGGAAGCC AGCAGCATAA ACTCCAGGGC TGTTCTGTCA ACCCCCACCA GACTCACCCC GCTCCACCAG CCCCGGCAGG CTTCTCCTTC CATCTCTCTG AAGCAACTTA CTGATGGGCC CTGCCAGCCA ATCACAGCCA GAATAACGTA TGATGTCACC AGCAGCCAAT CAGAGCTCCT CGTCAGCATA TGCAGAATTC TGTCATTTTA CTAGGGTGAT GAAATTCCCA AGCAACACCA TCCTTTTCAG ATAAGGGCAC TGAGGCTGAG AGAGGAGCTG AAACCTACCC GGCGTCACCA CACACAGGTG GCAAGGCTGG GACCAGAAAC CAGGACTGTT GACTGCAGCC CGGTATTCAT TCTTTCCATA GCCCACAGGG CTGTCAAAGA CCCCAGGGCC TAGTCAGAGG CTCCTCCTTC CTGGAGAGTT CCTGGCACAG AAGTTGAAGC TCAGCACAGC CCCCTAACCC CCAACTCTCT CTGCAAGGCC TCAGGGGTCA GAACACTGGT GGAGCAGATC CTTTAGCCTC TGGATTTTAG GGCCATGGTA GAGGGGGTGT TGCCCTAAAT TCCAGCCCTG GTCTCAGCCC AACACCCTCC AAGAAGAAAT

Name/ SEQ ID NO.	Sequence
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CB Promoter SEQ ID NO: 24	gacgacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcc catatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgcccaacg acccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggactttcc attgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaagtgtatc atatgccaagtacgcccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctatta ccatggtcgaggtgagccccacgttctgcttcactctccccatctccccccccctccccacccc caattttgtatttatttatttttttaattattttgtgcagcgatgggggcgggggggggggggg ggcgcgcgccaggcggggcggggcggggcgaggggcggggcggggcgaggcggagaggtgcgg cggcagccaatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggcggc ggccctataaaaagcgaagcgcgcggcgggcgg
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Best/GRK1 Tandem Promoter SEQ ID NO: 26	GTCGACAAATTCTGTCATTTTACTAGGGTGATGAAATTCCCAAGCAACACCATCCTTTTCAGA TAAGGGCACTGAGGCTGAGAGAGGAGCTGAAACCTACCCGGGGTCACCACACACAGGTGGCAA GGCTGGGACCAGAAACCAGGACTGTTGACTGCAGCCCGGTATTCATTCTTTCCATAGCCCACA GGGCTGTCAAAGACCCCAGGGCCTAGTCAGAGGCTCCTCCTTCCTGGAGAGTTCCTGGCACAG AAGTTGAAGCTCAGCACAGCCCCCTAACCCCCAACTCTCTCTGCAAGGCCTCAGGGGTCAGAA CACTGGTGGAGCAGATCCTTTAGCCTCTGGATTTTAGGGCCATGGTAGAGGGGGTGTTGCCCT AAATTCCAGCCCTGGTCTCAGCCCAACACCCTCCAAGAAGAAATTAGAGGGGCCATGGCCAGG CTGTGCTAGCCGTTGCTTCTGAGCAGATTACAAGAAGGGACTAAGACAAGGACTCCTTTGTGG AGGTCCTGGCTTAGGGAGTCAAGTGACGGCGGCTCAGCACTCACGTGGGCAGTGCCAGCCTCT AAGAGTGGGCAGGGGCACTGGCCACAGAGTCCCAGGGAGTCCCACCAGCCTAGTCGCCAGAtC TAGAGGGCCCCAGAAGCCTGGTGGTTGTTTGTCCTTCTCAGGGGAAAAGTGAGGCGGCCCCTT GGAGGAAGGGGCCGGGCAGAAGATCTAATCGGATTCCAAGCAGCTCAGGGGATTGTCTTTTTC TAGCACCTTCTTGCCACTCCTAAGCGTCCTCCGTGACCCCGGCTGGGATTTAGCCTGGTGCTG TGTCAGCCCCGGGCTCCCAGGGGCTTCCCAGTGGTCCCCAGGAACCCTCGACAGGGCCAGGGC GTCTCTCTCGTCCAGCAAGGGCAGGGACGGGCCACAGGCCAAGGGCCTTAAGC
SV40 Intron SEQ ID NO: 27	gtaagtttagtctttttgtcttttatttcaggtcccggatccggtggtggtgcaaatcaaaga actgctcctcagtggatgttgcctttacttctag
Upstream Kozak sequence SEQ ID NO: 28	GCCACC

Name/ SEQ ID NO.	Sequence
CAG(DEL5) SEQ ID NO: 29	gactagttattaatagtaatcaattacggggtcattagttcatagcccatatatggagttccg cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgac gtcaataatgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggt ggagtatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagtacgcc ccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagtacatgaccttatg ggactttcctacttggcagtacatctacgtattagtcatcgctattaccatggtcgaggtgag ccccacgttctgcttcactctccccatctccccccccctccccacccccaattttgtatttatt tatttttaattatttttgtgcagcgatgggggcgggggggggggggggggcgcgcgccaggcgg ggcggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcggcagccaatcagag cggcgcgctccgaaagtttccttttatggcgaggcggcggcggcggcggccctataaaaagcg aagcgcgcggcgggcgggagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgc ctcgcgccgcccgccccggctctgactgaccgcgttactcccacaggtgagcgggcgggacgg cccttctcctccgggctgtgcgagccgcagccattgccttttatggtaatcgtgcgagagggc gcagggacttcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcacccc ctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggcct tcgtgcgtcgccgcgccgccgtcccctttctcccctctccagcctcggggctgtccgcgggggga cggctgccttcgggggggacggggcagggcggggttcggcttctggcgtgtgaccggcggctc tagagcctctgctaaccatgttcatgccttcttctttttcctacagctcctgggcaacgtgct ggttattgtgctgtctcatcattttggcaaag
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Table 1a. Other regulatory sequences

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LMTP19 SEQ ID NO:42	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggccctgcatgcgaagatcttcgaacaaggctgtgggggactgagggcaggctgtaaca ggcttgggggccagggcttatacgtgcctgggactcccaaagtattactgttccatgttcccg gcgaagggccagctgtcccccgccagctagactcagcacttagtttaggaaccagtgagcaag tcagcccttggggcagcccatacaaggccatggggctgggcaagctgcacgcctgggtccggg gtgggcacggtgcccgggcaacgagctgaaagctcatctgctctcaggggcccctccctgggg acagcccctcctggctagtcacaccctgtaggctcctctatataacccaggggcacaggggct gccctcattctaccaccacctccacagcacagacagacactcaggagccagccagcgtcgaga tcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggccagctaagtgg tactctcccagagactgtctgactcacgccacccctccaccttggacacaggacgctgtggt ttctgagccaggtacagtgactcctttcggtaagtgcagtggaagctgtacactgcccaggca aagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagccctgtttgc tcctccgataactggggtgaccttggttaatattcaccagcagcctccccgttgcccctctg gatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccaccact gacctgggacagt
LMTP20 SEQ ID NO:43	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggcccttcagattaaaaataactgaggtaagggcctgggtaggggaggtggtgtgagac gctcctgtctctcctctatctgcccatcggccctttggggaggaggaatgtgcccaaggacta aaaaaaggccatggagccagaggggcgagggcaacagaccttttcatgggcaaaccttggggcc ctgctgaagctttggcccactacgggtttaggctgcccatgtaaggaggcaaggcctggggac acccgagatgcctggttataattaacccagacatgtggctgccccccccccccccaacacctg ctgcctctaaaaataaccctgtccctggtggatcccctgcatgcgaagatcttcgaacaaggc

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ApoE.hAAT SEQ ID NO:44	aggctcagaggcacacaggagtttctgggctcaccctgccccctccaaccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agaggggtacccggggatcttgctaccagtggaacagccactaaggattctgcagtgagagca gagggccagctaagtggtactctcccagagactgtctgactcacgccacccctccaccttgg acacaggacgctgtggtttctgagccaggtacaatgactcctttcggtaagtgcagtggaagc tgtacactgcccaggcaaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtgg acttagcccctgtttgctcctccgataactggggtgaccttggttaatattcaccagcagcct cccccgttgcccctctggatccactgcttaaatacggacgaggacagggccctgtctcctcag cttcaggcaccaccactgacctgggacagt
Alpha-Mic/Bik Enhancer (Mic/BikE) SEQ ID NO:45	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgt ttgctctggttaataatctcaggagcacaaacattcc
Tandem (2) alpha-Mic/Bik Enhancers (2 Mic/BikE) SEQ ID NO:46	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgt ttgctctggttaataatctcaggagcacaaacattccaggttaatttttaaaaagcagtcaaa agtccaagtggcccttggcagcatttactctctctgtttgctctggttaataatctcaggagc acaaacattcc
ApoE Hepatic Control Region containing ApoE Enhancer SEQ ID NO:47	aggctcagaggcacacaggagtttctgggctcaccctgccccctccaaccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agaggg
Tandem (2) ApoE Enhancers SEQ ID NO:48	aggctcagaggcacacaggagtttctgggctcaccctgccccctccaaccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggtctagaaggctcagaggcacacaggagtttctgggctcaccctgccccctccaacc cctcagttcccatcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaact tcagcctactcatgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagcc ctccctgcctgctgaccttggagctggggcagaggtcagagacctctctg

hAAT Promoter SEQ ID NO:49	gatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggccagctaagt ggtactctcccagagactgtctgactcacgccacccccctccaccttggacacaggacgctgtg gtttctgagccaggtacaatgactcctttcggtaagtgcagtggaagctgtacactgcccagg caaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctgttt gctcctccgataactggggtgaccttggttaatattcaccagcagcctccccgttgcccctc tggatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccacca ctgacctgggacagt
hAAT(ΔATG) Promoter SEQ ID NO:50	gatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggccagctaagt ggtactctcccagagactgtctgactcacgccacccccctccaccttggacacaggacgctgtg gtttctgagccaggtacagtgactcctttcggtaagtgcagtggaagctgtacactgcccagg caaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctgttt gctcctccgataactggggtgaccttggttaatattcaccagcagcctccccgttgcccctc tggatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccacca ctgacctgggacagt
Mck Enhancer (MckE) SEQ ID NO:51	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccg agatgcctggttataattaacccagacatgtggctgccccccccccccccaa cacctgctgcctctaaaaataaccctgtccctggtggatc
Tandem (2) Mck Enhancers (2 MckE) SEQ ID NO:52	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccgagatgcctggt tataattaacccagacatgtggctgccccccccccccccaacacctgctgcctctaaaaataa ccctgtccctggtggatcccactacgggtttaggctgcccatgtaaggaggcaaggcctgggg acacccgagatgcctggttataattaacccagacatgtggctgccccccccccccccaacacc tgctgcctctaaaaataaccctgtccctggtggatc
Tandem Mck (3) Enhancers (3 MckE) SEQ ID NO:53	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccgagatgcctggt tataattaacccagacatgtggctgccccccccccccccaacacctgctgcctctaaaaataa ccctgtccctggtggatcccactacgggtttaggctgcccatgtaaggaggcaaggcctgggg acacccgagatgcctggttataattaacccagacatgtggctgccccccccccccccaacacc tgctgcctctaaaaataaccctgtccctggtggatcccactacgggtttaggctgcccatgta aggaggcaaggcctggggacacccgagatgcctggttataattaacccagacatgtggctgcc ccccccccccccaacacctgctgcctctaaaaataaccctgtccctggtggatc
Myosin heavy chain enhancer (MhcE) SEQ ID NO:54	cccttcagattaaaaataactgaggtaagggcctgggtaggggaggtggtgtgagacgctcct gtctctcctctatctgcccatcggccctttggggaggaggaatgtgcccaaggactaaaaaaa ggccatggagccagaggggcgagggcaacagacctttcatgggcaaaccttggggccctgctg aagctttggc

[0094] In certain embodiments, the viral vectors provided herein comprise one or more regulatory elements other than a promoter. In certain embodiments, the viral vectors provided herein comprise an enhancer. In certain embodiments, the viral vectors provided herein comprise a repressor. In certain embodiments, the viral vectors provided herein comprise an intron (e.g. VH4 intron (SEQ ID NO: 8), SV40 intron (SEQ ID NO: 27), or a chimeric intron (β-globin/Ig Intron) (SEQ ID NO:7). The viral vectors may also include a Kozak sequence to promote translation of the transgene product, for example GCCACC (SEQ ID NO: 28).

[0095] In certain embodiments, the viral vectors provided herein comprise a polyadenylation sequence downstream of the coding region of the transgene. Any polyA site that signals termination of transcription and directs the synthesis of a polyA tail is suitable for use in AAV vectors of the present disclosure. Exemplary polyA signals are derived from, but not limited to, the following: the SV40 late gene, the rabbit β-globin gene (SEQ ID NO: 6), the bovine growth hormone (BPH) gene, the human growth hormone (hGH) gene, the synthetic polyA (SPA) site, and the bovine growth hormone (bGH) gene. *See*, *e.g.*, Powell and Rivera-Soto, 2015, *Discov. Med.*, 19(102):49-57.

5.1.4 Signal Peptides

[0096] In certain embodiments, the vectors provided herein comprise components that modulate protein delivery. In certain embodiments, the viral vectors provided herein comprise one or more signal peptides. Signal peptides (also referred to as "signal sequences") may also be referred to herein as "leader sequences" or "leader peptides". In certain embodiments, the signal peptides allow for the transgene product to achieve the proper packaging (*e.g.*, glycosylation) in the cell. In certain embodiments, the signal peptides allow for the transgene product to achieve the proper localization in the cell. In certain embodiments, the signal peptides allow for the transgene product to achieve secretion from the cell.

[0097] There are two general approaches to select a signal sequence for protein production in a gene therapy context or in cell culture. One approach is to use a signal peptide from proteins homologous to the protein being expressed. For example, a human antibody signal peptide may be used to express IgGs in CHO or other cells. Another approach is to identify signal peptides optimized for the particular host cells used for expression. Signal peptides may be interchanged between different proteins or even between proteins of different organisms, but usually the signal sequences of the most abundant secreted proteins of that cell type are used for protein expression. For example, the signal peptide of human albumin, the most abundant protein in plasma, was found to substantially increase protein production yield in CHO cells. However, certain signal peptides may retain function and exert activity after being cleaved from the expressed protein as "post-targeting functions". Thus, in specific embodiments, the signal peptide is selected from signal peptides of the most abundant proteins secreted by the cells used for expression to avoid the post-targeting functions. In a certain embodiment, the signal sequence is fused to both the heavy and light chain sequences. In another embodiment, one signal sequence is present in the transgene and is fused to whichever sequence (heavy or light chain) is at the N-terminus of the transgene. An exemplary sequence is MYRMQLLLLIALSLALVTNS

(SEQ ID NO: 55) which can be encoded by a nucleotide sequence of SEQ ID NO: 56 (see **Table 2**, **FIGS 2A-2E**). Alternatively, signal sequences that are appropriate for expression, and may cause selective expression or directed expression of the HuPTM mAb or Fab or scFv in the eye/CNS, muscle, or liver are provided in Tables 2, 3, and 4, respectively, below.

Table 2. Signal peptides for expression in eye/CNS

Signal Peptide Origin	**SEQ ID NO:**	**Sequence**
Mutant interleukin 2 signal peptide	55	MYRMQLLLLIALSLALVTNS
Mutant interleukin 2 signal peptide coding sequence	56	atgtataggatgcaactgctcctcctgattgctctgagcctggctcttgtgaccaactct
VEGF-A signal peptide	57	MNFLLSWVHWSLALLLYLHHAKWSQA
Fibulin-1 signal peptide	58	MERAAPSRRVPLPLLLLGGLALLAAGVDA
Vitronectin signal peptide	59	MAPLRPLLILALLAWVALA
Complement Factor H signal peptide	60	MRLLAKIICLMLWAICVA
Opticin signal peptide	61	MRLLAFLSLLALVLQETGT
Albumin signal peptide	62	MKWVTFISLLFLFSSAYS
Chymotrypsinogen signal peptide	63	MAFLWLLSCWALLGTTFG
Interleukin-2 signal peptide	64	MYRMQLLSCIALILALVTNS
Trypsinogen-2 signal peptide	65	MNLLLILTFVAAAVA

Table 3. Signal peptides for expression in liver (SEQ ID NOs: 66-86) and muscle (SEQ ID NOs: 87-103) cells.

Signal Peptide Origin	**SEQ ID NO:**	**Sequence**
Human Serum albumin	66	MKWVTFISLLFLFSSAYS

Signal Peptide Origin	SEQ ID NO:	Sequence
Human α-1 Antitrypsin (SERPINA1)	67	MPSSVSWGILLLAGLCCLVPVSLA
Human Apolipoprotein A-1	68	MKAAVLTLAVLFLTGSQA
Human Apolipoprotein A-2	69	MKLLAATVLLLTICSLEG
Human Apolipoprotein B-100	70	MDPPRPALLALLALPALLLLLLAGARA
Human Coagulation Factor IX	71	MQRVNMIMAESPGLITICLLGYLLSAEC
Human Complement C2	72	MGPLMVLFCLLFLYPGLADS
Human Complement Factor H-related Protein 2 (CFHR2)	73	MWLLVSVILISRISSVGG
Human Complement Factor H-related Protein 5 (CFHR5)	74	MLLLFSVILISWVSTVGG
Human Fibrinogen α-chain (FGA)	75	MFSMRIVCLVLSVVGTAWT
Human Fibrinogen β-chain (FGB)	76	MKRMVSWSFHKLKTMKHLLLLLLCVFLVKS
Human Fibrinogen γ-chain (FGG)	77	MSWSLHPRNLILYFYALLFLSSTCVA
Human α-2-HS-Glycoprotein (AHSG)	78	MKSLVLLLCLAQLWGCHS
Human Hemopexin (HPX)	79	MARVLGAPVALGLWSLCWSLAIA
Human Kininogen-1	80	MKLITILFLCSRLLLSLT
Human Mannose-binding protein C (MBL2)	81	MSLFPSLPLLLLSMVAASYS
Human Plasminogen (PLMN)	82	MEHKEVVLLLLLFLKSGQG
Human Prothrombin (Coagulation Factor II)	83	MAHVRGLQLPGCLALAALCSLVHS
Human Secreted Phosphoprotein 24	84	MISRMEKMTMMMKILIMFALGMNYWSCSG
Human Anti-thrombin-III (SERPINC1)	85	MYSNVIGTVTSGKRKVYLLSLLLIGFWDCVTC
Human Serotransferrin (TF)	86	MRLAVGALLVCAVLGLCLA

Signal Peptide Origin	SEQ ID NO:	Sequence
Human SPARC	87	MRAWIFFLLCLAGRALA
Human Collagen alpha-1(I) chain	88	MFSFVDLRLLLLLAATALLTHG
Human Lactotransferrin	89	MKLVFLVLLFLGALGLCLA
Human Complement C3	90	MGPTSGPSLLLLLTHLPLALG
Human Lumican	91	MSLSAFTLFLALIGGTSG
Human Gelsolin isoform 1	92	MAPHRPAPALLCALSLALCALSLPVRA
Human Pro-cathepsin H	93	MWATLPLLCAGAWLLGVPVCGA
Human SERPINF1	94	MQALVLLLCIGALLGHSSC
Human SERPINE1	95	MQMSPALTCLVLGLALVFGEGSA
Human Cathepsin D	96	MQPSSLLPLALCLLAAPASA
Human TIMP1	97	MAPFEPLASGILLLLWLIAPSRA
Human Fibronectin	98	MLRGPGPGLLLLAVQCLGTAVPSTGASKSKR
Human Complement C1s subcomponent	99	MWCIVLFSLLAWVYA
Human Cathepsin L1	100	MNPTLILAAFCLGIASA
Human Cathepsin B	101	MWQLWASLCCLLVLANA
Human Salivary acidic proline-rich phosphoprotein ½	102	MLLILLSVALLAFSSA
Human Follistatin-related protein 1	103	MWKRWLALALALVAVAWVRA

Table 4. Linker Sequences

ID	SEQ ID NO:	Sequence
GSG linker	104	GSG
Furin linker	105	RKRR
Furin linker	106	RRRR
Furin linker	107	RRKR
Furin linker	108	RKKR
T2A	109	EGRGSLLTCGDVEENP**GP**
T2A	110	GSGEGRGSLLTCGDVEENP**GP**
P2A	111	ATNFSLLKQAGDVEENP**GP**
P2A	112	GSGATNFSLLKQAGDVEENP**GP**
E2A	113	QCTNYALLKLAGDVESNP**GP**
E2A	114	GSGQCTNYALLKLAGDVESNP**GP**
F2A	115	APVKQTLNFDLLKLAGDVESNP**GP**
F2A	116	GSGAPVKQTLNFDLLKLAGDVESNP**GP**
Furin-T2A	117	RKRREGRGSLLTCGDVEENPGP
Furin-GSG-T2A	118	RKRRGSGEGRGSLLTCGDVEENPGP
Furin-F2A	119	RKRRAPVKQTLNFDLLKLAGDVESNPGP

ID	SEQ ID NO:	Sequence
Furin-GSG-F2A	120	RKRRGSGAPVKQTLNFDLLKLAGDVESNPGP
Furin-GSG-T2A	121	agaaagagaagaggctctggagaaggcagaggctccc tgctgacatgtggggatgttgaagagaatcctgggcc t
Furin	122	agaaagagaaga
Furin-GSG linker	123	agaaagagaagaggctctgga
GSG linker	124	ggctctgga
T2A	125	gaaggcagaggctccctgctgacatgtggggatgttg aagagaatcctgggcct
G4S	126	GGGGS
G4Sx2	127	GGGGSGGGGS
G4Sx3	128	GGGGSGGGGSGGGGS
G4Sx4	129	GGGGSGGGGSGGGGSGGGGS
G4Sx5	130	GGGGSGGGGSGGGGSGGGGSGGGGS

5.1.5 Untranslated regions

[0098] In certain embodiments, the viral vectors provided herein comprise one or more untranslated regions (UTRs), *e.g.*, 3' and/or 5' UTRs. In certain embodiments, the UTRs are optimized for the desired level of protein expression. In certain embodiments, the UTRs are optimized for the mRNA half-life of the transgene. In certain embodiments, the UTRs are optimized for the stability of the mRNA of the transgene. In certain embodiments, the UTRs are optimized for the secondary structure of the mRNA of the transgene.

5.1.6 Inverted terminal repeats

[0099] In certain embodiments, the viral vectors provided herein comprise one or more inverted terminal repeat (ITR) sequences. ITR sequences may be used for packaging the recombinant gene expression cassette into the virion of the viral vector. In certain embodiments, the ITR is from an AAV, *e.g.*, AAV8 or AAV2 (*see, e.g.*, Yan et al., 2005, J. Virol., 79(1):364-379; United States Patent No. 7,282,199 B2, United States Patent No. 7,790,449 B2, United States Patent No. 8,318,480 B2, United States Patent No. 8,962,332 B2 and International Patent Application No. PCT/EP2014/076466, each of which is incorporated herein by reference in its entirety). In preferred embodiments, nucleotide sequences encoding the ITRs may, for example, comprise the nucleotide sequences of SEQ ID NOS:9 (5'-ITR) or 11 (3'-ITR). In certain embodiments, the modified ITRs used to produce self-complementary vector, *e.g.*, scAAV, may be used (*see, e.g.*, Wu, 2007, Human Gene Therapy, 18(2):171-82, McCarty et al, 2001, Gene Therapy, Vol 8, Number 16, Pages 1248-1254; and U.S.

Patent Nos. 6,596,535; 7,125,717; and 7,456,683, each of which is incorporated herein by reference in its entirety). In preferred embodiments, nucleotide sequences encoding the modified ITRs may, for example, comprise the nucleotide sequences of SEQ ID NOS:9 (5'-ITR) or 11 (3'-ITR) or modified for scAAV, SEQ ID NO:10 (m 5'ITR) or SEQ ID NO:12 (m 3' ITR).

5.1.7 Transgenes

[0100] The transgenes encode an scFv disclosed herein.

5.1.8.1 Constructs for Expression of the mAb or scFv

[0101] In certain embodiments, the transgenes encode a full length heavy chain (including the heavy chain variable domain, the heavy chain constant domain 1 (C_H1), the hinge and Fc domain) and a full length light chain (light chain variable domain and light chain constant domain) that upon expression associate to form antigen-binding antibodies with Fc domains. The recombinant AAV constructs express the intact (i.e., full length) or substantially intact HuPTM mAb in a cell, cell culture, or in a subject. ("Substantially intact" refers to mAb having a sequence that is at least 95% identical to the full-length mAb sequence.) The nucleotide sequences encoding the heavy and light chains may be codon optimized for expression in human cells and have reduced incidence of CpG dimers in the sequence to promote expression in human cells. See for example, the codon optimized sequences of C5-D-mab (SEQ ID NOs: 205, 206, 214, or 215) or C5-A-mab (SEQ ID NO: 207-209, or 216-218) of **Table 8**. In embodiments, the transgenes encode a full-length form of any of the therapeutic antibodies disclosed herein, for example, the Fab fragment of which depicted in **FIGS. 2A-2E** herein and including, in certain embodiments, the associated Fc domain provided in **Table 6**.

[0102] The full length mAb encoded by the transgene described herein preferably have the Fc domain of the full-length therapeutic antibody or is an Fc domain of the same type of immunoglobulin as the therapeutic antibody to be expressed. In certain embodiments, the Fc region is an IgG Fc region, but in other embodiments, the Fc region may be an IgA, IgD, IgE, or IgM. The Fc domain is preferably of the same isotype as the therapeutic antibody to be expressed, for example, if the therapeutic antibody is an IgG1 isotype, then the antibody expressed by the transgene comprises an IgG1 Fc domain. The antibody expressed from the transgene may have an IgG1, IgG2, IgG3 or IgG4 Fc domain.

[0103] The Fc region of the intact mAb has one or more effector functions that vary with the antibody isotype. The effector functions can be the same as that of the wild-type or the therapeutic antibody or can be modified therefrom to add, enhance, modify, or inhibit one or more effector functions using the Fc modifications disclosed in Section 5.1.9, infra. In certain embodiments, the

HuPTM mAb transgene encodes a mAb comprising an Fc polypeptide comprising an amino acid sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence set forth in the Fc domain polypeptides of the therapeutic antibodies described herein as set forth in **Table 6** for C5-D-mab, C5-A-mab, C5-C-mab, C5-B-mab, or an exemplary Fc domain of an IgG1, IgG2 or IgG4 isotype as set forth in **Table 6**. In some embodiments, the HuPTM mAb comprises a Fc polypeptide of a sequence that is a variant of the Fc polypeptide sequence in **Table 6** in that the sequence has been modified with one or more of the techniques described in Section 5.1.9, *infra*, to alter the Fc polypeptide's effector function. In other embodiments, the transgene encodes a surrogate antibody for use in NHP or other animal models, for example the antibody BB5.1 as a C5 binding surrogate for at least C5-A-mab or C5-C-mab.

[0104] In some embodiments, provided are constructs comprising a transgene that encodes an scFv that bind to C5. In some embodiments, the transgene encodes an scFv comprising an amino acid sequence of SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO: 200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO: 203, or SEQ ID NO:204. In some embodiments, the nucleotide sequence encoding the anti-C5 scFv is SEQ ID NO: 224, SEQ ID NO: 227, or SEQ ID NO: 230. Also provided are nucleic acids comprising nucleotide sequence encoding an anti-C5 scFv, including having an amino acid sequence of SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO: 200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO: 203, or SEQ ID NO:204.

[0105] In some embodiments, provided are exemplary recombinant AAV constructs such as the constructs shown in **FIG. 1A**, for gene therapy administration to a human subject in order to express an intact or substantially intact HuPTM mAb in the subject. Gene therapy constructs are designed such that both the heavy and light chains are expressed in tandem from the vector including the Fc domain polypeptide of the heavy chain. In certain embodiments, the transgene encodes a transgene with heavy and light chain Fab fragment polypeptides as shown in **Table 7**, yet have a heavy chain that further comprises an Fc domain polypeptide C terminal to the hinge region of the heavy chain (including an IgG1, IgG2 or IgG4 Fc domain or the C5-D-mab, C5-A-mab, C5-C-mab, C5-B-mab as in **Table 6**). In specific embodiments, the transgene is a nucleotide sequence that encodes the following: Signal sequence-heavy chain Fab portion (including hinge region)-heavy chain Fc polypeptide-Furin-2A linker-signal sequence-light chain Fab portion.

[0106] In specific embodiments for expressing an intact or substantially intact mAb in ocular tissue cell types, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) Control elements, which include a) an ocular-tissue specific promoter or constitutive promoter, b) optionally an intron, such as a chicken β-actin intron or VH4 intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy chain Fab of an anti-C5 mAb (e.g. the C5-D-mab, C5-A-mab, C5-C-mab,or C5-B-mab); an Fc polypeptide associated with the therapeutic antibody (**Table 6**) or of the same isotype as the native form of the therapeutic antibody, such as an IgG isotype amino acid sequence from **Table 6**; and the light chain of an anti-C5 mAb (e.g. the C5-D-mab, C5-A-mab, C5-C-mab, or C5-B-mab), wherein the heavy chain (Fab and Fc region) and the light chain are separated by a self-cleaving furin (F)/F2A or T2A or flexible linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. Exemplary constructs are provided in **FIGS. 1A and 1B.**

[0107] In specific embodiments for expressing an scFv form of a mAb in ocular tissue cell types, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) Control elements, which include a) an ocular-tissue specific promoter or constitutive promoter, b) optionally an intron, such as a chicken β-actin intron or VH4 intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding an scFv in which the heavy and light chain variable domains are connected via a flexible, non-cleavable linker, such as GGGGSGGGGSGGGGS (SEQ ID NO: 128). In certain embodiments, the construct expresses, from the N-terminus, NH_2-signal sequence-V_L-linker-V_H-COOH or NH_2-signal sequence-V_H-linker-V_L-COOH. In certain embodiments, the construct encodes, from the N-terminus, NH_2-signal sequence-V_L-GGGGSGGGGSGGGGS-V_H-COOH or NH_2-signal sequence-V_H- GGGGSGGGGSGGGGS-V_L-COOH. In certain embodiments, the linker is GGGGS (SEQ ID NO: 126), GGGGSGGGGS (SEQ ID NO: 127), GGGGSGGGGSGGGGS (SEQ ID NO: 128), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 129) or GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 130). In certain embodiments, the signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 55) or a signal sequence from **Table 2**. In certain embodiments, the VH is SEQ ID NO: 184 and VL is SEQ ID NO: 185, wherein VH is SEQ ID NO: 186 and VL is SEQ ID NO: 187, wherein VH is SEQ ID NO: 188 and the VL is SEQ ID NO: 189, or wherein VH is SEQ ID NO: 190 and VL is SEQ ID NO: 191. Exemplary constructs are provided in **FIG. 1C** and **Table 7** (amino acid sequences).

[0108] In specific embodiments, provided are polynucleotides comprising nucleotide sequences encoding the heavy and light chain variable regions are SEQ ID NO: 205 and SEQ ID NO: 206, or SEQ ID NO: 207 and SEQ ID NO: 209, or SEQ ID NO: 208 and SEQ ID NO: 209, or SEQ ID NO: 210 and SEQ ID NO: 211, or SEQ ID NO: 212 and SEQ ID NO: 213. Exemplary constructs are provided in **FIG. 1C** and **Table 8** (nucleotide sequences). In specific embodiments, the nucleotide sequences encoding the scFvs are SEQ ID NO: 224, SEQ ID NO: 227 or SEQ ID NO: 230.

[0109] In specific embodiments, provided are AAV vectors comprising a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 260), or, alternatively, an AAV9, AAV3B, or AAVrh73 capsid (or a variant thereof) or alternatively AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249) (see Table A); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an intact or substantially intact anti-C5 mAb; operably linked to one or more regulatory sequences that control expression of the transgene in ocular tissue type cells, such as RPE cells, BrM cells, choriocapillaris cells, photoreceptor cells (rods and/or cones), retinal ganglion cells.

[0110] The rAAV vectors that encode and express the full-length therapeutic antibodies may be administered to treat or prevent or ameliorate symptoms of a disease or condition amenable to treatment, prevention or amelioration of symptoms with the therapeutic antibodies, such as dry AMD. Also provided are methods of expressing HuPTM mAbs in human cells using the rAAV vectors and constructs encoding them.

5.1.8.2 Constructs for Expression of Antigen Binding Fragments

[0111] In some embodiments, the transgenes express antigen binding fragments, e.g. a Fab fragment (an HuGlyFab) or a $F(ab')_2$, nanobody, or an scFv based upon a therapeutic antibody disclosed herein. **FIGS. 2A-2E** and section 5.4. provide the amino acid sequence of the heavy and light chains of the Fab fragments of the therapeutic antibodies (see also **Table 7**, which provides the amino acid sequences of the Fab heavy and light chains of the therapeutic antibodies).

[0112] In some embodiments, provided are constructs comprising a transgene that encodes an scFv that bind to C5. In some embodiments, the transgene encodes an scFv comprising an amino acid sequence of SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO:198, SEQ ID NO:199,

SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, or SEQ ID NO: 204. In some embodiments, the nucleotide sequence encoding the anti-C5 scFv is SEQ ID NO: 224, SEQ ID NO: 227, or SEQ ID NO: 230.

[0113] Certain of these nucleotide sequences are codon optimized for expression in human cells. See for example, the codon optimized sequences encoding C5-D-mab (SEQ ID NOs: 205 and 206) or C5-A-mab (SEQ ID Nos: 207-209) in **Table 8**. The transgene may encode a Fab fragment using nucleotide sequences encoding the amino acid sequences provided in **Table 7**, but not including the portion of the hinge region on the heavy chain that forms interchain di-sulfide bonds (*e.g.*, the portion containing the sequence CPPCPA (SEQ ID NO: 132)). Heavy chain Fab domain sequences that do not contain a CPPCP (SEQ ID NO: 131) sequence of the hinge region at the C-terminus will not form intrachain disulfide bonds and, thus, will form Fab fragments with the corresponding light chain Fab domain sequences, whereas those heavy chain Fab domain sequences with a portion of the hinge region at the C-terminus containing the sequence CPPCP (SEQ ID NO: 131) will form intrachain disulfide bonds and, thus, will form Fab_2 fragments. For example, in some embodiments, the transgene may encode a scFv comprising a light chain variable domain and a heavy chain variable domain connected by a flexible linker in between (where the heavy chain variable domain may be either at the N-terminal end or the C-terminal end of the scFv), and optionally, may further comprise a Fc polypeptide (*e.g.*, IgG1, IgG2, IgG3, or IgG4) on the C-terminal end of the heavy chain. Alternatively, in other embodiments, the transgene may encode $F(ab')_2$ fragments comprising a nucleotide sequence that encodes the light chain and the heavy chain sequence that includes at least the sequence CPPCA (SEQ ID NO: 133) of the hinge region, as depicted in **FIGS. 2A-2E** which depict various regions of the hinge region that may be included at the C-terminus of the heavy chain sequence. In embodiments, the hinge region is the sequence EPKSCDKTH (SEQ ID NO: 159). Pre-existing anti-hinge antibodies (AHA) may cause immunogenicity and reduce efficacy. Thus, in certain embodiments, for the IgG1 isotype, C-terminal ends with D221 or ends with a mutation T225L or with L242 can reduce binding to AHA. (See, e.g., Brezski, 2008, J Immunol 181: 3183-92 and Kim, 2016, 8: 1536-1547). For IgG2, the risk of AHA is lower since the hinge region of IgG2 is not as susceptible to enzymatic cleavage required to generate endogenous AHA. (*See, e.g.*, Brezski, 2011, MAbs 3: 558-567).

Table 5. Hinge Regions

SEQ ID NO:	Sequence
131	CPPCP

SEQ ID NO:	Sequence
132	CPPCPA
133	CPPCA
134	EPKSCDKTHTCPPCPAPELLGG
135	EPKSCDKTHLCPPCPAPELLGG
136	EPKSCDKTHL
137	EPKSCDKTHT
138	EPKSCDKTHTCPPCPA
139	EPKSCDKTHLCPPCPA
140	EPKSCDKTHTCPPCPAPELLGGPSVFL
141	EPKSCDKTHLCPPCPAPELLGGPSVFL
142	EPKSCDKTHTCPPCPAPEAAGG
143	EPKSCDKTHTCPPCPAPEAAGGPSVFL
144	EPKSCDKTHLCPPCPAPEAAGGPSVFL
145	ERKSCVECPPCPAPPVAG
146	ERKSCVECPPCPA
147	ESKYGPPCPPCPAPEFLGG
148	ESKYGPPCPPCPA
149	ESKYGPPCPSCPA
150	ESKYGPPCPPCPAPEFLGGPSVFL
151	ERKCCVECPPCPAPPVAG
152	ERKCCVECPPCPA
153	EPKSCDKTHTCPPCPAPELAGA
154	EPKSCDKTHTCPPCPAPELAGAPSVFL
155	EPKSCDKTHLCPPCPAPELAGAPSVFL
156	EPKSCDKTHTCPPCPAPEFEGG
157	EPKSCDKTHTCPPCPAPEFEGGPSVFL
158	EPKSCDKTHLCPPCPAPEFEGGPSVFL
159	EPKSCDKTH
160	ESKYGPPCPSCPAPEFLGGPSVFL

[0114] In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a constitutive or inducible (e.g., hypoxia-inducible or rifamycin-inducible) promoter sequence or a tissue specific promoter/regulatory region, for example, one of the regulatory regions provided in **Table 1** or **1a**, and b) a sequence encoding the transgene (*e.g.*, a HuGlyFab or scFv). In certain embodiments, the sequence encoding the transgene comprises multiple ORFs separated by IRES elements. In certain embodiments, the ORFs encode the heavy and light chain domains of the HuGlyFab. In certain embodiments, the sequence encoding the transgene comprises multiple subunits in one ORF separated by F/F2A sequences or F/T2A sequences. In certain embodiments, the sequence comprising the transgene encodes the heavy and light chain domains of

the HuGlyFab separated by an F/F2A sequence or a F/T2A sequence. In certain embodiments, the sequence comprising the transgene encodes the heavy and light chain variable domains of the HuGlyFab separated by a flexible peptide linker (as an scFv). In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a constitutive or an inducible promoter sequence or a tissue specific promoter, such as one of the promoters or regulatory regions in **Table 1** or **1a**, and b) a sequence encoding the transgene (*e.g.*, a HuGlyFab), wherein the transgene comprises a nucleotide sequence encoding a signal peptide, a light chain and a heavy chain Fab portion separated by an IRES element. In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a constitutive or a hypoxia-inducible promoter sequence or regulatory element listed in **Table 1** or **1a**, and b) a sequence encoding the transgene comprising a signal peptide, a light chain and a heavy chain sequence separated by a cleavable F/F2A sequence (SEQ ID NOs:119 or 120) or a F/T2A sequence (SEQ ID NOs:117 or 118) or a flexible peptide linker.

[0115] In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a first ITR sequence, b) a first linker sequence, c) a constitutive or an inducible promoter sequence or a tissue specific promoter or regulatory region, d) a second linker sequence, e) an intron sequence, f) a third linker sequence, g) a first UTR sequence, h) a sequence encoding the transgene (*e.g.*, a HuGlyFab), i) a second UTR sequence, j) a fourth linker sequence, k) a poly A sequence, l) a fifth linker sequence, and m) a second ITR sequence.

[0116] In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a first ITR sequence, b) a first linker sequence, c) a constitutive or an inducible promoter sequence or a tissue specific regulatory region, d) a second linker sequence, e) an intron sequence, f) a third linker sequence, g) a first UTR sequence, h) a sequence encoding the transgene (*e.g.*, HuGlyFab), i) a second UTR sequence, j) a fourth linker sequence, k) a poly A sequence, l) a fifth linker sequence, and m) a second ITR sequence, wherein the transgene comprises a signal, and wherein the transgene encodes a light chain and a heavy chain sequence separated by a cleavable F/2A sequence.

[0117] In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a first ITR sequence, b) a first linker sequence, c) a constitutive or an inducible promoter sequence or a tissue specific regulatory region, d) a second linker sequence, e) an intron sequence, f) a third linker sequence, g) a first UTR sequence, h) a sequence encoding the

transgene (*e.g.*, VH–(linker)-VL or VL-(linker)-VH), i) a second UTR sequence, j) a fourth linker sequence, k) a poly A sequence, l) a fifth linker sequence, and m) a second ITR sequence.

5.1.9. Fc Region Modifications

[0118] In certain embodiments, the transgenes encode full length or substantially full length heavy and light chains that associate to form a full length or intact antibody. ("Substantially intact" or "substantially full length" refers to a mAb having a heavy chain sequence that is at least 95% identical to the full-length heavy chain mAb amino acid sequence and a light chain sequence that is at least 95% identical to the full-length light chain mAb amino acid sequence). Accordingly, the transgenes comprise nucleotide sequences that encode, for example, the light and heavy chains of the Fab fragments including the hinge region of the heavy chain and C-terminal of the heavy chain of the Fab fragment, an Fc domain peptide. **Table 6** provides the amino acid sequence of the Fc polypeptides for C5-D-mab, C5-A-mab, C5-C-mab, and C5-B-mab. Alternatively, an IgG1, IgG2, or IgG4 Fc domain, the sequences of which are provided in **Table 6** may be utilized.

[0119] The term "Fc region" refers to a dimer of two "Fc polypeptides" (or "Fc domains"), each "Fc polypeptide" comprising the heavy chain constant region of an antibody excluding the first constant region immunoglobulin domain. In some embodiments, an "Fc region" includes two Fc polypeptides linked by one or more disulfide bonds, chemical linkers, or peptide linkers. "Fc polypeptide" refers to at least the last two constant region immunoglobulin domains of IgA, IgD, and IgG, or the last three constant region immunoglobulin domains of IgE and IgM and may also include part or all of the flexible hinge N-terminal to these domains. For IgG, e.g., "Fc polypeptide" comprises immunoglobulin domains Cgamma2 (Cγ2, often referred to as CH2 domain) and Cgamma3 (Cγ3, also referred to as CH3 domain) and may include the lower part of the hinge domain between Cgamma1 (Cγ1, also referred to as CH1 domain) and CH2 domain. Although the boundaries of the Fc polypeptide may vary, the human IgG heavy chain Fc polypeptide is usually defined to comprise residues starting at T223 or C226 or P230, to its carboxyl-terminus, wherein the numbering is according to the EU index as in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Services, Springfield, Va.). For IgA, e.g., Fc polypeptide comprises immunoglobulin domains Calpha2 (Cα2) and Calpha3 (Cα3) and may include the lower part of the hinge between Calpha1 (Cα1) and Cα2.

[0120] In certain embodiments, the Fc polypeptide is that of the therapeutic antibody or is the Fc polypeptide corresponding to the isotype of the therapeutic antibody). In still other embodiments,

the Fc polypeptide is an IgG Fc polypeptide. The Fc polypeptide may be from the IgG1, IgG2, or IgG4 isotype (see **Table 6**) or may be an IgG3 Fc domain, depending, for example, upon the desired effector activity of the therapeutic antibody. In some embodiments, the engineered heavy chain constant region (CH), which includes the Fc domain, is chimeric. As such, a chimeric CH region combines CH domains derived from more than one immunoglobulin isotype and/or subtype. For example, the chimeric (or hybrid) CH region comprises part or all of an Fc region from IgG, IgA and/or IgM. In other examples, the chimeric CH region comprises part or all a CH2 domain derived from a human IgG1, human IgG2, or human IgG4 molecule, combined with part or all of a CH3 domain derived from a human IgG1, human IgG2, or human IgG4 molecule. In other embodiments, the chimeric CH region contains a chimeric hinge region.

TABLE 6. Table of Fc Domain Amino Acid Sequences

Fc	Chain/ SEQ ID NO.	Sequence
IgG1	Fc domain /SEQ ID NO: 161	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
IgG2	Fc domain /SEQ ID NO: 162	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDISVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
IgG4	Fc domain /SEQ ID NO: 163	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
C5-D-mab	Fc domain /SEQ ID NO: 164	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVLHEAL HAHYTRKELS LSP
C5-A-mab	Fc domain	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ

Fc	Chain/ SEQ ID NO.	Sequence
	/SEQ ID NO: 165	VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
C5-C-mab	Fc domain/ SEQ ID NO:166	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVLHEAL HSHYTQKSLS LSLGK
C5-B-mab	Fc domain /SEQ ID NO: 167	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK

[0121] In some embodiments, the recombinant vectors encode therapeutic antibodies comprising an engineered (mutant) Fc regions, *e.g.* engineered Fc regions of an IgG constant region. Modifications to an antibody constant region, Fc region or Fc fragment of an IgG antibody may alter one or more effector functions such as Fc receptor binding or neonatal Fc receptor (FcRn) binding and thus half-life, CDC activity, ADCC activity, and/or ADPC activity, compared to a corresponding antibody having a wild-type IgG constant region, or an IgG heavy chain constant region without the recited modification(s). Accordingly, in some embodiments, the antibody may be engineered to provide an antibody constant region, Fc region or Fc fragment of an IgG antibody that exhibits altered binding (as compared to a reference or wild-type constant region without the recited modification(s)) to one or more Fc receptors (e.g., FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, FcγRIIIB, FcγRIV, or FcRn receptor). In some embodiments, the antibody an antibody constant region, Fc region or Fc fragment of an IgG antibody that exhibits a one or more altered effector functions such as CDC, ADCC, or ADCP activity, compared to a corresponding antibody having a wild-type IgG constant region, or an IgG constant without the recited modification(s).

[0122] "Effector function" refers to a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions include FcγR-mediated effector functions such as ADCC and ADCP and complement-mediated effector functions such as CDC.

[0123] An "effector cell" refers to a cell of the immune system that expresses one or more Fc receptors and mediates one or more effector functions. Effector cells include but are not limited to monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and T cells, and may be from any organism including but not limited to humans, mice, rats, rabbits, and monkeys.

[0124] "ADCC" or "antibody dependent cell-mediated cytotoxicity" refers to the cell-mediated reaction wherein nonspecific cytotoxic effector (immune) cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell.

[0125] "ADCP" or "antibody dependent cell-mediated phagocytosis" refers to the cell-mediated reaction wherein nonspecific cytotoxic effector (immune) cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell.

[0126] "CDC" or "complement-dependent cytotoxicity" refers to the reaction wherein one or more complement protein components recognize bound antibody on a target cell and subsequently cause lysis of the target cell.

[0127] In some embodiments, the modifications of the Fc domain include, but are not limited to, the following modifications and combinations thereof, with reference to EU numbering of an IgG constant region (see **FIG. 5**): 233, 234, 235, 236, 237, 238, 239, 248, 249, 250, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 297, 298, 301, 303, 305, 307, 308, 309, 311, 312, 315, 318, 320, 322, 324, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 340, 342, 344, 356, 358, 359, 360, 361, 362, 373, 375, 376, 378, 380, 382, 383, 384, 386, 388, 389, 398, 414, 416, 419, 428, 430, 433, 434, 435, 437, 438, and 439.

[0128] In certain embodiments, the Fc region comprises an amino acid addition, deletion, or substitution of one or more of amino acid residues 251-256, 285-290, 308-314, 385-389, and 428-436 of the IgG. In some embodiments, 251-256, 285-290, 308-314, 385-389, and 428-436 (EU numbering of Kabat; see **FIG. 5**) is substituted with histidine, arginine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, or glutamine. In some embodiments, a non-histidine residue is substituted with a histidine residue. In some embodiments, a histidine residue is substituted with a non-histidine residue.

[0129] Enhancement of FcRn binding by an antibody having an engineered Fc leads to preferential binding of the affinity-enhanced antibody to FcRn as compared to antibody having wild-

type Fc, and thus leads to a net enhanced recycling of the FcRn-affinity-enhanced antibody, which results in further increased antibody half-life. An enhanced recycling approach allows highly effective targeting and clearance of antigens, including e.g. "high titer" circulating antigens, such as C5, cytokines, or bacterial or viral antigens.

[0130] Provided in certain embodiments are modified constant region, Fc region or Fc fragment of an IgG antibody with enhanced binding to FcRn in serum as compared to a wild-type Fc region (without engineered modifications). In some instances, antibodies, e.g. IgG antibodies, are engineered to bind to FcRn at a neutral pH, *e.g.*, at or above pH 7.4, to enhance pH-dependence of binding to FcRn as compared to a wild-type Fc region (without engineered modifications). In some instances, antibodies, e.g. IgG antibodies, are engineered to exhibit enhanced binding (e.g. increased affinity or K_D) to FcRn in endosomes (*e.g.*, at an acidic pH, *e.g.*, at or below pH 6.0) relative to a wild-type IgG and/or reference antibody binding to FcRn at an acidic pH, as well as in comparison to binding to FcRn in serum (*e.g.*, at a neutral pH, e.g., at or above pH 7.4). Provided are antibodies with an engineered antibody constant region, Fc region or Fc fragment of an IgG antibody that exhibits an improved serum or resident tissue half-life, compared to a corresponding antibody having a wild-type IgG constant region, or an IgG constant without the recited modification(s);

[0131] Non-limiting examples of such Fc modifications include, *e.g.*, a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., LN/Y/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (e.g., H/F or Y or A), including 428L and 434A; or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 2591 (e.g., V2591), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a 252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P) (EU numbering; see **FIG 5**).

[0132] In some embodiments, the Fc region can be a mutant form such as hIgG1 Fc including M252 mutations, e.g. M252Y and S254T and T256E ("YTE mutation") exhibit enhanced affinity for human FcRn (Dall'Acqua, et al., 2002, J Immunol 169:5171-5180) and subsequent crystal structure of this mutant antibody bound to hFcRn resulting in the creation of two salt bridges (Oganesyan, et al. 2014, JBC 289(11): 7812–7824). Antibodies having the YTE mutation have been administered to

monkeys and humans, and have significantly improved pharmacokinetic properties (Haraya, et al., 2019, Drug Metabolism and Pharmacokinetics, 34(1):25-41).

[0133] In some embodiments, modifications to one or more amino acid residues in the Fc region may reduce half-life in systemic circulation (serum), however result in improved retainment in tissues (e.g. in the eye) by disabling FcRn binding (e.g. H435A, EU numbering of Kabat) (Ding et al., 2017, MAbs 9:269-284; and Kim, 1999, Eur J Immunol 29:2819).

[0134] In some embodiments, the Fc domain may be engineered to activate all, some, or none of the normal Fc effector functions, without affecting the Fc polypeptide's (e.g. antibody's) desired pharmacokinetic properties. Fc polypeptides having altered effector function may be desirable as they may reduce unwanted side effects, such as activation of effector cells, by the therapeutic protein.

[0135] Methods to alter or even ablate effector function may include mutation(s) or modification(s) to the hinge region amino acid residues of an antibody. For example, IgG Fc domain mutants comprising 234A, 237A, and 238S substitutions, according to the EU numbering system, exhibit decreased complement dependent lysis and/or cell mediated destruction. Deletions and/or substitutions in the lower hinge, e.g. where positions 233-236 within a hinge domain (EU numbering) are deleted or modified to glycine, have been shown in the art to significantly reduce ADCC and CDC activity.

[0136] In specific embodiments, the Fc domain is an aglycosylated Fc domain that has a substitution at residue 297 or 299 to alter the glycosylation site at 297 such that the Fc domain is not glycosylated. Such aglycosylated Fc domains may have reduced ADCC or other effector activity.

[0137] Non-limiting examples of proteins comprising mutant and/or chimeric CH regions having altered effector functions, and methods of engineering and testing mutant antibodies, are described in the art, e.g. K.L. Amour, et al., Eur. J. Immunol. 1999, 29:2613–2624; Lazar et al., Proc. Natl. Acad. Sci. USA 2006, 103:4005; US Patent Application Publication No. 20070135620A1 published June 14, 2007; US Patent Application Publication No. 20080154025 A1, published June 26, 2008; US Patent Application Publication No. 20100234572 A1, published September 16, 2010; US Patent Application Publication No. 20120225058 A1, published September 6, 2012; US Patent Application Publication No. 20150337053 A1, published November 26, 2015; International Publication No. WO20/16161010A2 published October 6, 2016; U.S. 9,359,437, issued June 7,2016; and US Patent No. 10,053,517, issued August 21, 2018, all of which are herein incorporated by reference.

[0138] The C-terminal lysines (-K) conserved in the heavy chain genes of all human IgG subclasses are generally absent from antibodies circulating in serum – the C-terminal lysines are cleaved off in circulation, resulting in a heterogeneous population of circulating IgGs. (van den Bremer et al., 2015, mAbs 7:672-680). In the vectored constructs for full length mAbs, the DNA encoding the C-terminal lysine (-K) or glycine-lysine (-GK) of the Fc terminus can be deleted to produce a more homogeneous antibody product *in situ*. (See, Hu et al., 2017 Biotechnol. Prog. 33: 786-794 which is incorporated by reference herein in its entirety).

5.1.10 Manufacture and testing of vectors

[0139] The viral vectors provided herein may be manufactured using host cells. The viral vectors provided herein may be manufactured using mammalian host cells, for example, A549, WEHI, 10T1/2, BHK, MDCK, COS1, COS7, BSC 1, BSC 40, BMT 10, VERO, W138, HeLa, 293, Saos, C2C12, L, HT1080, HepG2, primary fibroblast, hepatocyte, and myoblast cells. The viral vectors provided herein may be manufactured using host cells from human, monkey, mouse, rat, rabbit, or hamster.

[0140] The host cells are stably transformed with the sequences encoding the transgene and associated elements (*e.g.,* the vector genome), and the means of producing viruses in the host cells, for example, the replication and capsid genes (*e.g.*, the rep and cap genes of AAV). For a method of producing recombinant AAV vectors with AAV8 capsids, see Section IV of the Detailed Description of U.S. Patent No. 7,282,199 B2, which is incorporated herein by reference in its entirety. Genome copy titers of said vectors may be determined, for example, by TAQMAN® analysis. Virions may be recovered, for example, by $CsCl_2$ sedimentation.

[0141] Alternatively, baculovirus expression systems in insect cells may be used to produce AAV vectors. For a review, see Aponte-Ubillus et al., 2018, Appl. Microbiol. Biotechnol. 102:1045-1054 which is incorporated by reference herein in its entirety for manufacturing techniques.

[0142] In vitro assays, *e.g.*, cell culture assays, can be used to measure transgene expression from a vector described herein, thus indicating, *e.g.*, potency of the vector. In addition, in vitro neutralization assays can be used to measure the activity of the transgene expressed from a vector described herein. For example, Vero-E6 cells, a cell line derived from the kidney of an African green monkey, or HeLa cells engineered to stably express the ACE2 receptor (HeLa-ACE2), can be used to assess neutralization activity of transgenes expressed from a vector described herein. In addition, other characteristics of the expressed product can be determined, for example determination of the

glycosylation and tyrosine sulfation patterns associated with the HuGlyFab. Glycosylation patterns and methods of determining the same are discussed in Section 5.3, while tyrosine sulfation patterns and methods of determining the same are discussed in Section 5.3. In addition, benefits resulting from glycosylation/sulfation of the cell-expressed HuGlyFab can be determined using assays known in the art, *e.g.*, the methods described in Section 5.3.

[0143] Vector genome concentration (GC) or vector genome copies can be evaluated using digital PCR (dPCR) or ddPCR™ (BioRad Technologies, Hercules, CA, USA). In one example, ocular tissue samples, such as aqueous and/or vitreous humor samples, are obtained at several timepoints. In another example, several mice are sacrificed at various timepoints post injection. Ocular tissue samples are subjected to total DNA extraction and dPCR assay for vector copy numbers. Copies of vector genome (transgene) per gram of tissue may be measured in a single biopsy sample, or measured in various tissue sections at sequential timepoints will reveal spread of AAV throughout the eye. Total DNA from collected ocular fluid or tissue is extracted with the DNeasy Blood & Tissue Kit and the DNA concentration measured using a Nanodrop spectrophotometer. To determine the vector copy numbers in each tissue sample, digital PCR is performed with Naica Crystal Digital PCR system (Stilla technologies). Two color multiplexing system is applied to simultaneously measure the transgene AAV and an endogenous control gene. In brief, the transgene probe can be labelled with FAM (6-carboxyfluorescein) dye while the endogenous control probe can be labelled with VIC fluorescent dye. The copy number of delivered vector in a specific tissue section per diploid cell is calculated as: (vector copy number)/(endogenous control)×2. Vector copy in specific cell types or tissues, such as cornea, iris, ciliary body, schlemm's canal cells, trabecular meshwork, retinal cells, RPE cells, RPE-choroid tissue, or optic nerve cells, over time may indicate sustained expression of the transgene by the tissue.

5.1.11 Compositions

[0144] Pharmaceutical compositions suitable for administration to human subjects comprise a suspension of the recombinant vector in a formulation buffer comprising a physiologically compatible aqueous buffer, a surfactant and optional excipients. Such formulation buffer can comprise one or more of a polysaccharide, a surfactant, polymer, or oil. In some embodiments, the pharmaceutical composition comprises rAAV combined with a pharmaceutically acceptable carrier for administration to a subject. In one embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term

"carrier" refers to a diluent, adjuvant (*e.g.*, Freund's complete and incomplete adjuvant), excipient, or vehicle with which the agent is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, including, *e.g.*, peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a common carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Additional examples of pharmaceutically acceptable carriers, excipients, and stabilizers include, but are not limited to, buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight polypeptides; proteins, such as serum albumin and gelatin; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; 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™ as known in the art. The pharmaceutical composition of the present invention can also include a lubricant, a wetting agent, a sweetener, a flavoring agent, an emulsifier, a suspending agent, and a preservative, in addition to the above ingredients. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like.

[0145] In some embodiments, the pharmaceutical composition comprises viscosity promoting agent(s). Example formulations for the delivery of AAV include those in WO 2022/076549 and WO 2021/071835, each of which is hereby incorporated by reference in their entireties.

[0146] In some embodiments, the reference pharmaceutical composition comprises 1% carboxymethyl cellulose high viscosity grade. In some embodiments, the reference pharmaceutical composition comprises 0.2 to 15% carboxymethyl cellulose (CMC) high viscosity grade, CMC high viscosity grade, CMC medium viscosity grade, hydroxypropyl methylcellulose (HPMC), HPMC, hydroxyethyl cellulose (HES), CMC low viscosity grade, and/or poloxamer 407.

[0147] In some embodiments, the pharmaceutical composition comprises hyaluronic acid as a viscosity promoting agent. In some embodiments, the hyaluronic acid comprises a molecular weight

of from about 1 MDa to about 2 MDa. The hyaluronic acid can comprise a molecular weight of, for example, about 1 MDa, about 1.5 MDa, about 1.58 MDa, or about 2.0 MDa. In some embodiments, the hyaluronic acid comprises a molecular weight of about 1.58 MDa. In some embodiments, the hyaluronic acid comprises a molecular weight of about 2.0 MDa. In embodiments the HA may be obtained from various sources including ThermoFisher, Lifecore Biomedical, and the like, and is pharmaceutical grade HA. Hyaluronic acid is also known as Sodium hyaluronate [CAS No. 9067-32-7, Formula: $(C_{14}H_{20}NO_{11}Na)n$]. Various sources include but are not limited to the list in Table B.

Table B: Several available sources for HA

Hyaluronic Acid Product name (Cas#9067-32-7) [Formula: (C14H20NO11Na)n]	Supplier, catalog#	Molecular Weight
Sodium hyaluronate, 95%	ThermoFisher Scientific, 251770050	1.5-2.2 MDa
Sodium hyaluronate	Lifecore Biomedical, Part# HA15M-1 or HA15M-5	1.58 MDa (range 1.01M-1.80M)
Sodium hyaluronate	Lifecore Biomedical, Part# HA700K	500K-749kDa
Sodium hyaluronate	Lifecore Biomedical, Part# HA1M	750K-1.0MDa
Sodium hyaluronate	Lifecore Biomedical, Custom	>1.8MDa

[0148] In embodiments, the pharmaceutical formulation comprises from about 0.5% w/v to about 1.0% w/v hyaluronic acid. In embodiments, the pharmaceutical formulation comprises from about 0.6% w/v to about 0.9% w/v hyaluronic acid. In embodiments, the pharmaceutical formulation comprises from about 0.7% w/v to about 0.8% w/v hyaluronic acid.

[0149] In embodiments, the pharmaceutical formulation comprises about 0.5% w/v hyaluronic acid, about 0.6% w/v hyaluronic acid, about 0.7% w/v hyaluronic acid, about 0.8% w/v hyaluronic acid, about 0.9% w/v hyaluronic acid or about 1.0% w/v hyaluronic acid.

[0150] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 40.0 mg/mL (4% w/v) sucrose, and about 0.001% (0.01 mg/mL) poloxamer 188.

[0151] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 0.5% w/v hyaluronic acid.

[0152] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 0.6% w/v hyaluronic acid.

[0153] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 0.7% w/v hyaluronic acid.

[0154] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 0.8% w/v hyaluronic acid.

[0155] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 0.9% w/v hyaluronic acid.

[0156] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 1.0% w/v hyaluronic acid.

[0157] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 40.0 mg/mL (4% w/v) sucrose, and about 0.001% (0.01 mg/mL) poloxamer 188.

[0158] In embodiments, the AAV is in a pre-formulated solution at: about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 40.0 mg/mL (4% w/v)

sucrose, about 0.001% (0.01 mg/mL) poloxamer 188, and about 1% carboxymethylcellulose (CMC) high viscosity grade.

5.2 Methods of Treating dry AMD

[0159] In another aspect, methods for treating dry AMD (age-related AMD) or dry AMD with geographic atrophy, or other indications that can be treated with an anti-C5 antibody in a subject in need thereof (a composition for use in the treatment of dry AMD or other indication that can be treated with an anti-C5) comprising the administration, including ocular administration, of recombinant AAV particles comprising an expression cassette encoding an C5-D-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 195 or 203), C5-D-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 196), C5-A-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 197), C5-A-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 198), C5-C-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 199), C5-C-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 200), C5-B-mab Vectorized scFv mAb (H-L) (SEQ ID NO: 201), or C5-B-mab Vectorized scFv mAb (L-H) (SEQ ID NO: 202) packaged in an rAAV particle comprising engineered capsid proteins capsid protein of AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249) (see Table A) are provided. A subject in need thereof includes a subject suffering from dry AMD, or a subject pre-disposed thereto, *e.g.*, a subject at risk of developing dry AMD, or other indication that may be treated with an anti-C5 antibody. Subjects to whom such gene therapy is administered can be those responsive to anti-C5 antibody e.g., C5-D-mab, C5-A-mab, C5-C-mab, C5-B-mab antibody. In particular embodiments, the methods encompass treating patients who have been diagnosed with dry AMD, and, in certain embodiments, identified as responsive to treatment with an anti-C5 antibody, or considered a good candidate for therapy with an anti-C5 antibody. In specific embodiments, the patients have previously been treated with an anti-C5 antibody. To determine responsiveness, the anti-C5 antibody or antigen-binding fragment transgene product(e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

[0160] In specific embodiments, provided are methods of treating dry AMD or other indication amenable to treatment with an anti-C5 antibody in a human subject in need thereof comprising: administering to the eye, for example, intravitreal, subretinal, suprachoroidal, intracameral, or intranasal, or liver and/or muscle by systemic administration (including intravenous or intramuscular)

of said subject a therapeutically effective amount of a recombinant nucleotide expression vector, such as an AAV vector, comprising a transgene encoding a C5-D-mab scFv (HL) or C5-A-mab scFv (HL) operably linked to one or more regulatory sequences that control expression of the transgene in human ocular tissue cells (such as retinal cells, BrM cells, choriocapillaris cells, RPE cells and/or choroid cells), so that a depot is formed that releases a HuPTM form of mAb or antigen-binding fragment thereof. Subretinal, intravitreal, intracameral, or suprachoroidal administration should result in expression of the transgene product in one or more of the following retinal cell types: Bruch's membrane (BrM), including epithelial cells thereof, choriocapillaris, human photoreceptor cells (cone cells, rod cells); horizontal cells; bipolar cells; amarcrine cells; retina ganglion cells (midget cell, parasol cell, bistratified cell, giant retina ganglion cell, photosensitive ganglion cell, and muller glia); and retinal pigment epithelial cells or other ocular tissue cell: cornea cells, iris cells, ciliary body cells, a schlemm's canal cells, a trabecular meshwork cells, RPE-choroid tissue cells, or optic nerve cells.

[0161] The recombinant vectors can be administered in any manner such that the recombinant vector enters ocular tissue cells, e.g., by introducing the recombinant vector into the eye. Such vectors should further comprise one or more regulatory sequences that control expression of the transgene in human ocular tissue cells and/or human liver and muscle cells include, but are not limited to, human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), a human red opsin (RedO) promoter (SEQ ID NO: 14), a CAG promoter (SEQ ID NO: 2), a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), a CB promoter or CB Long promoter (SEQ ID NO: 24 or 25) or a Best1/GRK1 tandem promoter (SEQ ID NO: 26) (see also Tables 1 and 1a). In embodiments, the artificial genome comprises one of the nucleotide sequences of SEQ ID NO 225, SEQ ID NO: 229, SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, SEQ ID NO: 242, SEQ ID NO: 276, or SEQ ID NO: 277. In embodiments, the vector is self-complementary. In embodiments, the vector is single stranded.

[0162] The methods described herein treat, slow the progression of, reduce the severity of or prevent dry (age related) AMD in a human subject in need of the treatment. The treatment, slowing progression of, reduction of severity or prevention may be assessed relative to the subject prior to treatment, a comparable untreated subject or according to the natural history of the disease. In embodiments, treating a subject with the AAV vectors and pharmaceutical compositions disclosed herein can reduce the likelihood of vision threatening events. Vision threatening events include a

number of vision-threatening complications, such as geographic atrophy lesions, geographic atrophy lesion progression and/or growth. The methods of the invention may reduce the progression of geographic atrophy, including within the fovea, slow retinal cell loss, slow the loss of central vision, increase or slow the loss of visual acuity, etc.

[0163] The subject may be at risk or have a predisposition to develop dry AMD based upon age, and/or risk factors such as history of smoking, obesity, cardiovascular disease or diabetes.

5.3.N- Anti-C5 Constructs and Formulations for dry AMD

[0164] Compositions and methods are described for the delivery of HuPTM mAb or the antigen-binding fragment thereof, such as HuPTM Fab, that bind to C5 (and inhibit complement activation) derived from an anti-C5 antibody and indicated for treating dry AMD. In certain embodiments, the HuPTM mAb has the amino acid sequence of C5-D-mab, C5-A-mab, C5-C-mab, or C5-B-mab or an antigen binding fragment thereof. The amino acid sequence of Fab fragment of these antibodies is provided in **FIGS. 2A-2E** (see also **Table 7**, which also provides amino acid sequences of certain full length and scFv constructs). Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an anti-C5 HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with dry AMD to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

[0165] In certain embodiments, provided is a construct encoding or an artificial genome in which the transgene operably linked to regulatory sequences is flanked by ITR sequences. In some embodiments, the artificial genome is self-complementary. The construct or artificial genome may comprise or consist of the nucleotide sequence of SEQ ID NOs: 225, 229, 232, 234, 236, 238, 242, 276, or 277. The artificial genome may comprise of the nucleotide sequence of any one of SEQ ID NOs: 225, 229, 232, 234, 236, 238, 242, 276, or 277. The artificial genome may comprise of the nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least 97%, at least about 98%, or at least about 99% identical to any one of SEQ ID NOs: 225, 229, 232, 234, 236, 238, 242, 276, or 277, which encodes and expresses a C5 antibody or antigen binding fragment thereof as described herein.

[0166] **Table 7** provides the amino acid sequences of Fab, scFv and full length heavy and light chains of the anti-C5 antibodies, and the expression products of the transgenes, including the signal

sequences and linkers, such as Furin/T2a linkers. **Table 8** provides a nucleotide sequence encoding the Fab and full length heavy and light chains of the antibodies, transgene coding sequences, and artificial genomes disclosed herein.

Table 7. Amino Acid Sequences of Heavy and Light Chains and Protein

mAb or Protein	Chain/ SEQ ID NO:	Sequences
C5-D-mab Fab	Heavy/ SEQ ID NO: 168	QVQLVESGGG LVQPGRSLRL SCAASGFTVH SSYYMAWVRQ APGKGLEWVG AIFTGSGAEY KAEWAKGRVT ISKDTSKNQV VLTMTNMDPV DTATYYCASD AGYDYPTHAM HYWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK *VEPKSCDKTH*
C5-D-mab	Light/ SEQ ID NO: 169	DIQMTQSPSS LSASVGDRVT ITCRASQGIS SSLAWYQQKP GKAPKLLIYG ASETESGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN TKVGSSYGNT FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC
C5-A-mab Fab IgG1	Heavy/ SEQ ID NO: 170	QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKRV *EPKSCDKTHT*
C5-A-mab Fab IgG2	Heavy/ SEQ ID NO: 171	QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV
C5-A-mab	Light/ SEQ ID NO: 172	DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
C5-C-mab Fab	Heavy/ SEQ ID NO: 173	QVQLVQSGAE VKKPGASVKV SCKASGHIFS NYWIQWVRQA PGQGLEWMGE ILPGSGHTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVE +/- CPPCPA+/- PPVAG
C5-C-mab	Light/ SEQ ID NO: 174	DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

mAb or Protein	Chain/ SEQ ID NO:	Sequences
C5-B-mab Fab	Heavy/ SEQ ID NO: 175	EVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IGPFFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARDT PYFDYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PEAAGGPSVFL
C5-B-mab	Light/ SEQ ID NO: 176	SYELTQPLSV SVALGQTARI TCSGDSIPNY YVYWYQQKPG QAPVLVIYDD SNRPSGIPER FSGSNSGNTA TLTISRAQAG DEADYYCQSF DSSLNAEVFG GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS
BB5.1 Full length heavy chain	Heavy/ SEQ ID NO: 177	QVQLQQPGAE LVRPGTSVKL SCKASGYTFT SSWMHWVKQR PGQGLEWIGV IDPSDSYTNY NQKFKGKATL TVDTSSSTAY MQLSSLTSED SAVYYCARGG GSSYNRYFDV WGTGTTVTVS SAKTTPPSVY PLAPGSAAQT NSMVTLGCLV KGYFPEPVTV TWNSGSLSSG VHTFPAVLQS DLYTLSSSVT VPSSPRPSET VTCNVAHPAS STKVDKKIVP RDCGCKPCIC TVPEVSSVFI FPPKPKDVLT ITLTPKVTCV VVDISKDDPE VQFSWFVDDV EVHTAQTQPR EEQFNSTFRS VSELPIMHQD WLNGKEFKCR VNSAAFPAPI EKTISKTKGR PKAPQVYTIP PPKEQMAKDK VSLTCMITDF FPEDITVEWQ WNGQPAENYK NTQPIMNTNG SYFVYSKLNV QKSNWEAGNT FTCSVLHEGL HNHHTEKSLS HSPGK
BB5.1	Light/ SEQ ID NO: 178	NIMMTQSPSS LAVSAGEKVT MSCKSSQSVL YSSNQKNYLA WYQQKPGQSP KLLIYWASTR ESGVPDRFTG SGSGTDFTLT ISSVQAEDLA VYYCHQYLSS RTFGGGTKLE IKRADAAPTV SIFPPSSEQL TSGGASVVCF LNNFYPKDIN VKWKIDGSER QNGVLNSWTD QDSKDSTYSM SSTLTLTKDE YERHNSYTCE ATHKTSTSPI VKSFNRGEC
C5-D-mab Vectorized Fab-fully encoded protein	SEQ ID NO: 179	**MYRMQLLLLI ALSLALVTNS** QVQLVESGGG LVQPGRSLRL SCAASGFTVH SSYYMAWVRQ APGKGLEWVG AIFTGSGAEY KAEWAKGRVT ISKDTSKNQV VLTMTNMDPV DTATYYCASD AGYDYPTHAM HYWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK V*EPKSCDKTH* RKRRGSGEGR GSLLTCGDVE ENPGP**MYRMQ LLLLIALSLA LVTNS**DIQMT QSPSSLSASV GDRVTITCRA SQGISSSLAW YQQKPGKAPK LLIYGASETE SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCQNTKVGS SYGNTFGGGT KVEIKRTVAA PSVFIFPPSD EQLKSGTASV VCLLNNFYPR EAKVQWKVDN ALQSGNSQES VTEQDSKDST YSLSSTLTLS KADYEKHKVY ACEVTHQGLS SPVTKSFNRG EC Leaders are shown in bold; Furin-2A linker is underlined; hinge region is shown in italic
C5-D-mab Vectorized fully encoded protein	SEQ ID NO: 180	**MYRMQLLLLI ALSLALVTNS** QVQLVESGGG LVQPGRSLRL SCAASGFTVH SSYYMAWVRQ APGKGLEWVG AIFTGSGAEY KAEWAKGRVT ISKDTSKNQV VLTMTNMDPV DTATYYCASD AGYDYPTHAM HYWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK

mAb or Protein	Chain/ SEQ ID NO:	Sequences
		V*EPKSCDKTH TCPPCP*APEL RRGPKVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKGLPSSIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVLHEALHA HYTRKELSLS PRKRRGSGEG RGSLLTCGDV EENPGP**MYRM QLLLLIALSL ALVTNS**DIQM TQSPSSLSAS VGDRVTITCR ASQGISSSLA WYQQKPGKAP KLLIYGASET ESGVPSRFSG SGSGTDFTLT ISSLQPEDFA TYYCQNTKVG SSYGNTFGGG TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC Leaders are shown in bold; Furin-2A linker is underlined; hinge region is shown in italic
C5-A-mab Vectorized Fab-IgG1 fully encoded protein	SEQ ID NO: 181	**MYRMQLLLLI ALSLALVTNS** QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKR*V* *EPKSCDKTH*T RKRRGSGEGR GSLLTCGDVE ENPGP**MYRMQ** **LLLLIALSLA LVTNS**DIQMT QSPSSLSASV GDRVTITCGA SENIYGALNW YQQKPGKAPK LLIYGATNLA DGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCQNVLNTP LTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC Leaders are shown in bold; Furin-2A linker is underlined; hinge region is shown in italic
C5-A-mab Vectorized Fab-IgG2 fully encoded protein	SEQ ID NO: 182	**MYRMQLLLLI ALSLALVTNS** QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV RKRRGSGEGR GSLLTCGDVE ENPGP**MYRMQ LLLLIALSLA** **LVTNS**DIQMT QSPSSLSASV GDRVTITCGA SENIYGALNW YQQKPGKAPK LLIYGATNLA DGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCQNVLNTP LTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC Leaders are shown in bold; Furin-2A linker is underlined; hinge region is shown in italic
C5-A-mab Vectorized fully encoded protein	SEQ ID NO: 183	**MYRMQLLLLI ALSLALVTNS** QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV *ERKCCVECPP CP*APPVAGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST

mAb or Protein	Chain/ SEQ ID NO:	Sequences
		YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGKRK RRGSGEGRGS LLTCGDVEEN PGP**MYRMQLL LLIALSLALV TNS**DIQMTQS PSSLSASVGD RVTITCGASE NIYGALNWYQ QKPGKAPKLL IYGATNLADG VPSRFSGSGS GTDFTLTISS LQPEDFATYY CQNVLNTPLT FGQGTKVEIK RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC Leaders are shown in bold; Furin-2A linker is underlined; hinge region is shown in italic
C5-D-mab Vectorized scFv mAb- fully encoded protein (H-L)	SEQ ID NO:195	QVQLVESGGGLVQPGRSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAI FTGSGAEYKAEWAKGRVTISKDTSKNQVVLTMTNMDPVDTATYYCASDAGYD YPTHAMHYWGQGTLVTVSSGGGGSGGGGSGGGGS DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGKAPKLLIYGAS ETESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNTKVGSSYGNTFGGG TKVEIKR *Heavy chain + linker + Light chain*
C5-D-mab Vectorized scFv mAb- fully encoded protein (L-H)	SEQ ID NO:196	DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGKAPKLLIYGAS ETESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNTKVGSSYGNTFGGG TKVEIKR GGGGSGGGGSGGGGS QVQLVESGGGLVQPGRSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAI FTGSGAEYKAEWAKGRVTISKDTSKNQVVLTMTNMDPVDTATYYCASDAGYD YPTHAMHYWGQGTLVTVSS *Light chain + linker + Heavy chain*
C5-A-mab Vectorized scFv mAb- fully encoded protein (H-L)	SEQ ID NO:197	QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SS GGGGSGGGGSGGGGS DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIKR *Heavy chain + linker + Light chain*
C5-A-mab Vectorized scFv mAb- fully encoded protein (L-H)	SEQ ID NO:198	DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIKR GGGGSGGGGSGGGGS QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSA *Light chain + linker + Heavy chain*
C5-C-mab Vectorized scFv mAb- fully encoded protein (H-L)	SEQ ID NO:199	QVQLVQSGAE VKKPGASVKV SCKASGHIFS NYWIQWVRQA PGQGLEWMGE ILPGSGHTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SS GGGGSGGGGSGGGGS DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIKR *Heavy chain + linker + Light chain*

mAb or Protein	Chain/ SEQ ID NO:	Sequences
C5-C-mab Vectorized scFv mAb- fully encoded protein (L-H)	SEQ ID NO:200	DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIKR GGGGSGGGGSGGGGS QVQLVQSGAE VKKPGASVKV SCKASGHIFS NYWIQWVRQA PGQGLEWMGE ILPGSGHTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SS *Light chain + linker + Heavy chain*
C5-B-mab Vectorized scFv mAb- fully encoded protein (H-L)	SEQ ID NO:201	EVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IGPFFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARDT PYFDYWGQGT LVTVSS GGGGSGGGGSGGGGS SYELTQPLSV SVALGQTARI TCSGDSIPNY YVYWYQQKPG QAPVLVIYDD SNRPSGIPER FSGSNSGNTA TLTISRAQAG DEADYYCQSF DSSLNAEVFG GGTKLTVL *Heavy chain + linker + Light chain*
C5-B-mab Vectorized scFv mAb- fully encoded protein (L-H)	SEQ ID NO:202	SYELTQPLSV SVALGQTARI TCSGDSIPNY YVYWYQQKPG QAPVLVIYDD SNRPSGIPER FSGSNSGNTA TLTISRAQAG DEADYYCQSF DSSLNAEVFG GGTKLTVL GGGGSGGGGSGGGGS EVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IGPFFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARDT PYFDYWGQGT LVTVSS *Light chain + linker + Heavy chain*
C5-D-mab.ScFv.HL (signal sequence underlined)	SEQ ID NO:203	MYRMQLLLLLIALSLALVTNSQVQLVESGGGLVQPGRSLRLSCAASGFTVHSS YYMAWVRQAPGKGLEWVGAIFTGSGAEYKAEWAKGRVTISKDTSKNQVVLTM TNMDPVDTATYYCASDAGYDYPTHAMHYWGQGTLVTVSSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGKAPKLLIYG ASETESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNTKVGSSYGNTFG GGTKVEIKR
C5-D-mab.scFv.LH (signal sequence underlined)	SEQ ID NO:204	MYRMQLLLLLIALSLALVTNSDIQMTQSPSSLSASVGDRVTITCRASQGISSS LAWYQQKPGKAPKLLIYGASETESGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQNTKVGSSYGNTFGGGTKVEIKRGGGGSGGGGSGGGGSQVQLVESGGG LVQPGRSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAIFTGSGAEYKA EWAKGRVTISKDTSKNQVVLTMTNMDPVDTATYYCASDAGYDYPTHAMHYWG QGTLVTVSS

Table 8. Nucleotide Sequences of Heavy and Light Chains, Expressed Polypeptides, Proteins, and Genomes

mAb, Protein or construct name	Chain/ SEQ ID NO:	Sequences
C5-D-mab Heavy Chain Fab	Heavy/ SEQ ID NO: 205	CAGGTGCAGCTGGTTGAATCTGGTGGTGGACTGGTGCAGCCTGGCAGAAGCC TGAGACTGTCTTGTGCTGCCTCTGGCTTCACAGTGCACAGCAGCTACTACAT GGCCTGGGTTAGACAGGCCCCTGGCAAAGGACTTGAGTGGGTTGGAGCCATC TTCACAGGCTCTGGGGCTGAGTATAAGGCTGAGTGGGCCAAGGGCAGAGTGA CCATCAGCAAGGACACCAGCAAGAACCAGGTGGTGCTGACCATGACCAACAT

		GGACCCTGTGGACACAGCCACCTACTACTGTGCCTCTGATGCTGGCTATGAC TACCCCACACATGCCATGCACTATTGGGGCCAGGGCACCCTGGTTACAGTGT CCTCTGCCTCTACAAAGGGCCCCTCTGTGTTTCCTCTGGCTCCTAGCAGCAA GAGCACCAGTGGTGGAACAGCTGCCCTGGGCTGTCTGGTCAAGGATTACTTC CCTGAGCCAGTGACTGTGTCCTGGAACTCTGGTGCACTGACCTCTGGGGTGC ACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGT GGTCACAGTGCCTAGCTCTAGCCTGGGCACCCAGACCTACATCTGCAATGTG AACCACAAGCCTAGCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGAGCT GTGACAAGACCCAC
C5-D-mab light chain	Light/ SEQ ID NO: 206	GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCTCTGTGGGAGACA GAGTGACCATCACCTGTAGAGCCAGCCAGGGCATCTCTAGCAGTCTGGCCTG GTATCAGCAGAAGCCTGGAAAGGCCCCTAAGCTGCTGATCTATGGGGCCTCT GAGACAGAATCTGGGGTGCCCAGCAGATTTTCAGGCTCTGGCTCTGGCACAG ACTTCACCCTGACCATTTCTAGCCTGCAGCCTGAGGACTTTGCCACCTACTA CTGCCAGAACACCAAAGTGGGCAGCAGCTATGGCAACACCTTTGGTGGTGGC ACCAAGGTGGAAATCAAGAGAACAGTGGCTGCCCCTTCTGTGTTCATCTTCC CACCATCTGATGAGCAGCTGAAGAGTGGCACAGCCTCTGTTGTGTGCCTGCT GAACAACTTCTACCCCAGAGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCC CTGCAGTCAGGCAACAGCCAAGAGTCTGTGACTGAGCAGGACAGCAAGGACT CCACCTACAGCCTGAGCAGCACCCTGACACTGAGCAAGGCTGACTATGAGAA GCACAAAGTGTATGCCTGTGAAGTGACCCACCAGGGGCTGAGCAGCCCTGTG ACCAAGAGCTTCAATAGAGGGGAGTGC
C5-A-mab Fab IgG1	Heavy/ SEQ ID NO: 207	CAGGTGCAGCTGGTTCAGTCTGGGGCTGAAGTGAAGAAACCTGGGGCCTCTG TGAAGGTGTCCTGCAAGGCCTCTGGCTACATCTTCAGCAACTATTGGATCCA GTGGGTCAGACAGGCCCCTGGCCAAGGACTTGAGTGGATGGGAGAGATCCTG CCTGGCTCTGGCAGCACAGAGTACACAGAGAACTTCAAGGACAGAGTGACCA TGACCAGAGACACCAGCACCTCCACAGTGTACATGGAACTGAGCAGCCTGAG ATCTGAGGACACAGCAGTGTACTATTGTGCCAGATACTTCTTTGGCAGCAGC CCCAACTGGTACTTTGATGTGTGGGGCCAGGGCACCCTGGTTACAGTGTCCT CTGCCTCTACAAAGGGCCCCTCTGTGTTTCCTCTGGCTCCTAGCAGCAAGAG CACCAGTGGTGGAACAGCTGCCCTGGGCTGTCTGGTCAAGGATTACTTCCCT GAGCCTGTGACTGTGTCCTGGAACTCTGGTGCACTGACCTCTGGGGTGCACA CCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTGGT CACAGTGCCTAGCTCTAGCCTGGGCACCCAGACCTACATCTGCAATGTGAAC CACAAGCCTAGCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGAGCTGTG ACAAGACCCACACC
C5-A-mab Fab IgG2	Heavy/ SEQ ID NO: 208	CAGGTGCAGCTGGTTCAGTCTGGGGCTGAAGTGAAGAAACCTGGGGCCTCTG TGAAGGTGTCCTGCAAGGCCTCTGGCTACATCTTCAGCAACTACTGGATTCA GTGGGTCAGACAGGCCCCTGGCCAAGGACTTGAGTGGATGGGAGAGATCCTG CCTGGCTCTGGCAGCACAGAGTACACAGAGAACTTCAAGGACAGAGTGACCA TGACCAGAGACACCAGCACCTCCACAGTGTACATGGAACTGAGCAGCCTGAG ATCTGAGGACACAGCAGTGTACTATTGTGCCAGATACTTCTTTGGCAGCAGC CCCAACTGGTACTTTGATGTGTGGGGCCAGGGCACCCTGGTTACAGTGTCCT CTGCCTCTACAAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTTGTAGCAGAAG CACCTCTGAGTCTACAGCTGCCCTGGGCTGCCTGGTCAAGGATTACTTTCCT GAGCCTGTGACTGTGTCCTGGAACTCTGGTGCTCTGACCTCTGGGGTGCACA CCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTGGT CACAGTGCCCAGCAGCAATTTTGGCACCCAGACCTACACCTGTAATGTGGAC CACAAGCCTAGCAACACCAAGGTGGACAAGACAGTG
C5-A-mab light chain	Light/ SEQ ID NO: 209	GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCTCTGTGGGAGACA GAGTGACAATCACCTGTGGGGCCTCTGAGAACATCTATGGGGCCCTGAACTG GTATCAGCAGAAGCCTGGAAAGGCCCCTAAGCTGCTGATATATGGGGCCACC AATCTGGCTGATGGGGTGCCCTCTAGATTTTCTGGCAGTGGCTCTGGCACAG ACTTCACCCTGACCATCAGTAGCCTGCAGCCTGAGGACTTTGCCACCTACTA CTGTCAGAATGTGCTGAACACCCCTCTGACCTTTGGCCAGGGCACCAAGGTG GAAATCAAGAGAACAGTGGCTGCCCCTTCTGTaTTCATCTTCCCACCATCTG

		ATGAGCAGCTGAAGAGTGGCACAGCCTCTGTTGTGTGCCTGCTGAACAACTT CTACCCCAGAGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTGCAGTCT GGCAACAGCCAAGAGTCTGTGACTGAGCAGGACAGCAAGGACTCCACCTACA GCCTGAGCAGCACCCTGACACTGAGCAAGGCTGACTATGAGAAGCACAAAGT GTATGCCTGTGAAGTGACCCACCAGGGGCTGAGCAGCCCTGTGACCAAGAGC TTCAATAGAGGGGAGTGC
C5-C-mab Heavy Chain Fab	Heavy/ SEQ ID NO: 210	caggtgcagctggtgcagagcggcgcggaagtgaaaaaaccgggcgcgagcg tgaaagtgagctgcaaagcgagcggccatatttttagcaactattggattca gtgggtgcgccaggcgccgggccagggcctggaatggatgggcgaaattctg ccgggcagcggccataccgaatataccgaaaactttaaagatcgcgtgacca tgacccgcgataccagcaccagcaccgtgtatatggaactgagcagcctgcg cagcgaagataccgcggtgtattattgcgcgcgctatttttttggcagcagc ccgaactggtattttgatgtgtggggccagggcaccctggtgaccgtgagca gcgcgagcaccaaaggcccgagcgtgtttccgctggcgccgtgcagccgcag caccagcgaaagcaccgcggcgctgggctgcctggtgaaagattattttccg gaaccggtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcata cctttccggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggt gaccgtgccgagcagcaactttggcacccagacctatacctgcaacgtggat cataaaccgagcaacaccaaagtggataaaaccgtggaacgcaaatgctgcg tggaa +/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC
C5-C-mab light chain	Light/ SEQ ID NO: 211	gatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgcggcgcgagcgaaaacatttatggcgcgctgaactg gtatcagcagaaaccgggcaaagcgccgaaactgctgatttatggcgcgacc aacctggcggatggcgtgccgagccgctttagcggcagcggcagcggcaccg attttaccctgaccattagcagcctgcagccggaagattttgcgacctatta ttgccagaacgtgctgaacaccccgctgacctttggccagggcaccaaagtg gaaattaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcg atgaacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaactt ttatccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagc ggcaacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctata gcctgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagt gtatgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagc tttaaccgcggcgaatgc
C5-B-mab Heavy Chain Fab	Heavy/ SEQ ID NO: 212	GAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCAGCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTACGCCATCAG CTGGGTGAGGCAGGCCCCCGGCCAGGGCCTGGAGTGGATGGGCGGCATCGGC CCCTTCTTCGGCACCGCCAACTACGCCCAGAAGTTCCAGGGCAGGGTGACCA TCACCGCCGACGAGAGCACCAGCACCGCCTACATGGAGCTGAGCAGCCTGAG GAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGACACCCCCTACTTCGAC TACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCC CCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGC CGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGC TGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGC AGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGGCCGCCGGCGGCCCCAGCGTGTTCCTG
C5-B-mab light chain	Light/ SEQ ID NO: 213	AGCTACGAGCTGACCCAGCCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCG CCAGGATCACCTGCAGCGGCGACAGCATCCCCAACTACTACGTGTACTGGTA CCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACGACGACAGCAAC AGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCG CCACCCTGACCATCAGCAGGGCCCAGGCCGGCGACGAGGCCGACTACTACTG CCAGAGCTTCGACAGCAGCCTGAACGCCGAGGTGTTCGGCGGCGGCACCAAG

		CTGACCGTGCTGGGCCAGCCCAAGGCCGCCCCCAGCGTGACCCTGTTCCCCC CCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAG CGACTTCTACCCCGGCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCC GTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAACAAGT ACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAG GAGCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAGAAGACCGTG GCCCCCACCGAGTGCAGC
Vectorized C5-D-mab Fab coding sequence	SEQ ID NO: 214	ATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCA CCAATTCTCAGGTGCAGCTGGTTGAATCTGGTGGTGGACTGGTGCAGCCTGG CAGAAGCCTGAGACTGTCTTGTGCTGCCTCTGGCTTCACAGTGCACAGCAGC TACTACATGGCCTGGGTTAGACAGGCCCCTGGCAAAGGACTTGAGTGGGTTG GAGCCATCTTCACAGGCTCTGGGGCTGAGTATAAGGCTGAGTGGGCCAAGGG CAGAGTGACCATCAGCAAGGACACCAGCAAGAACCAGGTGGTGCTGACCATG ACCAACATGGACCCTGTGGACACAGCCACCTACTACTGTGCCTCTGATGCTG GCTATGACTACCCCACACATGCCATGCACTATTGGGGCCAGGGCACCCTGGT TACAGTGTCCTCTGCCTCTACAAAGGGCCCCTCTGTGTTTCCTCTGGCTCCT AGCAGCAAGAGCACCAGTGGTGGAACAGCTGCCCTGGGCTGTCTGGTCAAGG ATTACTTCCCTGAGCCAGTGACTGTGTCCTGGAACTCTGGTGCACTGACCTC TGGGGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTG TCCTCTGTGGTCACAGTGCCTAGCTCTAGCCTGGGCACCCAGACCTACATCT GCAATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAAGGTGGAACC CAAGAGCTGTGACAAGACCCACAGAAAGAGAAGAGGCTCTGGAGAAGGCAGA GGCTCCCTGCTGACATGTGGGGATGTTGAAGAGAATCCTGGGCCTATGTATA GGATGCAACTGCTCCTCCTGATTGCTCTGAGCCTGGCTCTTGTGACCAACTC TGACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCTCTGTGGGAGAC AGAGTGACCATCACCTGTAGAGCCAGCCAGGGCATCTCTAGCAGTCTGGCCT GGTATCAGCAGAAGCCTGGAAAGGCCCCTAAGCTGCTGATCTATGGGGCCTC TGAGACAGAATCTGGGGTGCCCAGCAGATTTTCAGGCTCTGGCTCTGGCACA GACTTCACCCTGACCATTTCTAGCCTGCAGCCTGAGGACTTTGCCACCTACT ACTGCCAGAACACCAAAGTGGGCAGCAGCTATGGCAACACCTTTGGTGGTGG CACCAAGGTGGAAATCAAGAGAACAGTGGCTGCCCCTTCTGTGTTCATCTTC CCACCATCTGATGAGCAGCTGAAGAGTGGCACAGCCTCTGTTGTGTGCCTGC TGAACAACTTCTACCCCAGAGAAGCCAAGGTGCAGTGGAAGGTGGACAATGC CCTGCAGTCAGGCAACAGCCAAGAGTCTGTGACTGAGCAGGACAGCAAGGAC TCCACCTACAGCCTGAGCAGCACCCTGACACTGAGCAAGGCTGACTATGAGA AGCACAAAGTGTATGCCTGTGAAGTGACCCACCAGGGGCTGAGCAGCCCTGT GACCAAGAGCTTCAATAGAGGGGAGTGCTGA
Vectorized C5-D-mab Full Length coding sequence	SEQ ID NO: 215	ATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCA CCAATTCTCAGGTGCAGCTGGTTGAATCTGGTGGTGGACTGGTGCAGCCTGG CAGAAGCCTGAGACTGTCTTGTGCTGCCTCTGGCTTCACAGTGCACAGCAGC TACTACATGGCCTGGGTTAGACAGGCCCCTGGCAAAGGACTTGAGTGGGTTG GAGCCATCTTCACAGGCTCTGGGGCTGAGTATAAGGCTGAGTGGGCCAAGGG CAGAGTGACCATCAGCAAGGACACCAGCAAGAACCAGGTGGTGCTGACCATG ACCAACATGGACCCTGTGGACACAGCCACCTACTACTGTGCCTCTGATGCTG GCTATGACTACCCCACACATGCCATGCACTATTGGGGCCAGGGCACCCTGGT TACAGTGTCCTCTGCCTCTACAAAGGGCCCCTCTGTGTTTCCTCTGGCTCCT AGCAGCAAGAGCACCAGTGGTGGAACAGCTGCCCTGGGCTGTCTGGTCAAGG ATTACTTCCCTGAGCCAGTGACTGTGTCCTGGAACTCTGGTGCACTGACCTC TGGGGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTG TCCTCTGTGGTCACAGTGCCTAGCTCTAGCCTGGGCACCCAGACCTACATCT GCAATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAAGGTGGAACC CAAGAGCTGTGACAAGACCCACACCTGTCCTCCATGTCCTGCTCCAGAGCTG AGAAGAGGCCCCAAGGTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGA TGATCAGCAGAACCCCTGAAGTGACCTGTGTGGTGGTTGATGTGTCCCATGA GGACCCAGAAGTGAAGTTCAATTGGTATGTGGATGGGGTTGAAGTGCACAAT

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Vectorized C5-A-mab Fab IgG1 coding sequence	SEQ ID NO: 216	ATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCA CCAATTCTCAGGTGCAGCTGGTTCAGTCTGGGGCTGAAGTGAAGAAACCTGG GGCCTCTGTGAAGGTGTCCTGCAAGGCCTCTGGCTACATCTTCAGCAACTAT TGGATCCAGTGGGTCAGACAGGCCCCTGGCCAAGGACTTGAGTGGATGGGAG AGATCCTGCCTGGCTCTGGCAGCACAGAGTACACAGAGAACTTCAAGGACAG AGTGACCATGACCAGAGACACCAGCACCTCCACAGTGTACATGGAACTGAGC AGCCTGAGATCTGAGGACACAGCAGTGTACTATTGTGCCAGATACTTCTTTG GCAGCAGCCCCAACTGGTACTTTGATGTGTGGGGCCAGGGCACCCTGGTTAC AGTGTCCTCTGCCTCTACAAAGGGCCCCTCTGTGTTTCCTCTGGCTCCTAGC AGCAAGAGCACCAGTGGTGGAACAGCTGCCCTGGGCTGTCTGGTCAAGGATT ACTTCCCTGAGCCTGTGACTGTGTCCTGGAACTCTGGTGCACTGACCTCTGG GGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCC TCTGTGGTCACAGTGCCTAGCTCTAGCCTGGGCACCCAGACCTACATCTGCA ATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAGAGTGGAACCCAA GAGCTGTGACAAGACCCACACCAGAAAGAGAAGAGGCTCTGGAGAAGGCAGA GGCTCCCTGCTGACATGTGGGGATGTTGAAGAGAATCCTGGGCCTATGTATA GGATGCAACTGCTCCTCCTGATTGCTCTGAGCCTGGCTCTTGTGACCAACTC TGACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCTCTGTGGGAGAC AGAGTGACAATCACCTGTGGGGCCTCTGAGAACATCTATGGGGCCCTGAACT GGTATCAGCAGAAGCCTGGAAAGGCCCCTAAGCTGCTGATATATGGGGCCAC CAATCTGGCTGATGGGGTGCCCTCTAGATTTTCTGGCAGTGGCTCTGGCACA GACTTCACCCTGACCATCAGTAGCCTGCAGCCTGAGGACTTTGCCACCTACT ACTGTCAGAATGTGCTGAACACCCCTCTGACCTTTGGCCAGGGCACCAAGGT GGAAATCAAGAGAACAGTGGCTGCCCCTTCTGTaTTCATCTTCCCACCATCT GATGAGCAGCTGAAGAGTGGCACAGCCTCTGTTGTGTGCCTGCTGAACAACT TCTACCCCAGAGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTGCAGTC TGGCAACAGCCAAGAGTCTGTGACTGAGCAGGACAGCAAGGACTCCACCTAC AGCCTGAGCAGCACCCTGACACTGAGCAAGGCTGACTATGAGAAGCACAAAG TGTATGCCTGTGAAGTGACCCACCAGGGGCTGAGCAGCCCTGTGACCAAGAG CTTCAATAGAGGGGAGTGCTGA

Vectorized C5-A-mab Fab IgG2 coding sequence	SEQ ID NO: 217	ATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCA CCAATTCTCAGGTGCAGCTGGTTCAGTCTGGGGCTGAAGTGAAGAAACCTGG GGCCTCTGTGAAGGTGTCCTGCAAGGCCTCTGGCTACATCTTCAGCAACTAC TGGATTCAGTGGGTCAGACAGGCCCCTGGCCAAGGACTTGAGTGGATGGGAG AGATCCTGCCTGGCTCTGGCAGCACAGAGTACACAGAGAACTTCAAGGACAG AGTGACCATGACCAGAGACACCAGCACCTCCACAGTGTACATGGAACTGAGC AGCCTGAGATCTGAGGACACAGCAGTGTACTATTGTGCCAGATACTTCTTTG GCAGCAGCCCCAACTGGTACTTTGATGTGTGGGGCCAGGGCACCCTGGTTAC AGTGTCCTCTGCCTCTACAAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTTGT AGCAGAAGCACCTCTGAGTCTACAGCTGCCCTGGGCTGCCTGGTCAAGGATT ACTTTCCTGAGCCTGTGACTGTGTCCTGGAACTCTGGTGCTCTGACCTCTGG GGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCC TCTGTGGTCACAGTGCCCAGCAGCAATTTTGGCACCCAGACCTACACCTGTA ATGTGGACCACAAGCCTAGCAACACCAAGGTGGACAAGACAGTGAGAAAGAG AAGAGGCTCTGGAGAAGGCAGAGGCTCCCTGCTGACATGTGGGGATGTTGAA GAGAATCCTGGGCCTATGTATAGGATGCAACTGCTCCTCCTGATTGCTCTGA GCCTGGCTCTTGTGACCAACTCTGACATCCAGATGACACAGAGCCCTAGCAG CCTGTCTGCCTCTGTGGGAGACAGAGTGACAATCACCTGTGGGGCCTCTGAG AACATCTATGGGGCCCTGAACTGGTATCAGCAGAAGCCTGGAAAGGCCCCTA AGCTGCTGATATATGGGGCCACCAATCTGGCTGATGGGGTGCCCTCTAGATT TTCTGGCAGTGGCTCTGGCACAGACTTCACCCTGACCATCAGTAGCCTGCAG CCTGAGGACTTTGCCACCTACTACTGTCAGAATGTGCTGAACACCCCTCTGA CCTTTGGCCAGGGCACCAAGGTGGAAATCAAGAGAACAGTGGCTGCCCCTTC TGTaTTCATCTTCCCACCATCTGATGAGCAGCTGAAGAGTGGCACAGCCTCT GTTGTGTGCCTGCTGAACAACTTCTACCCCAGAGAAGCCAAGGTGCAGTGGA AGGTGGACAATGCCCTGCAGTCTGGCAACAGCCAAGAGTCTGTGACTGAGCA GGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACACTGAGCAAG GCTGACTATGAGAAGCACAAAGTGTATGCCTGTGAAGTGACCCACCAGGGGC TGAGCAGCCCTGTGACCAAGAGCTTCAATAGAGGGGAGTGCTGA
Vectorized C5-A-mab Full Length coding sequence	SEQ ID NO: 218	ATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCA CCAATTCTCAGGTGCAGCTGGTTCAGTCTGGGGCTGAAGTGAAGAAACCTGG GGCCTCTGTGAAGGTGTCCTGCAAGGCCTCTGGCTACATCTTCAGCAACTAC TGGATTCAGTGGGTCAGACAGGCCCCTGGCCAAGGACTTGAGTGGATGGGAG AGATCCTGCCTGGCTCTGGCAGCACAGAGTACACAGAGAACTTCAAGGACAG AGTGACCATGACCAGAGACACCAGCACCTCCACAGTGTACATGGAACTGAGC AGCCTGAGATCTGAGGACACAGCAGTGTACTATTGTGCCAGATACTTCTTTG GCAGCAGCCCCAACTGGTACTTTGATGTGTGGGGCCAGGGCACCCTGGTTAC AGTGTCCTCTGCCTCTACAAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTTGT AGCAGAAGCACCTCTGAGTCTACAGCTGCCCTGGGCTGCCTGGTCAAGGATT ACTTTCCTGAGCCTGTGACTGTGTCCTGGAACTCTGGTGCTCTGACCTCTGG GGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCC TCTGTGGTCACAGTGCCCAGCAGCAATTTTGGCACCCAGACCTACACCTGTA ATGTGGACCACAAGCCTAGCAACACCAAGGTGGACAAGACAGTGGAAAGAAA GTGCTGTGTGGAATGCCCTCCTTGTCCTGCTCCTCCAGTGGCTGGACCTTCT GTGTTTCTGTTCCCTCCAAAGCCTAAGGACACCCTGATGATCAGCAGAACCC CTGAAGTGACCTGTGTGGTGGTGGATGTGTCCCAAGAGGACCCTGAGGTGCA GTTCAATTGGTATGTGGATGGGGTTGAAGTGCACAATGCCAAGACCAAGCCT AGAGAGGAACAGTTCAACAGCACCTACAGAGTGGTGTCTGTGCTGACAGTGC TGCACCAGGACTGGCTGAATGGCAAAGAGTACAAGTGCAAGGTGTCCAACAA GGGCCTGCCTAGCAGCATTGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCA AGAGAACCCCAAGTGTACACCCTGCCTCCAAGCCAAGAGGAAATGACCAAGA ACCAGGTGTCCCTGACCTGCCTTGTGAAGGGCTTCTACCCCTCTGACATTGC TGTGGAATGGGAGTCCAATGGCCAGCCTGAAAACAACTACAAGACCACACCT CCTGTGCTGGACTCTGATGGCAGCTTCTTCCTGTACAGCAGACTGACAGTGG ACAAGTCCAGATGGCAAGAGGGCAATGTGTTCAGCTGCTCTGTGATGCATGA GGCCCTGCACAACCACTACACCCAGAAGTCTCTGTCTCTGAGCCTGGGCAAG

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CAG.C5-D-mab.Fab (5' ITR to 3' ITR) ITR sequences in italics	SEQ ID NO: 219	*ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcggg* *cgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagt* *ggccaactccatcactaggggttcct*CATATGcagggtaatggggatcctct agataggtaccctagtcgacattgattattgactagttattaatagtaatca attacggggtcattagttcatagcccatatatggagttccgcgttacataac ttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgac gtcaataatgacgtatgttcccatagtaacgccaatagggactttccattga cgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaag tgtatcatatgccaagtacgcccccctattgacgtcaatgacggtaaatggcc cgcctggcattatgcccagtacatgaccttatgggactttcctacttggcag tacatctacgtattagtcatcgctattaccatggtcgaggtgagccccacgt tctgcttcactctccccatctccccccccctccccaccccccaattttgtattt atttatttttttaattatttttgtgcagcgatgggggcgggggggggggggggg cgcgcgccaggcggggcggggcggggcgaggggcggggcggggcgaggcgga gaggtgcggcggcagccaatcagagcggcgcgctccgaaagtttccttttat ggcgaggcggcggcggcggcggcccctataaaaagcgaagcgcgcggcgggcg ggagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgc gccgcccgccccggctctgactgaccgcgttactcccacaggtgagcgggcg ggacggcccttctcctccgggctgtaattagcgcttggtttaatgacggctt gtttcttttctgtggctgcgtgaaagccttgaggggctccgggagggccctt tgtgcgggggggagcggctcgggggggtgcgtgcgtgtgtgtgtgcgtgggggag cgccgcgtgcggctccgcgctgcccggcggctgtgagcgctgcgggcgcggc gcggggctttgtgcgctccgcagtgtgcgcgaggggagcgcggccgggggcg gtgccccgcggtgcgggggggggctgcgagggggaacaaaggctgcgtgcgggg tgtgtgcgtgggggggtgagcaggggggtgtgggcgcgtcggtcgggctgcaa ccccccctgcaccccccctccccgagttgctgagcacggcccggcttcgggtg cggggctccgtacggggcgtggcgcggggctcgccgtgccgggcgggggggtg gcggcaggtgggggtgccgggcggggcggggccgcctcgggccggggagggc tcgggggagggggcgcggcggcccccggagcgccggcggctgtcgaggcgcgg cgagccgcagccattgccttttatggtaatcgtgcgagagggcgcagggact tcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcacc ccctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgg gcggggagggccttcgtgcgtcgccgcgccgccgtcccctttctcccctctcca gcctcggggctgtccgcgggggggacggctgccttcgggggggacggggcagg gcggggttcggcttctggcgtgtgaccggcggctctagagcctctgctaacc atgttcatgccttcttcttttttcctacagctcctgggcaacgtgctggttat tgtgctgtctcatcattttggcaaagAATTCGCCACCATGTACAGAATGCAG CTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCACCAATTCTCAGGTGC AGCTGGTTGAATCTGGTGGTGGACTGGTGCAGCCTGGCAGAAGCCTGAGACT GTCTTGTGCTGCCTCTGGCTTCACAGTGCACAGCAGCTACTACATGGCCTGG GTTAGACAGGCCCCTGGCAAAGGACTTGAGTGGGTTGGAGCCATCTTCACAG

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C5-A-mab scFv (H-L) cassette (ITR-ITR)	276	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcggg cgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagt ggccaactccatcactaggggttcctcatatgcagggtaatggggatcctct agataggtaccctagtcgacattgattattgactagttattaatagtaatca attacggggtcattagttcatagcccatatatggagttccgcgttacataac ttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgac gtcaataatgacgtatgttcccatagtaacgccaatagggactttccattga cgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaag tgtatcatatgccaagtacgcccccctattgacgtcaatgacggtaaatggcc cgcctggcattatgcccagtacatgaccttatgggactttcctacttggcag tacatctacgtattagtcatcgctattaccatggtcgaggtgagccccacgt tctgcttcactctccccatctccccccccctccccacccccaattttgtattt atttatttttttaattattttgtgcagcgatgggggcgggggggggggggggg cgcgcgccaggcgggcgggcggggcgaggggcggggcggggcgaggcgga gaggtgcggcggcagccaatcagagcggcgcgctccgaaagtttccttttat ggcgaggcggcggcggcggcggccctataaaaagcgaagcgcgcggcgggcg ggagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgc gccgcccgccccggctctgactgaccgcgttactcccacaggtgagcgggcg ggacggcccttctcctccgggctgtaattagcgcttggtttaatgacggctt gtttcttttctgtggctgcgtgaaagccttgaggggctccgggagggccctt

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C5-A-mab scFv (L-H) cassette (ITR-ITR)	277	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcggg cgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagt ggccaactccatcactaggggttcctcatatgcagggtaatggggatcctct agataggtaccctagtcgacattgattattgactagttattaatagtaatca attacggggtcattagttcatagcccatatatggagttccgcgttacataac ttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgac gtcaataatgacgtatgttcccatagtaacgccaatagggactttccattga cgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaag tgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcc cgcctggcattatgcccagtacatgaccttatgggactttcctacttggcag tacatctacgtattagtcatcgctattaccatggtcgaggtgagccccacgt tctgcttcactctccccatctccccccccctccccacccccaattttgtattt atttatttttttaattattttgtgcagcgatgggggcgggggggggggggggg cgcgcgccaggcggggcggggcggggcgaggggcggggcggggcgaggcgga

		gaggtgcggcggcagccaatcagagcggcgcgctccgaaagtttccttttat ggcgaggcggcggcggcggcggccctataaaaagcgaagcgcgcggcgggcg ggagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgc gccgcccgccccggctctgactgaccgcgttactcccacaggtgagcgggcg ggacggcccttctcctccgggctgtaattagcgcttggtttaatgacggctt gtttcttttctgtggctgcgtgaaagccttgaggggctccgggagggccctt tgtgcgggggggagcggctcgggggggtgcgtgcgtgtgtgtgtgtgcgtgggggag cgccgcgtgcggctccgcgctgcccggcggctgtgagcgctgcgggcgcggc gcgggggctttgtgcgctccgcagtgtgcgcgaggggagcgcggccgggggcg gtgccccgcggtgcgggggggggctgcgaggggaacaaaggctgcgtgcgggg tgtgtgcgtgggggggtgagcaggggggtgtgggcgcgtcggtcgggctgcaa ccccccctgcaccccctccccgagttgctgagcacggcccggcttcgggtg cggggctccgtacggggcgtggcgcggggctcgccgtgccgggcgggggggtg gcggcaggtgggggtgccgggcgggggcgggggccgcctcgggccggggagggc tcgggggaggggcgcggcggccccccggagcgccggcggctgtcgaggcgcgg cgagccgcagccattgccttttatggtaatcgtgcgagagggcgcagggact tcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcacc ccctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgg gcggggagggccttcgtgcgtcgccgcgccgccgtcccctttctcccctctcca gcctcggggctgtccgcgggggggacggctgccttcgggggggacggggcagg gcgggggttcggcttctggcgtgtgaccggcggctctagagcctctgctaacc atgttcatgccttcttctttttcctacagctcctgggcaacgtgctggttat tgtgctgtctcatcattttggcaaagaattcgccaccatgtacagaatgcag ctgctgctgctcattgccctgtctctggccctggtcaccaattctgacatcc agatgacacagtctccatctagcctgtctgccagcgtgggcgatagagtgac aatcacctgtggcgcctctgagaacatctacggcgccctgaattggtatcag cagaagcccggcaaggcccctaagctgctgatctacggagcaaccaatctgg cagatggagtgccaagcagattctccggctctggcagcggcacagactttac actgaccatctctagcctgcagcctgaggatttcgccacctactattgtcag aacgtgctgaatacaccactgacctttggccagggcacaaaggtggagatca agagaaccggaggaggaggctctggaggaggaggctctggcggcggcggcag ccaggtgcagctggtgcagtctggagcagaggtgaagaagccaggagcctcc gtgaaggtgtcttgcaaggccagcggctacatcttcagcaactattggattc agtgggtgaggcaggcaccaggacagggactggaatggatgggagagatcct gcctggctccggctctacagagtacaccgagaacttcaaggaccgggtgacc atgacaagagataccagcacatccaccgtgtatatggagctgagctccctga ggtccgaggacaccgccgtgtactattgcgcccgctacttctttggctctag ccccaactggtatttcgacgtgtggggccagggcacactggtgaccgtgtcc tcctaataactcgaggacggggtgaactacgcctgaggatccgatctttttc cctctgccaaaaattatggggacatcatgaagccccttgagcatctgacttc tggctaataaaggaaatttatttttcattgcaatagtgtgttggaatttttg tgtctctcactcggaagcaattcgttgatctgaatttcgaccacccataata cccattaccctgccagggtaatgggctagctgcggccgcaggaaccctagt gatggagttggccactccctctctgcgcgctcgctcgctcactgaggccggg cgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcg agcgagcgcgcag *ITR – CAG – signal sequence + C5-A-mab scFv (L-linker-H) – polyA -ITR*
C5-A-mab scFv (H-L) cassette (CAG-signal sequence + ScFv transgene-polyA)	278	gacattgattattgactagttattaatagtaatcaattacggggtcattagt tcatagcccatatatggagttccgcgttacataacttacggtaaatggcccg cctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatg ttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagta tttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagt acgcccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagt catcgctattaccatggtcgaggtgagccccacgttctgcttcactctcccc

		atctccccccctccccacccccaattttgtatttatttatttttttaattat tttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcggggc ggggcggggcgagggggcggggcggggcgaggcggagaggtgcggcggcagcc aatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggc ggcggccctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctg ccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgccccggctc tgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggct gcgtgaaagccttgaggggctccgggagggccctttgtgcgggggggagcggc tcgggggtgcgtgcgtgtgtgtgcgtggggagcgccgcgtgcggctccg cgctgcccggcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgct ccgcagtgtgcgcgaggggagcgcggccgggggcggtgccccgcggtgcggg gggggctgcgaggggaacaaaggctgcgtgcggggtgtgtgcgtgggggggt gagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccctgcacccccc tccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacgggg cgtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgc cgggcggggcggggccgcctcgggccggggagggctcgggggaggggcgcgg cggcccccggagcgccggcggctgtcgaggcgcggcgagccgcagccattgc cttttatggtaatcgtgcgagagggcgcagggacttcctttgtcccaaatct gtgcggagccgaaatctgggaggcgccgccgcaccccctctagcgggcgcgg ggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgt gcgtcgccgcgccgccgtcccctttctcccctctccagcctcggggctgtccgc ggggggacggctgccttcgggggggacggggcagggcggggttcggcttctg gcgtgtgaccggcggctctagagcctctgctaaccatgttcatgccttcttc tttttcctacagctcctgggcaacgtgctggttattgtgctgtctcatcatt ttggcaaagaattcgccaccatgtacagaatgcagctgctgctgctcattgc cctgtctctggccctggtcaccaattctcaggtgcagctggtgcagtctgga gcagaggtgaagaagccaggagcctccgtgaaggtgtcttgcaaggccagcg gctacatcttcagcaactattggattcagtgggtgaggcaggcaccaggaca gggactggaatggatgggagagatcctgcctggctccggctctacagagtac accgagaacttcaaggaccgggtgaccatgacaagagataccagcacatcca ccgtgtatatggagctgagctccctgaggtccgaggacaccgccgtgtacta ttgcgcccgctacttctttggctctagccccaactggtatttcgacgtgtgg ggccagggcacactggtgaccgtgtcctccggaggaggaggctctggaggag gaggctctggcggcggcggcagcgacatccagatgacacagtctccatctag cctgtctgccagcgtgggcgatagagtgacaatcacctgtggcgcctctgag aacatctacggcgccctgaattggtatcagcagaagcccggcaaggccccta agctgctgatctacggagcaaccaatctggcagatggagtgccaagcagatt ctccggctctggcagcggcacagactttacactgaccatctctagcctgcag cctgaggatttcgccacctactattgtcagaacgtgctgaatacaccactga cctttggccagggcacaaaggtggagatcaagagaacctaataactcgagga cggggtgaactacgcctgaggatccgatcttttccctctgccaaaaattat ggggacatcatgaagccccttgagcatctgacttctggctaataaaggaaat ttattttcattgcaatagtgtgttggaatttttgtgtctctcactcg *CAG – signal sequence + C5-A-mab scFv (H-linker-L) – polyA*
C5-A-mab scFv (L-H) cassette (CAG-signal sequence + ScFv transgene-polyA)	279	gacattgattattgactagttattaatagtaatcaattacggggtcattagt tcatagcccatatatggagttccgcgttacataacttacggtaaatggcccg cctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatg ttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagta tttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagt acgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagt catcgctattaccatggtcgaggtgagccccacgttctgcttcactctcccc atctccccccctccccacccccaattttgtatttatttatttttttaattat

		tttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcggggc ggggcggggcgagggcggggcggggcgaggcggagaggtgcggcggcagcc aatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggc ggcggccctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctg ccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgccccggctc tgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggct gcgtgaaagccttgaggggctccgggagggccctttgtgcgggggggagcggc tcgggggggtgcgtgcgtgtgtgtgtgcgtggggagcgccgcgtgcggctccg cgctgcccggcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgct ccgcagtgtgcgcgaggggagcgcggccgggggcggtgccccgcggtgcggg gggggctgcgaggggaacaaaggctgcgtgcggggtgtgtgcgtgggggggt gagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccctgcacccccc tccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacgggg cgtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgc cgggcggggcggggccgcctcgggccggggagggctcgggggaggggcgcgg cggcccccggagcgccggcggctgtcgaggcgcggcgagccgcagccattgc cttttatggtaatcgtgcgagagggcgcagggacttcctttgtcccaaatct gtgcggagccgaaatctgggaggcgccgccgcacccccctctagcgggcgcgg ggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgt gcgtcgccgcgccgccgtcccccttctccctccagcctcggggctgtccgc gggggacggctgccttcgggggggacggggcagggcggggttcggcttctg gcgtgtgaccggcggctctagagcctctgctaaccatgttcatgccttcttc tttttcctacagctcctgggcaacgtgctggttattgtgctgtctcatcatt ttggcaaagaattcgccaccatgtacagaatgcagctgctgctgctcattgc cctgtctctggccctggtcaccaattctgacatccagatgacacagtctcca tctagcctgtctgccagcgtgggcgatagagtgacaatcacctgtggcgcct ctgagaacatctacggcgccctgaattggtatcagcagaagcccggcaaggc ccctaagctgctgatctacggagcaaccaatctggcagatggagtgccaagc agattctccggctctggcagcggcacagactttacactgaccatctctagcc tgcagcctgaggatttcgccacctactattgtcagaacgtgctgaatacacc actgacctttggccagggcacaaaggtggagatcaagagaaccggaggagga ggctctggaggaggaggctctggcggcggcggcagccaggtgcagctggtgc agtctggagcagaggtgaagaagccaggagcctccgtgaaggtgtcttgcaa ggccagcggctacatcttcagcaactattggattcagtgggtgaggcaggca ccaggacagggactggaatggatgggagagatcctgcctggctccggctcta cagagtacaccgagaacttcaaggaccgggtgaccatgacaagagataccag cacatccaccgtgtatatggagctgagctccctgaggtccgaggacaccgcc gtgtactattgcgcccgctacttctttggctctagccccaactggtatttcg acgtgtggggccagggcacactggtgaccgtgtcctcctaataactcgagga cggggtgaactacgcctgaggatccgatcttttccctctgccaaaaattat ggggacatcatgaagccccttgagcatctgacttctggctaataaaggaaat ttattttcattgcaatagtgtgttggaatttttgtgtctctcactcg *CAG - signal sequence + C5-A-mab scFv (L-linker-H) - polyA*

Gene Therapy Methods

[0167] Provided are methods of treating human subjects for dry AMD by administration of a viral vector containing a transgene encoding an anti-C5 scFv which has an amino acid sequence of SEQ ID NO: 195, 196, 197, 198, 199, 200, 201, or 202. Also provided are methods of treating human subjects for dry AMD by administration of a viral vector containing a transgene encoding an anti-C5

scFv which has an amino acid sequence of one of SEQ ID NOs: 195, 196, 197, 198, 199, 200, 201, 202, 203, or 204. The scFv may be encoded by the nucleotide sequence of SEQ ID NO: 224, 227, or 230. The scFv may include a signal peptide and, in embodiments, has an amino acid sequence of SEQ ID NO: 203. The viral vector has an AAV capsid with tropism for human ocular tissues and comprises a capsid protein of AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249) (see Table A). The engineered capsids exhibit superior transgene product expression in retinal and RPE-choroid tissue, as well as aqueous and vitreous humor, following suprachoroidal delivery of an rAAV vector comprising any one of the capsid proteins of SEQ ID NO: 243, SEQ ID NO: 244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, or SEQ ID NO: 249, compared to a corresponding parental capsid. (See, *e.g.*, Example 24.) The transgene is operably linked by regulatory sequences that promote expression of the transgene in human ocular tissue cells (including in retinal cells, RPE, choroid, BrM, choriocapillaris, photoreceptor cells, retinal ganglion cells), for example a CAG (SEQ ID NO: 2) promoter or a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), or ocular specific promoter, such as a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), a human red opsin (RedO) promoter (SEQ ID NO: 14) or a Best1/GRK1 tandem promoter (SEQ ID NO: 26). Regulatory sequences may also include polyadenylation signal sequences and introns. The expression cassette comprising the transgene and operably linked regulatory sequences are flanked by ITR sequences, as an artificial AAV genome. The flanking ITR sequences may be configured to provide a self-complementary AAV (scAAV) genome. The recombinant vectors, including those as shown in **FIGS. 2A-2E,** can be administered in any manner such that the recombinant vector enters one or more ocular tissue cells. In particular embodiments, the recombinant AAV comprises an artificial genome of (or is produced using a *cis* plasmid or construct comprising) CAG.C5-D-mab.scFv (SEQ ID NO: 225) or CAG.C5-A-mab.scFv (SEQ ID NO: 276). In particular embodiments, the recombinant AAV comprises an artificial genome of (or is produced using a *cis* plasmid or construct comprising) C5-D-mab.scFv (SEQ ID NO: 224 or SEQ ID NO: 227 or SEQ ID NO: 230). In some embodiments, the expression cassette (promoter to polyA) comprises SEQ ID NO: 226, SEQ ID NO: 228, SEQ ID NO: 231, SEQ ID NO: 233, SEQ ID NO: 235, SEQ ID NO: 237, SEQ ID NO: 239, SEQ ID NO: 241, SEQ ID NO: 278, or SEQ ID NO:

279. In some embodiments, the artificial genome comprises SEQ ID NO: 225, SEQ ID NO: 229, SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, SEQ ID NO: 242, SEQ ID NO: 276, or SEQ ID NO: 277. In certain embodiments, the artificial genome is self-complementary.

[0168] In other embodiments, the transgene encoding an anti-C5 scFv is for a C5-D scFv, a C5-A scFv, a C5-C scFv, or a C5-D scFv. In particular embodiments, the anti-C5 scFv has an amino acid sequence of SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, or SEQ ID NO: 202.

[0169] Provided also are method of administering recombinant AAV vectors comprising a transgene which is a scFv. In some embodiments, the transgene encodes an scFv with the structure: signal sequence – VH – linker – VL – polyA. In some embodiments, the transgene encodes an scFv with the structure: signal sequence – VL – linker – VH – poly A. In some embodiments, the linker is GGGGS (SEQ ID NO: 126), GGGGSGGGGS (SEQ ID NO: 127), GGGGSGGGGSGGGGS (SEQ ID NO: 128), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 129) or GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 130). In some embodiments, the signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 55) or a signal sequence from Table 2. In some embodiments, the VH is SEQ ID NO: 184 and VL is SEQ ID NO: 185, wherein VH is SEQ ID NO: 186 and VL is SEQ ID NO: 187, wherein VH is SEQ ID NO: 188 and the VL is SEQ ID NO: 189, or wherein VH is SEQ ID NO: 190 and VL is SEQ ID NO: 191.

[0170] Provided also are methods of administering recombinant AAV vectors (including for methods of treating dryAMD) comprising an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and an artificial genome comprising SEQ ID NO: 225, SEQ ID NO: 229, SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, SEQ ID NO: 242, SEQ ID NO: 276, or SEQ ID NO: 277, or an artificial genome that is 95%, 96%, 97%, 98%, or 99% identical thereto and encodes a functional anti-C5 scFv.

[0171] Therapeutically effective doses of any of these recombinant vectors should be administered in any manner such that the recombinant vector enters ocular tissue cells (e.g., retinal cells), e.g., via subretinal, intravitreal, intracameral, or suprachoroidal injection or intranasal administration. Alternatively, the vector is administered peripherally (for example, intravenously, intramuscularly or subcutaneously) such that the recombinant vector transduces liver and/or muscle

cells, creating a depot in liver and/or muscle tissue which express the transgene product into the bloodstream, delivering the therapeutic to ocular tissues.

[0172] Alternatively, suprachoroidal administration results in expression of the transgene product in cells of the eye, creating a depot in one or more ocular tissue cells such as RPE or photoreceptor cells of the patient that continuously supplies the anti-C5 scFv to ocular tissues of the subject. The transgene expression results in therapeutically effective levels of the anti-C5 scFv in the aqueous humor, the vitreous humor, retinal tissue, the RPE, the BrM or choriocapillaris. In some embodiments, provided herein is a method of suprachoroidal administration for treating a pathology of the eye, comprising administering to the suprachoroidal space in the eye of a human subject in need of treatment a recombinant viral vector comprising a nucleotide sequence encoding a therapeutic product such that the therapeutic product is expressed and results in treatment of the pathology of the eye. In some embodiments, the administering step is by injecting the recombinant viral vector into the suprachoroidal space using a suprachoroidal drug delivery device. In some embodiments, the suprachoroidal drug delivery device comprises a microneedle. In some embodiments, the suprachoroidal drug delivery device is a microinjector.

[0173] Currently available technologies for suprachoroidal space (SCS) delivery exist. SC injections have been achieved with scleral flap technique, catheters and standard hypodermic needles, as well as with microneedles. A hollow-bore microneedle with a length matched to the thickness of the sclera, for example a 900 μm-long or 1100 μm-long microneedle (SCS Microinjector®, Clearside Biomedical, Inc.), inserted in the eye has been shown to deliver therapeutic agents to the posterior segment of the eye via the suprachoroidal space (Rai UDJ, et al. The suprachoroidal pathway: a new drug delivery route to the back of the eye. *Drug Discov Today*. 2015;20(4):491-495; Moisseiev E, et al. The suprachoroidal space: from potential space to a space with potential. *Clin Ophthalmol*. 2016;10:173-178; Chiang B, et al. The suprachoroidal space as a route of administration to the posterior segment of the eye. *Adv Drug Deliv Rev*. 2018;126:58-66). The SCS Microinjector has been approved for suprachoroidal use clinically with XIPERE®.

[0174] Recombinant AAV vector compositions, such as the rAAV compositions described herein, achieve delivery of the transgene to the posterior segment of the eye, including retinal cells, RPE and photoreceptor cells, via suprachoroidal administration (Ewing, TM, et al. 2022 *Retinal Physician* 19:24-26). In some embodiments, a method of administering an rAAV vector composition comprises inserting a needle, e.g. a microneedle, into the suprachoroidal space of the eye without the

needle penetrating through the choroid ("suprachoroidal administration or injection"). rAAV vector compositions can be injected into the eye using a microneedle, typically locating the needle approximately 4-4.5 mm from the limbus, into the pars plana. By way of non-limiting example, the microneedle is inserted into the sclera at a perpendicular angle, then the needle hub is depressed to create a sealing gasket effect, then the injection of a pharmaceutical composition comprising the rAAV vector is performed over 5–10 seconds. In some embodiments, the administration step is performed under local anesthesia (e.g. anesthesia administered before the suprachoroidal injection). In other embodiments, topical steroid or other anti-inflammatory may be applied to the eye before or after insertion of the needle.

[0175] Oxular Limited is developing a SCS device and delivery system (Oxulumis) that advances an illuminated cannula in the suprachoroidal space. The Orbit device (Gyroscope) is a specially-designed system enabling cannulation of the suprachoroidal space with a flexible cannula (for example, the flexible cannula is inserted between the sclera and the choroid). A microneedle inside the cannula is advanced into the subretinal space to enable targeted dose delivery. *Ab interno* access to the SCS can also be achieved using micro-stents, which serve as minimally-invasive glaucoma surgery (MIGS) devices. Examples include the CyPass® Micro-Stent (Alcon, Fort Worth, Texas, US) and iStent® (Glaukos), which are surgically implanted to provide a conduit from the anterior chamber to the SCS to drain the aqueous humor without forming a filtering bleb.

[0176] In some embodiments, the suprachoroidal drug delivery device is a syringe with a 1 millimeter 30 gauge needle. In some embodiments, the syringe has a larger circumference (e.g., 29 gauge needle). During an injection using this device, the needle pierces to the base of the sclera and fluid containing drug enters the suprachoroidal space, leading to expansion of the suprachoroidal space. As a result, there is tactile and visual feedback during the injection. Following the injection, the fluid flows posteriorly and absorbs dominantly in the choroid and retina. This results in the production of transgene protein from all retinal cell layers and choroidal cells. Using this type of device and procedure allows for a quick and easy in-office procedure with low risk of complications.

[0177] In some embodiments, a microneedle or syringe is used to administer the rAAV compositions described herein. In some embodiments, a microneedle or syringe comprises a needle having an effective length of about 2000 microns or less. In other embodiments, a microneedle or syringe comprises a needle having an effective length between about 500 microns to about 2000 microns, or between about 800 microns to about 1200 microns. In some embodiments, a microneedle

or syringe comprises a needle having an effective length of about 800 μm, about 850 μm, about 900 μm, about 950 μm, about 1000 μm, about 1100 μm, or about 1200 μm. In some embodiments, a microneedle or syringe is selected based on the viscosity of a pharmaceutical composition (e.g., liquid formulation). In some embodiments, a microneedle is selected based on the pressure resulted in the eye (e.g., in the SCS) when a pharmaceutical composition (e.g., liquid formulation) is administered. For example, a pharmaceutical composition (e.g., liquid formulation) having medium or high viscosity may benefit from the use of a wider microneedle for injection. In some embodiments, the pressure in the SCS is lower when a wider microneedle is used as compared to the pressure obtained when a narrower microneedle is used. In some embodiments, 10 gauge needle, 11 gauge needle, 12 gauge needle, 13 gauge needle, 14 gauge needle, 15 gauge needle, 16 gauge needle, 17 gauge needle, 18 gauge needle, 19 gauge needle, 20 gauge needle, 21 gauge needle, 22 gauge needle, 23 gauge needle, 24 gauge needle, 25 gauge needle, 26 gauge needle, 27 gauge needle, 28 gauge needle, 29 gauge needle, 30 gauge needle, 31 gauge needle, 32 gauge needle, 33 gauge needle, or 34 gauge needle is used. In some embodiments, a 27 gauge needle is used. In some embodiments, a 28 gauge needle is used. In some embodiments, a 29 gauge needle is used. In some embodiments, a 30 gauge needle is used. In some embodiments, a 31 gauge needle is used. In some embodiments, a gauge that is smaller than a 27 gauge needle is used. In some embodiments, a gauge that is larger than a 27 gauge needle is used. In some embodiments, a gauge that is smaller than a 28 gauge needle is used. In some embodiments, a gauge that is smaller than a 30 gauge needle is used. In some embodiments, a gauge that is higher than a 30 gauge needle is used.

[0178] Devices used to carry out the methods described herein comprise any one of the devices disclosed in International Publication No. WO2011139713, International Publication No. WO2014036009, International Publication No. WO2014074823, International Publication No. WO2014179698, International Publication No. WO2015126694, International Publication No. WO2016044404, International Publication No. WO2016040635, International Publication No. WO2017156227, International Publication No. WO2017218613, International Publication No. WO2019053466, International Publication No. WO2019202603, International Publication No. WO2021188803, and US Patent No. 11,273,072 each of which are hereby incorporated by reference in their entireties.

[0179] Subjects to whom such gene therapy is administered can be those responsive to anti-complement therapy. In certain embodiments, the methods encompass treating patients who have been

diagnosed with dry AMD, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-C5 antibody, or considered a good candidate for therapy with an anti-C5 antibody. In specific embodiments, the patients have previously been treated with C5-D-mab, C5-A-mab, C5-C-mab, C5-B-mab or other complement activation inhibitor, and have been found to be responsive to thereto. To determine responsiveness, the anti-C5 transgene product (e.g., produced in cell culture, bioreactors, etc.) may be administered directly to the subject.

[0180] In embodiments, administration of the recombinant AAV comprising a construct for expressing a transgene encoding the C5-D-mab scFv (HL) or C5-A-mab scFv (HL) in ocular tissues results in reduction or slowing the progression of one or more symptoms of dry AMD within 10 days, 20 days, 30 days, 40 days, 6 months, 9 months or 1 year after administration of the AAV. In embodiments, the administration results in a slowing or reduction in the rate of the progression of geographic atrophy, including of the fovea, in the subject relative to an untreated subject or as expected in the subject based upon natural history of dry AMD, for example as measured by fundus autofluorescence (FAF). In embodiments, the administration results in an improvement or reduction in the rate of loss of visual acuity or best corrected visual acuity (BCVA), for example, as measured by a standard ETDRS chart or to improve visual function as measured by dark adaptation methodology; to improve contrast sensitivity by the Pelli-Robson test or to reduce the drusen area or accumulation of drusen. In other embodiments, the dose of therapeutic gene delivered by gene therapy is sufficient to inhibit complement activation without exacerbating choroidal neovascularization (CNV).

[0181] However, in all cases because the transgene product is continuously produced, maintenance of lower concentrations can be effective. Notwithstanding, because the transgene product is continuously produced, maintenance of lower concentrations can be effective. The concentration of the transgene product can be measured in patient blood serum samples.

[0182] Pharmaceutical compositions suitable for subretinal, intravitreal, intranasal, intracameral, suprachoroidal, or systemic (intravenous, intramuscular or subcutaneous) administration comprise a suspension of the recombinant vector comprising the transgene encoding the C5-D-mab scFv (HL) or C5-A-mab scFv (HL) in a formulation buffer comprising a physiologically compatible aqueous buffer. The formulation buffer can comprise one or more of a polysaccharide, a surfactant, polymer, or oil.

[0183] Combinations of delivery of the C5-D-mab scFv (HL) or C5-A-mab scFv (HL), to the eye, liver and/or muscles accompanied by delivery of other available treatments are encompassed by the methods provided herein. The additional treatments may be administered before, concurrently, or subsequent to the gene therapy treatment. Available treatments for a subject with dry AMD that could be combined with the gene therapy provided herein include but are not limited to, elamipretide, risuteganib, photobiomodulation, brimonidine tartrate, kamuvudine, Xiflam, or doxycycline, and others and administration with anti-C5 antibody.

5.6. Monitoring of Efficacy

[0184] The compositions and methods described herein may be assessed for efficacy using any method for assessing efficacy in treating, preventing, or ameliorating dry AMD. The assessment may be determined in animal models or in human subjects. The efficacy on visual deficits may be measured by best corrected visual acuity (BCVA), for example, assessing the increase in numbers of letters or lines and where efficacy may be assessed as an increase in greater than or equal to 2 ETDRS lines or reduction in geographic atrophy, including of the fovea, to be assessed by visual inspection.

[0185] The compositions and methods described herein may be assessed for efficacy using any method for assessing efficacy in treating, preventing, or ameliorating dry AMD. The assessment may be determined in animal models or in human subjects. The efficacy on visual deficits may be measured by best corrected visual acuity (BCVA), for example, assessing the increase in numbers of letters or lines and where efficacy may be assessed as an increase in greater than or equal to 2 ETDRS lines or an increase in logMAR. Physical changes to the eye, including changes in geographic atrophy may be measured Optical Coherence Tomography, using methods known in the art.

[0186] The compositions and methods described herein may be assessed for efficacy using *in vitro* complement inhibition assays, such as membrane attack complex ("MAC") formation, C5a generation and hemolysis. Complement inhibition assays can be performed in any appropriate cell type, such as ARPE19 cells (MAC and C5a assays), iPSC-derived RPE cells (MAC and C5a assays) or sheep/rabbit erythrocytes (hemolysis assay). MAC formation assays measure the deposition of MAC on the surface of RPE cells (% relative inhibition of MAC formation). C5a generation assays measure the ability of the C5 antibody to prevent C5 cleavage (less C5 cleavage = less C5a). Hemolysis assays allow the comparison of complement inhibition among different complement inhibitors (50% complement inhibition dose (ng/ml) (CH_{50}; AH_{50}).

[0187] Animal models may be used to assess the recombinant vectors encoding the C5-D-mab scFv (HL) or C5-A-mab scFv (HL) for expression, therapeutic effect and adverse effects. Animal models may include a humanized C3-/C5- rodent model or a NaIO3 induction rat or mouse model, or a CFH-/- mouse model. Animals may be administered vectors described herein, for example, subretinally or suprachoroidally, and then assessed for geographic atrophy (or change therein) by OCT, retinal pathology (damage to RPE), and other assessments of dry AMD pathology, as well as reduction in C3a or C5a, cleavage of C3 or C5 or other markers of complement activation.

[0188] Endpoints may include, but are not limited to, mean change in geographic atrophy in the study eye from baseline to 12, 16, 20, 24, or 28 weeks or at time of administration, if earlier, proportion of responders in the study eye at 12, 16, 20, 24, or 28 weeks, mean change in best corrected visual acuity from baseline to 12, 16, 20, 24, or 28 weeks, change from baseline in quality of life/patient reported outcome assessments, mean change in visual acuity from baseline to 12, 16, 20, 24, or 28 weeks.

6. EXAMPLES

6.1 EXAMPLE 1: C5-D-mab Fab cDNA-Based Vector

[0189] A C5-D-mab Fab cDNA-based vector was constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of C5-D-mab (amino acid sequences being SEQ ID NOs. 168 and 169, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is the nucleotide sequence of SEQ ID NOs. 205 and 206, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:55). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:118 or 120) to create a bicistronic vector. The vector additionally includes the constitutive promoter CAG (SEQ ID NO: 2). Alternatively, other constitutive promoters, such as mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:5), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 26), or an inducible promoter, such as a hypoxia-inducible promoter, may be used. The artificial genome from the 5' ITR to the 3' ITR is shown in SEQ ID NO: 219.

6.1A EXAMPLE 1A: C5-D-mab scFv cDNA-Based Vector

[0190] A C5-D-mab scFv cDNA-based vector was constructed comprising a transgene comprising nucleotide sequences encoding the heavy and light chain sequences of C5-D-mab scFv and a linker sequence (amino acid sequences for VH-linker-VL and VL-linker-VH being SEQ ID NOs. 195, 196, and 203). The nucleotide sequence coding for the scFv portion of the heavy and light chain is the nucleotide sequence of SEQ ID NO. 224, respectively. Additionally, the transgene comprises a nucleotide sequence encoding a linker sequence (amino acid sequence being SEQ ID NOs: 126, 127, 128, 129, and 130). The transgene also comprises nucleotide sequences that encodes a interleukin 2 signal peptide (SEQ ID NO: 56) (amino acid sequence being MYRMQLLLLIALSLALVTNS (SEQ ID NO:55)).

[0191] The vector additionally includes the constitutive promoter CAG (SEQ ID NO: 2). Alternatively, other constitutive promoters, such as mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:5), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 26), or an inducible promoter, such as a hypoxia-inducible promoter, may be used. The artificial genome from the 5' ITR to the 3' ITR is shown in SEQ ID NO: 225 or 232.

6.2 EXAMPLE 2: C5-A-mab IgG1 Fab cDNA-Based Vector

[0192] An C5-A-mab Fab IgG1 cDNA-based vector was constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of C5-A-mab (amino acid sequences being SEQ ID NOs. 170 and 172, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is the nucleotide sequence of SEQ ID NOs. 207 and 209, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:55). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:118 or 120) to create a bicistronic vector. The vector additionally includes the constitutive promoter CAG (SEQ ID NO: 2). Alternatively, other constitutive promoters, such as mU1a, EF1a, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:5), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 26), or an inducible promoter, such as a hypoxia-inducible promoter, may be used. The sequence of the vector from the 5' ITR to the 3' ITR is shown in SEQ ID NO: 221.

6.3 EXAMPLE 3: C5-A-mab IgG2 Fab cDNA-Based Vector

[0193] An C5-A-mab Fab cDNA-based vector was constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of C5-A-mab (amino acid sequences being SEQ ID NOs. 171 and 172, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is the nucleotide sequence of SEQ ID NOs. 208 and 209, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:55). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:118 or 120) to create a bicistronic vector. The vector additionally includes the constitutive promoter CAG (SEQ ID NO: 2). Alternatively, other constitutive promoters, such as mU1a, EF1a, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:5), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 26), or an inducible promoter, such as a hypoxia-inducible promoter, may be used. The sequence of the vector from the 5' ITR to the 3' ITR is shown in SEQ ID NO: 222.

6.3 EXAMPLE 3A: C5-A-mab scFv cDNA-Based Vector

[0194] A C5-A-mab scFv cDNA-based vector was constructed comprising a transgene comprising nucleotide sequences encoding the heavy and light chain sequences of C5-A-mab scFv and a linker sequence (amino acid sequences for V_H-linker-V_L and V_L-linker-V_H being SEQ ID NOs. 197 and 198, respectively). Additionally, the transgene comprises a nucleotide sequence encoding a linker sequence (amino acid sequence being SEQ ID NOs: 126, 127, 128, 129, and 130). The transgene also comprises nucleotide sequences that encodes a interleukin 2 signal peptide (SEQ ID NO: 56) (amino acid sequence being MYRMQLLLLIALSLALVTNS (SEQ ID NO:55)).

[0195] The vector additionally includes the constitutive promoter CAG (SEQ ID NO: 2). Alternatively, other constitutive promoters, such as mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO: 5), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 26), or an inducible promoter, such as a hypoxia-inducible promoter, may be used. The artificial genome from the 5' ITR to the 3' ITR is shown in SEQ ID NO: 276 and 277.

6.4 EXAMPLE 4: C5-C-mab Fab cDNA-Based Vector

[0196] A C5-C-mab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of C5-C-mab (amino acid sequences may be SEQ ID NOs. 173 and 174, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 210 and 211, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:55). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:118 or 120) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG (SEQ ID NO: 2), mU1a, EF1a, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:5), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 26), or an inducible promoter, such as a hypoxia-inducible promoter.

6.5 EXAMPLE 5: C5-B-mab Fab cDNA-Based Vector

[0197] A C5-B-mab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of C5-B-mab (amino acid sequences being SEQ ID NOs. 175 and 176, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 212 and 213, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:55). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:118 or 120) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG (SEQ ID NO: 2), mU1a, EF1a, a CB or CB long promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:5), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 26), or an inducible promoter, such as a hypoxia-inducible promoter.

6.6 EXAMPLE 6: Expression of C5-A-mab, and C5-D-mab in HEK293 cells

[0198] *Cis* plasmids pITR-CAG-C5-A-mab.IgG1 (SEQ ID NO: 221) or pITR-CAG-C5-D-mab (SEQ ID NO: 219) were transfected into HEK293 cells. Supernatant and pellet samples were collected and run on a non-reducing gel (**FIG. 6A**), with a band representing full length antibodies

observed in the supernatant of the cell culture, or run on a reducing gel **(FIG. 6B)**, indicating heavy and light chains of the antibodies seen in both cell pellet and supernatant.

6.7 EXAMPLE 7: NaIO3 Induction Mouse Model

[0199] A NaIO3 induced model of dry AMD in rodents (inducing RPE damage) will be used to assess the anti-C3, anti-C5 antibodies and CFHL-1 protein AAV constructs. AAV8 constructs, AAV8.CAG.C5-D-mab.Fab (SEQ ID NO: 219), AAV8.CAG.C5-D-mab.full (SEQ ID NO:NO:220) , AAV8.C5-A-mab.Fab.IgG1 (SEQ ID NO: 221), AAV8.C5-A-mab.Fab.IgG2 (SEQ ID NO: 222), and AAV8.C5-A-mab.full (SEQ ID NO: 223) will be administered to humanized C3-/C5- mice at a dose of 1E7, 1E8 or 1E9 subretinally or suprachoroidally. 28 days later, NaIO3 will be administered to the mouse to induce geographic atrophy. One week later, the eyes of the mice will be assessed by fundus and for visual function deficits and then will be sacrificed and eyes assessed for inhibition of RPE damage and photoreceptor loss and for transgene, C3 and C5 levels.

6.8 EXAMPLE 8: Hemolysis Assay

[0200] All C5 inhibitor expression cassettes utilized in this study were constructed with a CAG promoter and rabbit beta-globin polyA. All transgenes were codon-optimized and CpG depleted. Cis-plasmids were initially screened in the assay following transfection in 293T cells and then subsequently packaged as AAV8 viral vectors (including scAAV8 vectors) for further study.

[0201] The classical pathway of complement activation (CP) is initiated primarily by immune complexes. The standard assay for the overall functional activity of this pathway is the CH50. This assay uses sheep erythrocytes coated with rabbit antibodies (referred to as EA) to activate the complement system.

[0202] Such classical complement pathway-related hemolysis inhibition assay was employed using supernatant collected from plasmids (encoding complement inhibitors as described herein) transfected into HEK293T cells. The supernatants (containing the complement inhibitor, or negative controls containing media without inhibitor or containing a vectorized antibody to a non-complement related target) were collected and applied to sheep erythrocytes coated with optimum levels of rabbit anti-sheep erythrocyte IgM antibodies suspended at 5 x 10^8 cells/ml in Gelatin Veronal Buffered saline (GVB++ Buffer) in the wells of an assay plate. Percent hemolysis was compared to a positive test hemolytic solution containing normal human serum that has been titrated up to 50% hemolysis. Percent hemolysis was calculated as such: % hemolysis = (test sample hemolysis (OD405)-

background hemolysis (OD405))/(maximal hemolysis (OD405)-background hemolysis (OD405)) X 100.

[0203] The neat supernatant collected from HEK293 cells transfected with vectorized C5-D-mab or BB5.1 plasmids (different vectorized forms IgG, Fab or ScFv) or a recombinant protein C5 inhibitor were tested in the assay for the % of lysis of the EA as an indication of inhibition of complement activation (**FIGS. 7A-7B**). Purified proteins of C5 inhibitors were tested at series concentrations (nM) to determine the minimum concentration necessary to lyse 50% of the cells (1 CH50 Unit) (**FIGS 8A-8F**). Activation of the classical pathway requires calcium and magnesium ions. The initial reactions include binding of C1 and activation of C2 and C4 to form a C3 convertase. This enzyme cleaves C3 which promotes cleavage of C5 and activation of the membrane attack pathway (proteins C5, C6, C7, C8 and C9). These five components assemble in the membrane of the sheep erythrocyte and lyse the cell. The release of hemoglobin is subsequently quantitated to measure the total complement activity present in the sample.

[0204] C5 inhibitors expressed in HEK293 cells suppress complement pathway activation in hemolysis inhibition assays at varying degrees. The scFv formats displayed strong inhibition of complement (**FIGS. 7A-B**). Recombinant purified forms of each C5 inhibitor displayed potent inhibition of complement activation in classical and alternative hemolysis assays (**FIGS 8A-F**).

6.9 EXAMPLE 9 Binding Kinetics and Affinity of Recombinant purified forms of each C5 inhibitor

[0205] The generated recombinant purified proteins of each C5 inhibitor (expressed in HEK293 cells as above) were compared by their IC50 values in both the classical and alternative complement pathways. The binding kinetics and affinity of each C5 inhibitor to human, cynomolgus macaque, and mouse C5 were measured with the OctetRED384 system, as follows.

a. Affinity and kinetics for **human** Complement C5:

[0206] The assay was performed at 30°C and at 1000 rpm. Biotinylated Human Complement C5 Protein was firstly immobilized onto SA biosensor. C5-D-mab IgG and Ab fragments and Coversin was applied as analyte for association and dissociation steps.

Table 9. Assay conditions for human C5 assay after optimization

Method	Ligand	Ligand Conc. (µg/ml)	Immobil-ization Level (nm)	Analyte	Analyte Conc. (nM)	Association Time	Dissociation Time
SA	Biotinylated Human Complement C5 Protein	2.5	-0.8	C5-D-mab IgG	20, 10, 5, 2.5	100	300
		2.5	-1.2	C5-D-mab-Fab-His6	30, 15, 7.5, 3.75, 1.88	110	300
		2.5	-1.8	C5-D-mab scFv.HL	20, 10, 5, 2.5	90	300
		3	-2.0	Protein C5 inhibitor	200, 100, 50	130	300

b. Affinity and kinetics for cynomolgus Complement C5:

[0207] The assay was performed at 30°C and at 1000 rpm. Biotinylated cyno C5 antigen was firstly immobilized onto SA biosensor. C5-D-mab IgG and Ab fragments and a recombinant C5 inhibitor protein were applied as analyte for association and dissociation steps.

Table 10. Assay conditions for cyno C5 assay after optimization

Method	Ligand	Ligand Conc. (µg/ml)	Immobil-ization Level (nm)	Analyte	Analyte Conc. (nM)	Association Time	Dissociation Time
SA	Biotinylated Cyno Complement C5 Protein	2.5	-0.8	C5-D-mab IgG	20, 10, 5, 2.5	100	600
		2.5	-1.2	C5-D-mab-Fab-His6	30, 15, 7.5, 3.75, 1.88	101	600
		2.5	-1.8	C5-D-mab scFv.HL	20, 10, 5, 2.5, 1.25	120	600
		2.5	-2.0	Protein C5 inhibitor	100, 50, 25, 12.5	100	200

c. Affinity and kinetics for mouse Complement C5:

[0208] The assay was performed at 30°C and at 1000 rpm. Biotinylated mouse C5 antigen was firstly immobilized onto SA biosensor. BB5.1 IgG and Ab fragments were applied as analyte for association and dissociation steps.

Table 11. Assay conditions for mouse C5 assay after optimization (surrogate anti-mouse C5 mAb)

Method	Ligand	Ligand Conc. (µg/ml)	Immobil-ization Level (nm)	Analyte	Analyte Conc. (nM)	Association Time	Dissociation Time
SA	Biotinylated Mouse Complement C5 Protein	1.0	-0.6	BB5.1 IgG	2.5, 1.5, 0.0625, 0.3125	100	600
		2.0	-1.6	BB5.1-Fab-His6	20, 10, 5, 2.5, 1.25	120	180
		2.0	-2.0	BB5.1 scFv.LH	10, 5, 2.5, 1.25	100	180

[0209] The assay was performed at 30°C and at 1000 rpm. Biotinylated mouse C5 antigen was firstly immobilized onto SA biosensor. C5-D-mab IgG and Ab fragments and Coversin were applied as analyte for association and dissociation steps.

Table 12. Assay conditions for mouse C5 assay after optimization (cross-species C5 binders)

Method	Ligand	Ligand Conc. (µg/ml)	Immobil-ization Level (nm)	Analyte	Analyte Conc. (nM)	Association Time	Dissociation Time
SA	Biotinylated Mouse Complement C5 Protein	1.7	-0.6	C5-D-mab IgG	10, 5, 2.5	110	500
		1.7	-1.2	C5-D-mab-Fab-His6	30, 15, 7.5, 3.75, 1.88	102	181
		2.5	-1.2	C5-D-mab scFv.HL	20, 10, 5, 2.5	120	180
		2.5	-3.0	Protein C5 inhibitor	200, 100, 50	100	200

[0210] All three formats of anti-human C5 inhibitor (C5-D-mab) demonstrated KD values for human and cyno C5 in the low to high picomolar range, whereas the C5 inhibitor bound less strongly with a low nanomolar affinity constant. Anti-Mouse (BB5.1) and Anti-human (C5-D-mab) C5 inhibitors with the same vectorized antibody format demonstrated comparable affinity to mouse C5. See **Table 13**.

Table 13

Ligand	Human C5	Cyno C5	Mouse C5
Analyte	**K_D (M)**	**K_D (M)**	**K_D (M)**
Anti-hC5 IgG	3.136E-11	1.310E-11	2.291E-11
Anti-hC5 Fab	4.001E-10	6.023E-11	4.142E-09
Anti-hC5 scFV	2.533E-10	8.454E-11	4.539E-09
Anti-mC5 IgG	N/A	N/A	1.214E-11
Anti-mC5 Fab	N/A	N/A	3.469E-09
Anti-mC5 scFV	N/A	N/A	3.692E-09
recombinant C5 inhibitor (C5I) protein	1.017E-08	5.092E-09	6.278E-09

6.10 EXAMPLE 10: Evaluation of AAV expressed C5 inhibitors in iPSC-derived RPE

[0211] Membrane attack complex (MAC) formation was measured. Briefly, ARPE19 cells or 4-5 weeks old fully matured, polarized iPSC-RPE (iRPE cells, Cellular Dynamics International Catalog, #: R1102) monolayers were used in the studies. ARPE19 or iRPE cells were treated for 24 h with purified recombinant C5 inhibitors in the culture media followed by 48 h with a second treatment of purified recombinant C5 inhibitors in the culture media along with 5% CC-HS (NHS, Complement technology), or 5% CI-HS (heat-inactivated CC-HS). Cells were fixed in 4% paraformaldehyde for 20 min, at RT and immunostained with antibodies or cell stain against C5b-9 (Invitrogen, MA5-28502), ZO-1 (Invitrogen, REF 40220), Phalloidin (AF-568 Phalloidin: Invitrogen A12380) and DAPI.

[0212] C5 inhibitors prevented C5 cleavage and reduced membrane attack complex (MAC) formation (**FIGS. 9A-C**, ARPE19; **FIGS. 9D-9H**, iPSC-derived RPE). iPSC-derived RPE transduced with AAV.anti-hC5 scFV (C5-D-mab scFv) at increasing MOIs demonstrate a dose-dependent increase in transgene product (TP) level in apical and basal compartments (**FIG. 9G**). The TP level (**FIG. 9G**) was consistent with mRNA/cDNA of AAV measured by ddPCR (**FIG. 9H**).

6.11 EXAMPLE 11: Evaluation of AAV expressed C5 inhibitors *in vivo*

[0213] AAV8-encoding C5 inhibitors were injected into wild-type mouse eyes via subretinal (SR) administration at 1E8 and 3E8 vg/eye. Anti-C5 scFV (anti-hC5: C5-D-mab or anti-mC5: BB5.1) delivered via AAV administered subretinally demonstrated a >10-fold higher TP level (**FIG. 10A** = ng/eye; **FIG. 10B** = pmol/eye) than IgG (full-length antibody) and Fab forms and similar levels to purified anti-mC5 IgG delivered intraperitoneal (IP) once per day. While AAV.anti-h5.IgG and AAV.anti-hC5.Fab SR delivery showed similar TP level in the retina and RPE / Choroid / Sclera, AAV.anti-hC5.scFV had higher level of TP in the RPE/Choroid/Sclera suggesting better penetration

of the anti-hC5.scFv to the outer ocular layers (**FIG. 10C** and **FIG. 10D and Table 14**). One-time subretinal delivery of AAV yielded high levels of TP in the mouse eye.

Table 14

Anti-hC5 TP ratio	vg/eye	IgG	Fab	scFv
RPE/Choroid/Sclera : Retina	1E8	3	1	12
	3E8	1	1	16

6.12 EXAMPLE 12: CAG Promoter Studies

[0214] CAG deletion mutants Del5, DelM and Del3 operably linked to a C5-D-mab scFv were made using standard molecular biology techniques. See **FIG. 11**. CAG-Delm has about 60% of the promoter strength as full-length CAG. See **FIG. 12**.

[0215] Either full length CAG or CAGdelm promoters controlling expression of a C5-D-mab scFv were packaged in an AAV8 capsid. The resultant AAV8 particles were used to transduce HEK293T cells at an MOI of 5e4, 1.5e5 or 5e5 and C5-D-mab scFv expression was measured (in ng) on days 1, 2, 3 and 6 post-transduction. See **FIG. 13A-D**. Even though the CAG del promoter has about 60% activity of full-length CAG, when combined with scFV formatted mAb in a condensed scAAV vector the expression levels are increased compared to ssAAV.

6.13 EXAMPLE 13: Investigational Study of AAV Test Articles Following Suprachoroidal Administration in NHP

[0216] The objective of this study is to evaluate the ocular tropism of up to two different adeno-associated virus (AAV) pools/libraries following suprachoroidal administration to female cynomolgus monkeys. See Table 15. Following dosing on Day 1, animals will be observed for 3 to 12 weeks for biodistribution sample collection to investigate the transduction protocol.

Table 15 – Group Assignment and Dose Levels

	Dosing Regimen		Dose Level[a] (GC/eye)	Dose Concentration (GC/mL)	Number of Animals[b]
Group	Left Eye	Right Eye			
1	AAV8.CAG. C5-D-mab-scFv-HL	AAV8.CAG. C5-D-mab-scFv-HL	$3X10^{12}$	$3X10^{13}$	3
2	AAV3B.CAG. C5-D-man-scFv-HL	AAV3B.CAG. C5-D-man-scFv-HL	$3X10^{12}$	$3X10^{13}$	3

GC: Genome copies
a: Dose levels are based on a dose volume of 100 µl/eye
b: Animals in Groups 1 and 2 will be designated as terminal sacrifice animals (based on survival).

Procedures

[0217] Animals will be dosed 100µl/eye via suprachoroidal injection on Day 1 of the dosing phase. The right eye will be dosed first. All post-dose collection times will be based on the time of the dosing of the left eye.

Ophthalmic Examinations

[0218] Ophthalmic examinations will be performed at least twice pre-dose. During the dosing phase, ophthalmic examinations will be performed on days 3, 8, 15, 17, 29, 31, 42, 57, 59, and 85.

[0219] Briefly, animals will be anesthetized with ketamine. Animals will be examined with a slit-lamp biomicroscope and indirect ophthalmoscope. The adnexa and anterior portion of both eyes will be examined using a slit-lamp biomicroscope. The ocular fundus of both eyes will be examined (where visible) using an indirect ophthalmoscope. Prior to examination with the indirect ophthalmoscope, pupils will be dilated with a mydriatic agent (e.g., 1% tropicamide).

Intraocular Pressure Measurements

[0220] Intraocular pressure measurements (IOPs) will be performed in conjunction with ophthalmic examinations (OEs). On days of OEs, intraocular pressure measurements (IOPs) will be conducted on eyes that have been previously dilated. Intraocular pressure measurements will be performed at least twice pre-dose. During the dosing phase, ophthalmic examinations will be performed on days 3, 8, 15, 17, 29, 31, 42, 57, 59, and 85.

[0221] Briefly, animals will be anesthetized with ketamine. The IOP measurements will be done using an applanation tonometer. A topical anesthetic (e.g., 0.5% proparacaine) will be applied before IOP measurements.

Spectral Domain Optical Coherence Tomography

[0222] Spectral domain optical coherence tomography (OCT or sdOCT) will be performed at least once pre-dose. During the dosing phase, OCT will be performed once during weeks 2, 4, 8, and 12.

[0223] Animals will be fasted (for at least 10 hours) before the procedure. Animals will be anesthetized with ketamine and maintained on sevoflurane. Pupils will be dilated with a mydriatic agent. OCT will be performed and the data will be evaluated. Imaging will be done in a manner to obtain axial views of the retinal surface in the posterior fundus. The instruments will be set to perform standard retinal scans (macular volume scans and/or line scans and/or circle scans). Additional

methods or scans may be used. A 55 degree lens may be used, if necessary.

Ocular Photography - Fundus

[0224] Ocular photography will be performed at least once pre-dose. During the dosing phase, ocular photography will be performed once during weeks 2, 4, 8, and 12.

[0225] Animals will be fasted (for at least 10 hours) before the procedure. Animals will be anesthetized with ketamine and dexmedetomidine. Pupils will be dilated with a mydriatic agent. Photographs will be taken with a wide angle lens and a digital fundus camera. Color photographs will be taken of each eye to include stereoscopic photographs of the posterior pole and nonstereoscopic photographs of two midperipheral fields (temporal and nasal); additional images will also be taken superior temporal, if possible.

Fundus Autofluorescent Imaging

[0226] Fundus Autofluorescent Imagining will be performed at least once pre-dose. During the dosing phase, fundus autofluorescent imaging will be performed once during weeks 2, 4, 8, and 12.

[0227] Animals will be fasted (for at least 10 hours) before the procedure. Animals will be anesthetized with ketamine and dexmedetomidine or ketamine and maintained on sevoflurane, as applicable. Pupils will be dilated with a mydriatic agent. Images will be taken with a Heidelberg SPECTRALIS® instrument. Fundus autofluorescence images, to include posterior pole and nonstereoscopic photographs of two midperipheral fields (temporal and nasal, if possible); additional images will also be taken superior temporal, if possible.

Anti-AAV2 and AAV8 Neutralizing Antibody (NAM) Analysis

[0228] Anti-AAV 2 and AAV8 neutralizing antibody analysis will be performed within 5 days of animal transfer pre-dose. During the dosing phase, anti-AAV 2 and AAV8 neutralizing antibody analysis will be performed prior to dosing on day 1 and on each day of scheduled sacrifice.

[0229] 2.4mL of blood will be taken from the femoral vein. An alternate site may be used if necessary, and the site of blood collection will be documented. Blood samples will be held at room temperature and allowed to clot prior to centrifugation. Samples will be centrifuged within 1 hour of collection, and serum will be harvested into two approximately equal aliquots. Following harvesting, samples will be placed on dry ice until stored in a freezer.

Anti-AAV9 Total Antibody (TAB) Analysis

[0230] Anti-AAV9 total antibody analysis will be performed within 5 days of animal transfer pre-dose.

[0231] 2.4mL of blood will be taken from the femoral vein. An alternate site may be used if necessary, and the site of blood collection will be documented. Blood samples will be held at room temperature and allowed to clot prior to centrifugation. Samples will be centrifuged within 1 hour of collection, and serum will be harvested into two approximately equal aliquots. Following harvesting, samples will be placed on dry ice until stored in a freezer.

Peripheral Blood Mononuclear Cell Isolation for ELISPOT

[0232] Peripheral blood mononuclear cells (PBMCs) will be isolated for ELISPOT at least once pre-dose. During the dosing phase, PBMCs will be isolated on days 15, 29, 57, and 85. Briefly, a 3mL blood sample will be collected from the femoral vein. An alternate site may be used if necessary.

Whole Blood Collection

[0233] Whole blood will be collected during the dosing phase on days 3, 8, 15, 29, 57, and 85. Briefly, a blood sample will be collected from the femoral vein. An alternate site may be used if necessary.

[0234] Whole Blood: Blood samples for whole blood collection will be maintained on wet ice or chilled cryo-racks following collection. Whole blood will be harvested and transferred into 3 approximately equal aliquots.

[0235] Serum: Blood samples for serum collection will be held at room temperature and allowed to clot prior to centrifugation. Samples will be centrifuged within 1 hour of collection, and serum will be harvested into 3 approximately equal aliquots. Following harvesting, whole blood and serum samples will be placed on dry ice until stored in a freezer.

Aqueous Humor Collection

[0236] Aqueous humor will be collected once during pre-dose. Aqueous humor will be collected once on days 15, 22, 29, 57 and 85. Briefly, a blood sample will be collected from the femoral vein. An alternate site may be used if necessary.

[0237] Aqueous humor samples from each eye will be placed into separate tubes with Watson barcoded labels, snap frozen in liquid nitrogen, and placed on dry ice until stored in a freezer. Aqueous humor samples will be analyzed for transgene product.

Blood Collection for Clinical Chemistry

[0238] Blood will be collected at least twice during pre-dose. Blood will be collected during the dosing phase on days 8, 15, 29, 57, and 85. Briefly, a blood sample will be collected from the femoral vein. An alternate site may be used if necessary. 1 mL will be collected for hematology, 1.8 mL will be collected for coagulation and 1 mL will be collected for clinical chemistry. Tests are provided in Table 16.

Table 16 – Blood Tests

Hematology	**Coagulation**	**Clinical Chemistry**
red blood cell (erythrocyte) count	prothrombin time	glucose
hemoglobin	fibrinogen	urea nitrogen
hematocrit	activated partial thromboplastin time	creatinine
mean corpuscular volume		total protein
mean corpuscular hemoglobin		albumin
mean corpuscular hemoglobin concentration		globulin
red cell distribution width		albumin:globulin ratio
absolute reticulocyte count		total cholesterol
platelet count		triglycerides
white blood cell (leukocyte) count		total bilirubin
absolute neutrophil count		aspartate aminotransferase
absolute lymphocyte count		alanine aminotransferase
absolute monocyte count		alkaline phosphatase
absolute eosinophil count		gamma glutamyltransferase
absolute basophil count		creatine kinase
absolute large unstained cell count		calcium
blood smear		inorganic phosphorus
		sodium
		potassium
		chloride

Ocular Fluid and Frozen Ocular Tissue Collection for Biodistribution and Transgene Product Analysis

[0239] The following ocular fluid/tissues from the left eye from 2 of 3 animals in Groups 1 and 2, and both eyes from 1 of 3 animals in Groups 1 and 2. Each eye (as applicable) will be enucleated. Immediately following enucleation, a sample of aqueous humor will be collected and divided into two approximately equal aliquots. Vitreous humor and the ocular tissues will then be collected. Vitreous humor will be collected and divided into two approximately equal aliquots. See Table 17.

[0240] The anterior segment of the eye will be removed and the eyes will be divided into four approximately equal quadrants (superior temporal [to include the area of the dose site], superior nasal, inferior temporal, and inferior nasal). Two approximately equal strips (located distal, and proximal to the optic disc) from each quadrant will be collected.

[0241] All other ocular tissues will be collected as single samples (one sample/tube). The tissues will be rinsed with saline and blotted dry, as appropriate. Following collection, samples will be placed in separate tubes and flash-frozen with liquid nitrogen and stored on dry ice (unless immediately stored in a freezer).

[0242] Ocular fluids and tissues will be collected using ultra-clean procedures, according to Labcorp SOPs, in order to minimize the risk for potential contamination. In addition, any work surfaces and non-disposable tools used will be cleaned with DNA Away Surface Decontaminant (Thermo Scientific, Catalog No. 7010 or equivalent) and RNAse decontamination solution (Invitrogen RNaseZap or equivalent) between animals.

Table 17 – Ocular Tissue Collection

Tissue	**Notes**
Aqueous humor	Up to 100 µL/eye, if possible
Vitreous humor	N/A
Choroid – retinal pigment epithelium (RPE)	Four different areas of tissue will be collected at different locations with respect to the optic disc (2 strips/quadrant [8 samples each of choroid-RPE, retina, and sclera for a total of 24 samples/eye])
Cornea	N/A
Iris-ciliary body (ICB)	N/A
Lens	N/A
Optic nerve	N/A
Retina	Four different areas of tissue will be collected at different locations with respect to the optic disc (2 strips/quadrant [8 samples each of choroid-RPE, retina, and sclera for a total of 24 samples/eye]) Filter paper will be used to collect the retina
Sclera	Four different areas of tissue will be collected at different locations with respect to the optic disc (2 strips/quadrant [8 samples each of choroid-RPE, retina, and sclera for a total of 24 samples/eye])

Tissue	Notes
Trabecular meshwork enriched with sclera	N/A
Posterior eye cup	Remaining portion containing the optic disc collected following collection of strips

Frozen Systemic Tissue Collection for Biodistribution and Transgene Product Analysis

[0243] The following tissues (see Table 18) will be collected and frozen for analysis of biodistribution and transgene product analysis.

Table 18 – Tissue Collection

Brain, left hemisphere (optic chiasm, occipital cortex, frontal cortex, hippocampus, cerebellum, lateral geniculate nucleus [LGN], thalamus, hypothalamus, and superior colliculus)
Brain, right hemisphere (optic chiasm, occipital cortex, frontal cortex, hippocampus, cerebellum, LGN, thalamus, hypothalamus, and superior colliculus)
Dorsal root ganglia (cervical, 2 bilateral pairs)
Dorsal root ganglia (lumbar, 2 bilateral pairs)
Dorsal root ganglia (thoracic, 2 bilateral pairs)
Dorsal root ganglia (sacral, 2 bilateral pairs)
Heart (apex)
Heart (ventricle, left)
Heart (ventricle, right)
Heart (atrium, left)
Heart (atrium, right)
Kidney (left)
Lacrimal gland (left; one sample only)
Lacrimal gland (right; one sample only)
Liver (left lateral lobe, proximal to portal vein)
Liver (right lateral lobe, proximal to portal vein)
Lymph node (mandibular, left)
Lymph node (mandibular, right)
Lymph node (parotid, left; one sample only)
Lymph node (parotid, right; one sample only)
Muscle (biceps brachii, left)
Muscle (diaphragm)
Muscle (gastrocnemius, left)
Muscle (quadriceps, left)
Muscle (tibialis anterior, left)
Spleen
Spinal cord (cervical)
Spinal cord (lumbar)
Spinal cord (thoracic)
Spinal cord (sacral)

6.14 EXAMPLES 14A and 14B: $NaIO_3$ Induction Mouse Models

[0244] **A.** A $NaIO_3$ induced model of dry AMD in rodents (sodium iodate-induced retinal degeneration model) was used to assess the anti-mouse C5 (mC5) antibody BB5.1. Recombinant anti-mC5 antibody BB5.1 (group 1) and an irrelevant isotype matched (mouse IgG1) antibody (group 2) were administered to C57BL/6J mice at a dose of 1 mg intraperitoneally (i.p.) daily. Table 19. Mice were evaluated on Day 0 for baseline electroretinography (ERG)/body weights (BW)/OCT, and then each administered a test antibody daily starting at Day 1 to Day 9. On Day 3, $NaIO_3$ was administered to each mouse intravenously to induce an inflammatory event in the eye. Mice were again evaluated for ERG/OCT on Day 6 and on Day 10, then sacrificed on Day 10 for tissue collection. Without being bound by any one theory, the induced inflammation from injection of $NaIO_3$ results in degeneration of the retinal pigment epithelium (RPE) layer of the eye causing RPE loss, and also the thinning of the photoreceptor layer, the outer nuclear layer (ONL) containing mostly photoreceptors. Thickness of the ONL can be visualized by optical coherence tomography (OCT) or immunohistochemical staining of the tissue.

[0245] n = 8 eyes/group were processed for hematoxylin & eosin (H&E) histopathology, n = 8 eyes/group were processed for retinal pigment epithelium (RPE)/choroid flatmount immunohistochemistry (IHC), n = 8 whole globes/group were snap frozen, and n = 8 whole globes were fixed in 4% paraformaldehyde (PFA).

Table 19: NaIO3 Study Design A

Group#	N (mice)	Tx (OU)	x Dose	Tx Volume/ ROA/ Frequency	Induction Agent	Induction Dose/Volume/ Route	In-Life Assessments	Time of Euthanasia/ Tissue Collection
1	16	BB5.1	1 mg/ mouse	100 µL (10.00 mg/mL) recombinant antibody IP QD on Days 1 to 9	$NaIO_3$	20 mg/kg BW 1% BW Volume IV Day 3	• **Full Ocular Exams (OEs):** Baseline • **OCT:** Baseline and Days 6 and 10 • **ERG:** Baseline and Days 6 and 10	Day 10: N=8 eyes/grp: Fixed for H&E N=8 eyes/grp: RPE/choroid flatmounts (DAPI, phalloidin, ZO1) N=8 eyes/grp: Whole globes snap frozen N=8 eyes/grp: Whole globes fixed in 4% PFA
2	16	Isotype Control Antibody (Mouse IgG1)	1 mg/ mouse					

[0246] Antibody product levels were detected in the eye as assessed following i.p. injection of recombinant anti-C5 BB5.1 antibody in Example 13 (FIGS. 10A-10B). In this $NaIO_3$ experiment, intraperitoneal injections of recombinant anti-C5 antibody (BB5.1) were shown to have a protective effect with respect to degeneration of the ONL in eyes of the treated mice. **Figures 14A-14C**. BB5.1 antibody significantly ameliorated ONL and retinal thinning as measured by OCT three days and seven days post $NaIO_3$ induction (day 6 and day 10, respectively). Thus, the increased thickness of the ONL in the presence of the expressed anti-C5 inhibitor as delivered by AAV vector indicates enhanced survival of photoreceptors in the eye.

[0247] ERGs were performed on both eyes using the Diagnosys ERG systems. Animals were dark adapted for a period of at least 12 hours prior to ERG. Under dark adaptation, eyes were dilated using a cocktail of tropicamide HCl 1% and phenylephrine HCl 2.5%. Before ERGs were recorded, pupil dilatation was checked to ensure full dilation. Animals were positioned on the ERG machine, then proparacaine HCl 0.5% and GenTeal were applied to the eyes, followed by the electrode contact and reference leads. Animals were placed on a warm water blanket to control body temperature and contact lens leads were placed on the eyes. A reference subcutaneous lead was placed in the head and a ground lead was placed near the tail of the animal. Light-adapted ERG with 30 cd/m2 background light immediately followed the dark-adapted series. There was a 5 minute light adaptation period

before the light-adapted signals were collected. Background light was used constantly for all light-adapted measurements.

[0248] Dark-adapted ERG:

[0249] Step 1-9: 0.001-10 cd*s/m2 scotopic ERG, each step advancing half log units in light intensity. Both ERG traces and oscillatory potentials were collected.

[0250] Step 10: Dark-adapted 150 cd/m2 scotopic c-wave measurement.

[0251] Light-adapted ERG:

[0252] Step 1-3: 1-10 cd*s/m2 photopic ERG, each step advancing half log units in light intensity. Both ERG traces and oscillatory potentials will be collected.

[0253] Step 4-7: 3.0 c cd*s/m2 photopic ERG flicker ERG at 10-40 Hz, each step advancing 10 Hz.

[0254] Following ERG and OCT procedures, animals received atipamezole (0.1-1 mg/kg SQ) to reverse the xylazine effects and were allowed to recover normally from the procedures.

[0255] During the scotopic a-wave measurements, the a-wave amplitudes of both groups at all timepoints was ~20-50 μV from -3.00 cd*s/m2 to -1.52 cd*s/m2 (Figure 3). At -1.52 cd*s/m2 s, the a-wave amplitude of both groups at baseline increased to ~220-240 μV at 1.00 cd*s/m2; the a-wave amplitude of Group 1 on Day 6 began increasing to a similar amplitude after -1.00 cd*s/m2. At -1.00 cd*s/m2 on Day 6, the a-wave amplitude of Group 2 increased to ~87 μV at 1.00 cd*s/m2. The Day 10 a-wave amplitude in both groups remained generally within the 30-40 μV range at all light intensities.

[0256] The Dark-adapted ERG recordings made at 3 and 7 days after $NaIO_3$ administration compared to baseline recordings showed that IP delivery of BB5.1 significantly improved a- and b-wave amplitudes 3 days following $NaIO_3$ administration, indicative of improved rod function **(FIG. 15A-15F)**. Rods are a type of photoreceptor cell in the retina that are sensitive to light levels and provide vision in low light. Rods are concentrated in the outer areas of the retina and also provide peripheral vision.

[0257] H&E histopathology was performed on n = 8 eyes/group. In general, in group 1, the retinal lesions were multifocal and mild, while in group 2, there were moderate to severe and diffuse. Furthermore, there was severe retinal photoreceptor disruption and diffuse retinal thinning in group 2 eyes, not observed in group 1. Eyes of group 1 were characterized in 3 out of 4 of animals with mild multifocal areas of RPE proliferation with migration into the retina, mild photoreceptor layer thinning,

and retinal outer nuclear layer disorganization. Eyes of group 2 all had moderate to severe and diffuse areas of RPE proliferation with moderate to severe photoreceptor layer disruption, outer nuclear layer disorganization, and diffuse retinal thinning. The observed lesions in group 1 were multifocal and mild, and in group 2, the lesions were diffuse and moderate to severe. Additionally, there was more severe retinal photoreceptor destruction and diffuse retinal thinning in group 2 eyes that was not observed in group 1 eyes.

[0258] **B.** A $NaIO_3$ induced model of dry AMD was then performed to assess AAV vector-expressed anti-C5 antibodies. AAV8.CAG.anti-hC5-D-mab.scFv.HL and AAV8.CAG.anti-mC5-BB5.1.IgG will be administered to C57BL/6J mice at a dose of 3E13 intravenously (IV). Briefly, mice will be evaluated for ERG/body weights (BW)/OCT analogously to the methods in Example 16A, and then each administered a test AAV vector at a dose of 3E13 vg/kg IV (**Table 20**). On Day 28, mice will again be evaluated for OCT/Fundus/ERG and $NaIO_3$ administered to each mouse intravenously on Day 29 to induce an inflammatory event in the eye.

Table 20: $NaIO_3$ Study Design B

Grp#	N	Tx	Tx Dose	Tx volume/ ROA	Induction Agent	Induction Dose/ Volume/Route	In-Life Assess-ments	Time of Euthanasia/ Tissue Collection
1	6	AAV8.CAG.anti-hC5-D-mab.scFv.HL	3E13 vg/kg	100 µl IV Day 0	$NaIO_3$	20 mg/kg BW 1% BW Volume IV Day 29	Body Weight: Day 0, Days 28 ~32 Ocular exam: Days 0, 28, and 32 OCT: Days 0, 28 and 32 ERG: Days 0, 28 and 32 Bleed: Days 14 and 28	Day 32: N=6 eyes/grp: Whole eye snap frozen N=6 eyes/grp: Whole eyes fixed in 4% PFA N=6 livers/grp: Snap frozen
2	6	AAV8.CAG.anti-mC5-BB5.1.IgG	3E13 vg/kg					
3	6	AAV8.null	3E13 vg/kg					

[0259] Several days following administration of $NaIO_3$ (~Day 32), the eyes of the mice will be assessed (OCT imaging, ERG, etc.) and then sacrificed, and the eyes will be further assessed for inhibition of RPE damage and photoreceptor loss and for vector genome (DNA and RNA) and transgene product (TP) levels.

6.15 EXAMPLE 15: Non-human primate (NHP) SCS administration of anti-C5 antibody-expressing vectors

[0260] Two cohorts of three female cynomolgus macaques each were dosed suprachoroidally in the superior temporal quadrant using a custom MedOne transscleral needle with either 1) AAV8.CAG.C5-D-mab.scFv.HL (n=5 eyes dosed at 3e12 GC/eye in 100uL; both eyes of two animals were dosed, while the right eye of the third animal was dosed and the left eye of this animal was not dosed and was used as a negative control), or 2) AAV3B.CAG. C5-D-mab.scFv.HL (n=5 eyes dosed at 3e12 GC/eye in 100uL, n=1 eye dosed at ~2e12 GC/eye in 70uL) (**Table 21**). Animals dosed with AAV8 were anti-AAV8 neutralizing antibody (Nab) and total antibody (Tab) negative, and animals dosed with AAV3B were anti-AAV3B Tab negative. Ophthalmic exams, fundus photography, optical coherence tomography, and fundus autofluorescence imaging were performed and intraocular pressure measurements and aqueous humor taps were also collected at regular intervals, and animals were euthanized on study day 85.

Table 21: Study Design

Metric	Study design
Test article	N=3 animals/6 eyes each for AAV8.CAG.C5-D-mab.scFv or AAV3B.CAG.C5-D-mab.scFv
NAb/TAb status	Performed for group assignment
Device	MedOne SCS needle
Study length	3 month in-life
Dose	3e12 GC/eye
In-life monitoring	Ophthalmic exams, IOP, OCT, fundus photography, FAF
Necropsy	Extensive frozen ocular (n=4/group), CNS, and peripheral collection; fixed eyes (n=2/group); serum/whole blood/PBMCs
Analysis	DNA/RNA BD, protein quantification and function (ELISA, hemolysis, mass spec), H&E staining to assess inflammation/infiltration

[0261] Two eyes administered AAV8, two eyes administered AAV3B, and one untreated eye were fixed and processed for histopathological analysis, with tissues from the remaining eyes collected frozen for DNA/RNA biodistribution and transgene product analysis. These tissues included: vitreous humor, retina, RPE/choroid, sclera, trabecular meshwork, iris/ciliary body, cornea, lens, and optic nerve. The posterior segment was dissected by cutting the posterior eye cup into quadrants and collecting a distal and a proximal strip from each quadrant. Each strip was then separated into retina, RPE/choroid, and sclera for analysis. The distal samples and the proximal samples from the temporal quadrants were each pooled (sample 3 and 4, respectively) for transgene product analysis (by ELISA), in addition to sample 5, which contained the macula. Nasal samples were taken for biodistribution, and both DNA and RNA were extracted from each sample. Peripheral tissues, including liver, heart, kidney, and spleen, from each animal were also collected frozen for biodistribution. Serum was also collected throughout the study to assess transgene product levels and anti-transgene product antibodies (ATPA).

[0262] AAV8 anti-C5-ScFv Vector results: Vector genome copy levels were assessed by ddPCR using primer/probes against polyA; for retina, RPE/choroid, and sclera, each data point represents a single sample from a single tissue sample from a single animal; for the other ocular tissues, each data point represents the singular extraction from that tissue. Vector genome copy levels ranged from ~1e2-1e7 GC/µg DNA (**FIG. 16A**). In the posterior segment, vector genome copies were highest in the sclera, followed by RPE/choroid, followed by retina, as is typical of delivery of AAV to the SCS. Vector DNA was also detected in a number of other ocular tissues, which did not always result in detectable RNA expression. RNA expression in retina and RPE/choroid were similar (**FIG. 16B**). Biodistribution in the left eye of animal 1 was determined to be profoundly lower than expected. Vector genome biodistribution was also evaluated in peripheral tissues, with vector genomes detected in the spleen of all 3 AAV8-dosed animals, in the liver of 2 of the 3 animals, and in the kidney of 1 of the 3 animals (**FIG. 16C**).

[0263] With the exception of an animal which established low vector transduction based on biodistribution data, anti-C5-scFv was detected in aqueous humor from all treated eyes throughout the course of the study (**FIGS. 17A and 17B**). The expression was largely stable, averaging 0.68ug anti-C5-scFv in AH at D29, with the exception of the right eye of animal 1, which rose throughout the course of the study (**FIG. 17C**). Excluding animal 1 left eye (low vector levels), anti-C5-scFv levels in the day 85 vitreous humor (VH) averaged 1.2 µg/mL (**FIG. 18A and 18B**). anti-C5-scFv was also

detected in the retina, RPE/choroid, and sclera of animals 2 and 3, with the greatest transgene product levels detected in RPE/choroid, achieving up to 6ng anti-C5-scFv/mg tissue (**FIGS. 19A-H**). Transgene product (TP) levels correlated with vector genome levels in retina and RPE/choroid, but did not in sclera. Minimal anti-C5-scFv was detected in the serum of animal 3 at any timepoint; serum aC5-scFv increased over time in both animals 1 and 2, decreasing by day 85, which correlated well with the degree of liver biodistribution in those animals (**FIGS. 20A-20C**).

[0264] Ophthalmic examination found that AAV8.CAG.aC5-scFv was well-tolerated in this study, with a single eye from a single animal presenting with mild (0.5+) vitreous cell on D29. No treatment-related changes in intraocular pressure were noted, and OCT assessments also found no treatment-related changes in ocular structure throughout the study. Histopathology analysis found slight inflammation in the sclera of 1/2 eyes that was determined to be related to the test article. All other histopathological findings were considered spontaneous, and no findings were considered adverse as there was no evidence of retinal degeneration nor clinical findings impacting ocular function.

[0265] AAV3B-anti-C5-scFv Vector results: Vector genome copy levels ranged from ~1e2-1e6 GC/µg DNA (based on ddPCR using primer/probes against polyA; for retina, RPE/choroid, and sclera, each data point represents a single sample from a single strip from a single animal; for the other ocular tissues, each data point represents the singular extraction from that tissue) (**FIGS. 21A-21C**). In the posterior segment, vector genome copies were highest in the sclera, followed by RPE/choroid, followed by retina, as is typical of delivery of AAV to the SCS. Vector genome levels in the posterior segment of P0102-OS were suggestive of poor transduction; transgene product data are presented +/- the datapoints from this eye. Vector DNA was also detected in a number of other ocular tissues. RNA expression was highest in retina and RPE/choroid, where transcript copies were similar, followed by iris/ciliary body and trabecular meshwork. Vector genomes were detected in the spleen of all 3 AAV3B-dosed animals, and biodistribution in heart, kidney, and liver was considered undetectable, as no datapoints gave signal >5-fold above background.

[0266] With the exception of P0102-OS (established low vector transduction based on biodistribution data), anti-C5-scFv was detected in aqueous humor from all treated eyes through study day 29 (**FIGS. 22A-22B**), averaging 1.5 µg aC5-scFv/mL AH. After D29, anti-C5-scFv levels continued to rise in 3/5 eyes, while levels in the AH of both eyes from P0101 dropped to undetectable levels, correlating with the development of ATPA (**FIG. 22C**). Excluding the one eye with poor

transduction and the other from the animal that developed ATPA, anti-C5-scFv levels in the D85 vitreous humor averaged 16.5 µg/mL (**FIGS. 23A-23B**). Excluding the one eye with poor transduction and the other from the animal that developed ATPA, aC5-scFv was detected in the retina, RPE/choroid, and sclera of the remaining treated eyes, with the greatest transgene product levels detected in RPE/choroid, achieving up to 225ng aC5-scFv/mg tissue (**FIGS. 24A-24H**). Transgene product levels correlated with vector genome levels in retina and RPE/choroid but did not in sclera. Minimal to no anti-C5-scFv was detected in the serum all three animals at any timepoint; low levels of detected anti-C5-scFv in the serum at D85 correlated well with the degree of liver biodistribution in those animals (**FIGS 25A-25C**). One of three animals (P0101) developed ATPA, first detected at D57, that correlated with a reduction in detectable anti-C5-scFv levels in AH, VH, and ocular tissues at D85.

[0267] Ophthalmic exams and ocular imaging found that AAV3B.CAG.anti-C5-D-mab.scFv was initially well-tolerated up to D57/week 8, when the retinas in both eyes of P0101 and P0103 were noted to present with a mottled appearance. Both eyes of P0101 presented with perivascular sheathing on D57 that lessened in intensity by D85 as well as minimal or slight vitreous cell on D57/D85, correlating with the development of ATPA. No treatment-related changes in intraocular pressure were noted. Histopathology analysis established the presence of choroidal infiltrates in P0101-OD and P0103-OD, as well as inflammation in the sclera of P0101-OD, which was considered test article related. All other histopathological findings were considered spontaneous, and no findings were considered adverse as there was no evidence of retinal degeneration nor clinical findings impacting ocular function.

6.16 EXAMPLE 16: NHP Subretinal administration

[0268] Four cynomolgus macaques each were dosed subretinally (SR) with AAV8.CAG.C5-D-mab.scFv.HL or vehicle (n=1 eye dosed with vehicle; n-3 eyes dosed at 1e10 GC/eye; n=4 eyes dosed at 1e11 GC/eye). One animal developed a cataract due to injection procedure (not TA related) and that animal was replaced. Several animals were also dosed with an AAV8 vector expressing a non-specific (NS) scFv using the same scFv framework.

[0269] Four punches of posterior ocular tissues were taken and the single punch with highest biodistribution (BD) is plotted (assumed dose site). Vector DNA was measured in ocular tissues 4 weeks-post SR injection. Similar results for vector transduction were seen in anti-C5 versus non-specific scFv (**FIG. 26**). Poor transduction of sclera tissue was anticipated and confirmed.

[0270] Aqueous humor (AH) was collected at day 15 and day 29 (two weeks and four weeks post-dose, respectively). TP (ScFv levels) were measured via ELISA using antigen-coated plates (coated with C5) and detecting TP with Protein-L HRP subset of values were confirmed by bioanalytical measurement by mass spectrometry demonstrating "free" and "total" TP levels are similar. TP expression is variable, but mostly dose-dependent for both scFvs (**FIGS. 27A-27B**). Two animals (non-specific scFV group) had detectable ATPA in serum, but still demonstrated increase in TP from D15 to D29. No ATPA was detected in anti-C5 treated animals.

[0271] TP expression was measured via ELISA in Vitreous humor (VH) using antigen-coated plates (C5) and detecting TP with Protein-L HRP (**FIGS. 28A-28B**). A subset of values were confirmed as before with mass spectrometry demonstrating "free" and "total" TP levels similar. TP expression is variable, but dose-dependent for both scFvs. Two animals (non-specific scFV group) had detectable ATPA in serum, but had TP expression within range of other samples, and no ATPA was detected in the anti-C5 treated animals. Vectorized scFv expression data was compared to a non-specific vectorized IgG (full-length) antibody. Note that the IgG data resulted from a different study and used different assays to measure the non-specific (non-C5) TP. However, the study plan was nearly identical and performed at the same research laboratory (**FIGS. 29A-29B**). Vectorized scFvs were more highly expressed in AH than the vectorized IgG format in this model. IgG was poorly tolerated at doses higher than 1E10, therefore a limited amount of data to compare expression at equivalent doses except the more highly expressed scFv 1E10 dose.

[0272] TP expression was also measured various ocular tissues. The four punches of tissues after vector biodistribution (DNA & RNA) were analyzed and the remaining posterior tissues from these eyes were separated into three tissue layers and homogenized for TP expression. TP was measured using same ELISA method as for AH and VH. Subretinal delivery of AAV-anti-C5-scFv vectors results in high anti-C5 scFv (TP) expression in retina, RPE-choroid, and sclera (**FIGS. 30A-30B**).

6.17 EXAMPLE 17: One-Month Evaluation of Expression of Formulated AAV Vectors Administered Suprachoroidally in Yucatan Minipigs

[0273] This example relates to the evaluation of biodistribution and expression of an AAV transgene product from different formulations of AAV vector carrying the transgene (*e.g.*, AAV.ScFvAntibody) in animals (*e.g.*, minipigs, such as Yucatan minipig) after a single suprachoroidal

injection. In brief, three (3) pigs receive each test article formulation via bilateral suprachoroidal injection using a 29-gauge needle approximately 1110 μm in length (performed once).

Table 22: Experimental Design

Group	n	Treatment (OU[#])			In-life assessments	Tissue collection
		Test article	Dose (GC/eye)	RoA/Vol/ Frequency		
1	1	Vehicle 1	n/a	SCS 100 μL Once on Day 1	Ocular Examinations: Baseline and Days 3, 8, 15, D17 & 29 OCT/BAF/IR/ Fundoscopy: Immediately post-dose, Day 15, & at termination AH Collection: Pre-dose and Day 15 (Grps 1-5) Blood Collection (for Plasma, Serum, & Whole Blood)*: Approximately 2 weeks pre-dose (serum only), pre-dose day of dosing, 0.5h, 1h, 2h, 4h, 24h, 48h, 72h, 120hr post-dose, Day 8, Day 15, & at termination	Day 29 or 30 (Grps 1-5): •Blood collected for plasma, serum, & whole blood, & animal exsanguinated • 1 eye/grp (Grps 1-5): Eye enucleated, AH retrieved, & globe fixed in Davidson's solution for histology • Remaining eye/grp (Grps 1-5): Eyes enucleated, AH retrieved, & globe snap frozen for dissections • Systemic tissues collected & snap frozen: *e.g.* brain, DRGs, spinal cord, heart, lung, liver, kidney, spleen, gonads, quadriceps • Tissues Collected from Snap Frozen Eyes: Globe quartered (superonasal, superotemporal, inferonasal, inferotemporal regions) and each quarter divided into
2	1	Vehicle 2	n/a			
3	3	Formulation 1	3.00E+12			
4	3	Formulation 2 + 0.7%HA)	3.00E+12			
5	3	Formulation 1	3.00E+11			

Group	n	Treatment (OU#)			In-life assessments	Tissue collection
		Test article	Dose (GC/eye)	RoA/Vol/ Frequency		2 "strips", with each strip dissected into retina, RPE/choroid, & sclera; optic nerve, ICB, VH, cornea, & lens also collected per eye

#- OU = Oculus Uterque (both eyes)

*- allowable time windows for timed collations are as follows: < 10 minutes, no window; 11-59 minutes, ± 1 minute; 1-6 hours, ± 5 minutes; 7-24 hours, ± 10 minutes; 24 hours or greater (Example: 48 or 72 hour), ± 15 minutes. Timepoints indicated as 'days' will occur during the day indicated

[0274] Test articles 3-5 were provided as follows:

[0275] Test article 3: AAV8.CAG.C5-D-mab.scFv.HL provided as a pre-formulated solution at a concentration of $3x10^{13}$ GC/mL (Frozen (-80°C)) in the following: 0.2 mg/mL potassium chloride, 0.2 mg/mL potassium phosphate monobasic, 5.84 mg/mL sodium chloride, 1.15 mg/mL sodium phosphate dibasic anhydrous, 40.0 mg/mL (4% w/v) sucrose, and 0.001% (0.01 mg/mL) poloxamer 188 (Formulation 1).

[0276] Test article 4: AAV8.CAG.C5-D-mab.scFv.HL provided as a pre-formulated solution at a concentration of $3x10^{13}$ GC/mL (Frozen (-80°C)) in the following: 0.2 mg/mL potassium chloride, 0.2 mg/mL potassium phosphate monobasic, 5.84 mg/mL sodium chloride, 1.15 mg/mL sodium phosphate dibasic anhydrous, 25.0 mg/mL (2.5% w/v) sucrose, 0.002% (0.02 mg/mL) poloxamer 188 and 0.7% hyaluronic acid (Formulation 2 + HA).

[0277] Test article 5: AAV8.CAG.C5-D-mab.scFv.HL provided as a pre-formulated solution at a concentration of $3x10^{12}$ GC/mL (Frozen (-80°C)) in the following: 0.2 mg/mL potassium chloride, 0.2 mg/mL potassium phosphate monobasic, 5.84 mg/mL sodium chloride, 1.15 mg/mL sodium phosphate dibasic anhydrous, 40.0 mg/mL (4% w/v) sucrose, and 0.001% (0.01 mg/mL) poloxamer 188 (Formulation 1).

Table 23:

Ingredient	Function	Quality Standard	Formulation 1 (4% Sucrose)		Formulation 2 (2.5% Sucrose)		Formulation 2 +HA	
			Concen-tration (mg/mL)	Concen-tration (mM) rounded to 3 s.f.	Concen-tration (mg/mL)	Concen-tration (mM) rounded to 3 s.f.	Concen-tration (mg/mL)	Concen-tration (mM) rounded to 3 s.f.
AAV8.CAG.C5-D-mab.scFv.HL	AAV vector delivery of ScFv transgene	Internal	Varies based on dose level	-	Varies based on dose level	-	Varies based on dose level	-
Sodium Chloride	Buffering Agent	USP, Ph.Eur, BP, JPE	5.8440	100	5.8440	100	5.8440	100
Potassium Chloride		USP, BP, Ph.Eur, JPE	0.20130	2.70	0.20130	2.70	0.20130	2.70
Sodium Phosphate Dibasic Anhydrous		USP, Ph.Eur, JPE	1.1500	8.10	1.1500	8.10	1.1500	8.10
Potassium Phosphate Monobasic		NF, BP, Ph.Eur	0.20000	1.47	0.20000	1.47	0.20000	1.47
Sucrose	Cryoprotectant	USP, NF, Ph.Eur, BP, JPE	40.000 (4% w/v)	117	25.000 (2.5% w/v)	73.0	25.000 (2.5% w/v)	73.0
Poloxamer 188	Surfactant	NF, Ph.Eur, JPE	0.010000 (0.001% w/v)	0.001	0.020000 (0.002% w/v)	0.002	0.020000 (0.002% w/v)	0.002
Hyaluronic Acid	Viscosity modifier	NF, Ph.Eur, JPE	-	-	-	-	0.7% w/v (or 0.5% w/v to about 1.0 % w/v)	
Water	Aqueous Vehicle	WFI	Approximately 971 mg/mL	Approximately 54 M	Approximately 981 mg/mL	Approximately 54 M	Approximately 981 mg/mL	Approximately 54 M

[0278] Suprachoroidal Dosing (Day 1): Animals will be fasted the night prior to dosing. Approximately fifteen (15) minutes prior to anesthesia, 1.0% tropicamide HCl will be applied topically to the ocular surface to induce mydriasis and atropine (0.05 mg/kg) IM or glycopyrrolate (0.01 mg/kg) IM will be administered to reduce risk of aspiration while under sedation. Animals will receive a single dose of buprenorphine (0.01-0.05 mg/kg) IM as an analgesic, and animals will be anesthetized per IACUC. The area around both eyes, including the eyelid, will be cleaned and sterilized, including the ocular surface. Animals will then be positioned beneath a surgical microscope with the first eye

upwards, and a surgical drape and eyelid speculum will be placed. The test article will be administered by suprachoroidal injection over 5-10 seconds using a Sponsor provided 29-gauge needle approximately 1100 μm in length, delivered to the supra-temporal quadrant 4-mm from the limbus between 10 and 11 o'clock in the right eye and between 1 and 2 o'clock in the left eye. Following the injection, the needle will be kept in the eye for approximately 5 seconds before being withdrawn. Upon withdrawal of the needle, a cotton-tipped applicator will be placed over the injection site for approximately 10 seconds. A topical drop of antibiotic ophthalmic solution will be applied to the ocular surface. Following dosing, animals will undergo post-dose OCT (to examine injection site as well as nasal-temporal area near injection site) and fundus imaging. Animals will be weighed prior to the start of dosing, weekly, and at the time of euthanasia. Ocular Examinations (OEs), Optical Coherence Tomography (OCT), Color Fundus Imaging, Blood Collections (for Serum, Plasma, & Whole Blood), and Tissue Collections will take place as per the experimental design.

[0279] **Example 18: Affinity Assays**

[0280] Affinity assays will be performed on anti-hC5-scFv01 demonstrate the species-specific affinity for human C5, mouse C5 and cynomolgus macaque C5.

[0281] Additionally, the study will examine specificity of anti-hC5-scFv01 action for human C5 and not other components of human complement pathway, i.e., human C6, C7, C1q, C3, C4, C5 des-arg, Factor B, and Factor H.

[0282] Bio-layer interferometry (BLI) is an optical technique that analyzes the interference pattern of white light reflected from two surfaces: a layer of immobilized protein on the biosensor tip and an internal reference layer. Any change in the number of molecules bound to the biosensor tip causes a shift in the interference pattern.

[0283] BLI will be used to examine the affinity of anti-hC5-scFv01 to various antigens. Briefly, the biosensor tip will be contacted to biotinylated antigen. Next, the biosensor tip will be contacted to anti-hC5-scFv01. Association of the ligand to the antigen will be measured.

[0284] Octet machine (Sartorious, Model: RED384), as supported by BLI technology was used to measure KD values between ligands (C5 proteins) and analytes (Anti-hC5-scFv01). Recombinant C5 proteins from all species were produced using CHO cell expression platforms. C5 proteins, as ligands for the assay, were biotinylated and loaded onto streptavidin sensors. The association and dissociation rates of C5:scFv01 complex were measured by Octet, and KD values were calculated.

[0285] Anti-hC5-scFv01 showed a strong binding affinity to all recombinant C5 proteins with KD values of ~200 pM to human C5 protein, of 92 pM to cynomolgus C5 protein, and of ~15 nM to mouse C5 protein. Anti-hC5-scFv01 shows a strong binding affinity in vitro towards the target protein, human C5. In addition, anti-hC5-scFv01 binds to C5 proteins from other species, albeit with slightly higher affinity to cynomolgus C5, and substantially lower affinity to mouse C5, demonstrating the suitability of anti-hC5-scFv01 for use as a C5 inhibitor in studies of mouse and non-human primate animal models.

Table 24:

Study	Ligand	Antigen	Data Output
Species cross reactivity assay (OCTET)	Anti-hC5-scFv01	Human C5, Mouse C5, Cynomolgus macaque C5	Affinity for mouse, human and cynomolgus macaque C5
Pathway Specificity	Anti-hC5-scFv01	Human: C6, C7, C1q, C3, C4, C5 des-arg, Factor B, Factor H	Affinity for off-target components of the Complement Pathway

Example 19A: Inhibition of complement Sheep RBC hemolysis assay

[0286] The classical pathway of complement activation (CP) is initiated primarily by immune complexes. The standard assay for the overall functional activity of this pathway is the CH50. This assay uses sheep erythrocytes coated with rabbit antibodies (referred to as EA) to activate the complement system.

[0287] Such classical complement pathway-related hemolysis inhibition assay will be employed using supernatant collected from HEK cells transfected with the plasmids (encoding complement inhibitors as described herein). The supernatants (containing the complement inhibitor, or negative controls containing media without inhibitor or containing an antibody or antigen binding fragment expressed from the plasmid to a non-complement related target) will be collected and applied to sheep erythrocytes coated with optimum levels of rabbit anti-sheep erythrocyte IgM antibodies suspended at 5 x 10^8 cells/ml in Gelatin Veronal Buffered saline (GVB++ Buffer) in the wells of an assay plate. Percent hemolysis will be compared to a positive test hemolytic solution containing normal human serum that has been titrated up to 50% hemolysis. Percent hemolysis is calculated as:

% hemolysis = (test sample hemolysis (OD405)-background hemolysis (OD405))/(maximal hemolysis (OD405)-background hemolysis (OD405)) X 100.

Table 25:

Study	Material	Test System	Data Expected
Hemolysis Assay	Anti-hC5-scFv01	Hemolysis sensitized sheep erythrocytes, human serum induced hemolysis	EC50 and EC10 for purified anti-hC5-scFv
Hemolysis Assay	VH, AH, Serum from NHPs treated with AV for anti-hC5-scFv01	Hemolysis sensitized sheep erythrocytes, human serum induced hemolysis	Proof of bioactivity of endogenous anti-hC5-scFv01

Example 19B: Inhibition of Complement activation PKPD human iRPE cells

[0288] Membrane attack complex (MAC) formation will be measured. Briefly, 4-5 weeks old fully matured, polarized iPSC-RPE (iRPE cells, Cellular Dynamics International Catalog, #: R1102) monolayers will be used in the studies. iRPE cells are transduced with AAV vectors (anti-C5-scFv01 transgene) at various doses in the culture media followed by a treatment of purified recombinant C5 inhibitors in the culture media along with 5% CC-HS (NHS, Complement technology), or 5% CI-HS (heat-inactivated CC-HS). Cells will be fixed in 4% paraformaldehyde for 20 min, at RT and immunostained with antibodies or cell stain against C5b-9 (Invitrogen, MA5-28502), ZO-1 (Invitrogen, REF 40220), Phalloidin (AF-568 Phalloidin: Invitrogen A12380) and DAPI.

Example 20: In Vivo Mouse IV and/or Transgenic PD study

[0289] A NaIO3 induced model of dry AMD in rodents (sodium iodate-induced retinal degeneration model) will be used to assess the modified AAV anti-hC5-scFv01 (also called C5-D-mab scFv (HL) (SEQ ID NO: 203)). Recombinant modified AAV anti-hC5-scFv01 vectors (groups 2-4 and 6) will be administered to C57BL/6J mice at a according to Table 3. Mice will be evaluated on Day 0 for baseline electroretinography (ERG)/body weights (BW)/OCT, and then each administered a test antibody at Day 0. On Day 0, NaIO3 will be administered to each mouse intravenously to induce an inflammatory event in the eye. Mice will again be evaluated for ERG/OCT on Day 32 and on Day 36, respectively, then sacrificed on Day 36 for tissue collection. Without being bound by any one theory, the induced inflammation from injection of NaIO3 results in degeneration of the retinal pigment epithelium (RPE) layer of the eye causing RPE loss, and also the thinning of the photoreceptor layer, the outer nuclear layer (ONL) containing mostly photoreceptors. Thickness of the ONL will be visualized by optical coherence tomography (OCT) or immunohistochemical staining of the tissue.

Table 26:

Grp #	N	Tx	Tx Dose	Tx volume / ROA	Induction Agent	Induction Dose	In-Life Assessments	Sample Analysis
1	10	AAV8 anti-hC5-scFv01 Positive Control	3E13 vg/kg	~100 µl IV Day 0	$NaIO_3$ IV Day 0	20 mg/kg BW	**OCT**: Baseline and Day 36 **ERG**: Baseline and Day 32 **Serum**: Baseline, Days 29, 35 **Necropsy**: Day 36	1 eye: TP levels (whole or dissected TBD) 1 eye: histopath D35 Blood/Serum:TP levels + hemolysis D29 Blood: Biodistribution
2	10	modAAV 8-anti-hC5-scFv01	Low dose vg/kg					
3	10	modAAV 8-anti-hC5-scFv01	Mid Dose vg/kg					
4	10	modAAV 8-anti-hC5-scFv01	High Dose vg/kg					
5	10	Vehicle (Negative Control)	NA					
6	10	modAAV 8-anti-hC5-scFv01	Mid or High Dose vg/kg		Saline	None		

[0290] Antibody product levels will be detected in the eye as assessed following i.p. injection of recombinant modified AAV anti-hC5-scFv01 vectors.

[0291] ERGs will be performed on both eyes using the Diagnosys ERG systems. Animals will be dark adapted for a period of at least 12 hours prior to ERG. Under dark adaptation, eyes will be dilated using a cocktail of tropicamide HCl 1% and phenylephrine HCl 2.5%. Before ERGs were recorded, pupil dilatation will be checked to ensure full dilation. Animals will be positioned on the ERG machine, then proparacaine HCl 0.5% and GenTeal will be applied to the eyes, followed by the electrode contact and reference leads. Animals will be placed on a warm water blanket to control body temperature and contact lens leads will be placed on the eyes. A reference subcutaneous lead will be placed in the head and a ground lead was placed near the tail of the animal. Light-adapted ERG with 30 cd/m2 background light will immediately follow the dark-adapted series. There will be a 5 minute

light adaptation period before the light-adapted signals will be collected. Background light will be used constantly for all light-adapted measurements.

[0292] Dark-adapted ERG:

[0293] Step 1-9: 0.001-10 cd*s/m2 scotopic ERG, each step advancing half log units in light intensity. Both ERG traces and oscillatory potentials will be collected.

[0294] Step 10: Dark-adapted 150 cd/m2 scotopic c-wave measurement.

[0295] Light-adapted ERG:

[0296] Step 1-3: 1-10 cd*s/m2 photopic ERG, each step advancing half log units in light intensity. Both ERG traces and oscillatory potentials will be collected.

[0297] Step 4-7: 3.0 c cd*s/m2 photopic ERG flicker ERG at 10-40 Hz, each step advancing 10 Hz.

[0298] Following ERG and OCT procedures, animals will receive atipamezole (0.1-1 mg/kg SQ) to reverse the xylazine effects and will be allowed to recover normally from the procedures.

[0299] H&E histopathology will be performed on n = 8 eyes/group.

Example 21: NHP Pilot Tolerability and Dose range finding

[0300] NHP will be administered AAV vectored anti-hC5-scFv01 (groups 2 and 3) or vehicle control according to Table 4.

Table 27:

Gp	Animal No. (Gender)	Treatment	Dose (gc/eye)	Route and Volume (µl)	Duration (months)
1	1 (M or F)	Vehicle	TBD	100 µl OU	1
2	2 (M or F)	AAV vectored anti-hC5-scFv01	1e11	100 µl OU	1
3	3 (M or F)	AAV vectored anti-hC5-scFv01	1e12	SCS 100 µl OU	1

[0301] The following endpoints will be examined: 1) Daily health checks, 2) Weekly clinical observations, 3) Weekly body weights, 4) Ophthalmic exams and IOP: Predose, Days 3, 8, 15, 17, 22, and at necropsy (Day 29), 5) OCT and Color fundus: Pre-dose and during week 4, 6) Aqueous Humor collection: Predose, Days 15, and at necropsy (Day 29), and 7) Blood Collection (TAB): Predose and at necropsy.

[0302] At termination, the following endpoints will be examined: 1) Biofluids: Blood (MOV), AH, VH, 2) Tissue collections for biodistribution (BioD) (Collected and analyzed): Eye (lens , iris-ciliary body, cornea, RPE, Choroid, Retina, Sclera [15 samples per eye]), Optic nerve, Ovary/teste,

liver, heart, 3) BioD Collections collected and stored: Adrenal Gland, Brain (3 samples), Cerebellum, DRG (2 pairs from 4 regions), Kidney, Lung, Lymph nodes (2), spleen, 4) VCN (biodistribution), 5) mRNA Transgene, 6) TP, 7) C5 and other complement factors, and 8) VH for activity assay.

Example 22: NHP Pilot Tolerability and Dose range finding

[0303] NHP will be administered AAV vectored anti-hC5-scFV (group 2) or vehicle control according to Table 30.

Table 28:

Gp	Animal No. (Gender)	Treatment	Dose (gc/eye)	Route and Volume (µl)	Duration (months)
1	1 (M or F)	Vehicle	TBD	100 µl OU	1
2	3 (M or F)	AAV vectored anti-hC5-scFv01	1e12	SCS 100 µl OU	1

[0304] The following endpoints will be examined: 1) Daily health checks, 2) Weekly clinical observations, 3) Weekly body weights, 4) Ophthalmic exams and IOP: Predose, Days 3, 8, 15, 17, 22, and at necropsy (Day 29), 5) OCT: Pre-dose and during week 4, 6) Fundus autofluorescence Imaging: Predose and during week 4, 7) Aqueous Humor collection: Predose, Day 15, and at necropsy, 8) Clin Path (HCC): Predose, Days 8, and at necropsy, 9) Tab: Predose and at necropsy, 10) Complement Analysis: Predose, Day 1 (1, 6 and 24 hrs post dose), Days 3, 8, 15, 22, and 29 (analytes: C3a, C4a, sC5b-9, Complement Bb), 11) PK Serum (TP): Predose, 24hr post dose and Days 8, 15, 22, and at necropsy, 12) Whole Blood for AAV Vector DNA analysis (ddPCR): Predose, 0.5h, 1h, 2h, 4h, 8h, 24h post dose and Days 8, 15, 22, and at necropsy, and 13) ATPA Serum: Predose, Days 8, 15, 22 and at necropsy.

[0305] At termination, the following endpoints will be examined: 1) BioD collections: Eye (lens , iris-ciliary body, cornea, RPE, Choroid, Retina, Sclera [15 samples per eye]), Adrenal gland, brain (3 samples), Cerebellum, DRG (2 pairs from 4 regions), Heart, Kidney, Liver, Lung, Lymph nodes (4), Muscle (quad), Optic nerve, Ovary/teste, Spinal cord, spleen (remaining tissues saved for histopath), 2) VCN (biodistribution), 3) mRNA Transgene, 4) TP, 5) C5 and other complement factors, and 6) VH for activity assay.

Example 23: TOX/BIOD: 3-month Single Dose Intravenous GLP NHP Study

[0306] NHP will be administered AAV vectored anti-hC5-scFV (groups 2 and 3) or vehicle control according to Table 6

Table 29:

Gp	Animal No. (Gender)	Treatment	Dose (gc/eye)	Route and Volume (ml)	Duration (months)
1	2M / 2F	Vehicle	-	SCS (0.1) OU	3
2	3M / 3F	AAV vectored anti-hC5-scFv01	3e11	SCS (0.1) OU	3
3	3M / 3F	AAV vectored anti-hC5-scFv01	1e12	SCS (0.1) OU	3
4	3M / 3F	AAV vectored anti-hC5-scFv01	3e12	SCS (0.1) OU	3

[0307] The following endpoints will be examined: 1) Daily health checks, 2) Weekly clinical observations, 3) Weekly body weights, 4) Ophthalmic exams and IOP: Predose, Days 8, 15, 30, 60 and at necropsy (D 60), 5) Clin Path (HCCUA): Predose, Days 8, 15, 30, 60 and at necropsy, 6) Complement Analysis: Predose, Day 1 (1, 6 and 24 hrs post dose), Days 3, 8, 15, 22, 29, 57, and 92 (analytes C3a, C4a, sC5b-9, Complement Bb), 7) Whole Blood for AAV Vector DNA analysis (ddPCR): Predose, Days 8, 15, 30, 60 and at necropsy, 8) Tab: Within 15 Days of arrival, Predose, Day 8, and at necropsy, 9) Bioanalytical (TP): Predose, Days 8, 15, 22, 29, 60 and at necropsy, 10) Viral shedding (Urine, tears, Nasal swabs, Oral swabs, Feces): Prior to dose, Days 3, 15, Week 6, and at necropsy, 11) PBMCs (Isolated from blood): Prior to dose, Day 30, and at necropsy, 12) ATPA Serum: Once prior to arrival, Predose, Days 15, 30, 60 and at necropsy, 13) Electroretinography: Once prior to dose and once in week 13, 14) OCT: Pre-dose, during weeks 4 and 8 and during week 13, 15) Fundus autofluorescence Imaging: Pre-dose, during weeks 4 and 8 and during week 13, 16) Ocular Photography (Color fundus imaging): Predose, during weeks 4, 8 and 13, and 17) Fluorescein Angiography: Performed once prior to dose and once during week 13.

[0308] At termination, the following endpoints will be examined: 1) blood (MOV), AH, VH, 2) BioD collections: Eye (lens , iris-ciliary body, cornea, RPE, Choroid, Retina, Sclera (15 samples per eye), Adrenal gland, brain (2 samples), Cerebellum, DRG (2 pairs from 4 regions), Heart, Kidney, Liver, Lung, Lymph nodes (4), Muscle (quad), Ovary/teste, Spinal cord, spleen, 3) Full tissues for Histopath, 4) VCN (biodistribution), 5) mRNA Transgene, 6) TP, 7) C5 and other complement factors, and 8) VH for activity assay.

Example 24: Assessment of Selected Capsids *in vivo*

[0309] AAV capsid sequences modified by peptide insertions with (AAV8.590 library hits) or without additional substitutions (AAV8.456 library hits) were further evaluated in *in vivo* for bio-distribution in test animals using next generation sequencing (NGS) and quantitative PCR.

[0310] Studies were performed where selected vectors from the library were produced by methods described in these Examples, or by standard methods of triple transfection utilizing Rep/cap *trans* plasmid (containing the engineered capsid gene sequence), *cis plasmid* encoding a transgene, and helper gene plasmid. The engineered vectors of interest were injected individually into test animals, *e.g.* NHPs, mice or rats, and DNA and RNA determinations from extracted tissues are compared to the parental vectors. Quantitative PCR (qPCR) can be done on a QuantStudio 5 (Life Technologies, Inc.) or any standard method such as ddPCR, using primer-probe combinations specific for the transgene.

[0311] From the studies where individual vectors are injected into test animals for characterization, formalin fixed eyes may be, *e.g.* sectioned at 40μm thickness on a vibrating blade microtome (VT1000S, Leica) and the floating sections probed with antibodies against transgene (or viewed for fluorescence if fluorescent transgene) to look at the cellular distribution of the delivered vectors.

[0312] Recent clinical advancements delivering adeno-associated viral (AAV) vectors into the suprachoroidal space (SCS) have established the feasibility and value of this in-office route of administration in ocular gene therapy. The identification of engineered capsids optimized for SCS delivery that both efficiently transduce ocular tissue in a targeted fashion and display favorable off-target transduction profiles would enable widespread use of this route of administration.

[0313] Subsequently these variants were evaluated in additional in vivo and in vitro model systems. These results validate the utility of the NAVIGATE platform and its ability to identify AAV variants that significantly outperform parental serotypes and that have the potential to be developed as gene therapy treatments in ophthalmology.

NHP Study

[0314] NHP Library Down-selection Summary: As described hereinabove, several high diversity peptide insertion libraries (up to 10^8 variants per library) were designed and produced, each encoding AAV cap under the control of the CMV promoter with randomized 7-mer insertions at VR-IV or VR-VIII of AAV8. The libraries were delivered intraocularly to non-human primates (NHP,

cynomolgus macaques). Leveraging a directed evolution platform NAVIGATE (Novel AAV Vector Intelligent Guided Adaptation Through Evolution), 2-4k novel variants overall were identified and enriched in retina and RPE-choroid from each high diversity library, which were then re-packaged and administered to NHP via SCS delivery. Several capsid variants (12 AAV8.VR-IV and 10 AAV8.VR-VIII) were chosen for final library down-selection. Each variant (as well as parental control AAV8) was produced individually with genomes encoding a barcoded CAG.tdTomato cassette, pooled, and delivered to NHP, again by SCS delivery, at a dose of 3e12 GC/eye. Briefly, Cynomolgus monkeys ("NHPs"; n=3 per test article group) were administered AAV8.456 or AAV8.590 capsids carrying a CAG.TdTomato transgene, 1E12 GC/eye SCS administration per animal. Following 3 weeks, animals were sacrificed and eyes and several peripheral tissues were collected. TdTomato genome (cDNA) and transcripts (mRNA) were detected by digital PCR and plotted against a reference gene. Results show that relative abundance adjusted for input (RAAFI) (DNA and mRNA) was increased in retina and RPE-choroid (RPE-C) for several AAV8.456 or AAV8.590 vectors in the pool compared to parental AAV8 or wtAAV3B vector (**FIGS. 38A-B**). Four capsids/vector with high abundance are shown in Table 30A (with further results in Tables 30B-30G representing single capsid studies).

Table 30A.

Capsid	**Average AAV3B fold change RNA: retina**	**Average AAV3B fold change RNA: RPE-C**	**Average AAV8 fold change RNA: retina**	**Average AAV8 fold change RNA: RPE-C**
AAV8.456.RIQMGTK^ (AAV8.1)	26	162	84	50
AAV8.456.RQKNAMV^ (AAV8.2)	24	129	76	41
AAV8.590.GDNTTFRRA (AAV8.3)	2	132	10	32
AAV8.590.GRTIRGDLA^ (AAV8.4)	7	740	29	176

^ Also evaluated in the single vector mini-pig cohort

[0315] **FIGs. 38A-38B** also illustrate the enrichment of SCS-delivered vectors having engineered capsids packaging a fluorescent protein, showing the majority of the tested capsids resulted in greater than 10X abundance over parental AAV8 capsid.

[0316] The data from the present NHP study for AAV8.456 and AAV8.590 mRNA distribution in ocular tissues shows that RNA expression of transgene from these variant capsids is greatly enriched and transduction of retina and RPE-choroid tissue over scleral tissue is better than wildtype AAV8 upon SCS administration which may be desirable for certain transgenes.

[0317] NHP Single Vector Study: AAV8 variants AAV8.1, AAV8.2, AAV8.4 (also named PEPIN8.1, PEPIN8.2 and PEPIN8.4) were administered as individual vectors carrying the anti-hC5-scFv01 transgene in an NHP study similar to above. AAV8 variants AAV8.1, AAV8.2, AAV8.4 produce greater than 10 times more protein in ocular tissues (retina/RPE-C) and biofluids (AH/VH) than AAV8 following SCS delivery of scFv01 transgene in NHPs (n=6 eyes at 3e12 GC/eye) (**FIGS. 33A-33C**).

Table 30F

	Max. AAV8 TP (scFv01) fold change	
Variant	Retina	RPE-C
AAV8.1	11	13
AAV8.2	17	19
AAV8.4	4	4

Table 30G

	Max. AAV8 TP (scFv01) fold change	
Variant	AH	VH
AAV8.1	10.8	9
AAV8.2	11.4	11.2
AAV8.4	4.5	5

[0318] All variants expressed transgene mRNA in retina more efficiently than parental serotypes as measured by average RNA relative abundance across multiple samples per eye. AAV8.VR-IV/AAV8.VR-VIII insertion variants were up to >30-fold and up to >50-fold improved, respectively, when compared to the parental serotypes. Most AAV8-based insertion variants also expressed >20-fold more transgene mRNA in RPE-choroid compared to AAV8, with the top variant producing in excess of 200-fold more mRNA than AAV8. Numerous variants with advantageous off-target transduction profiles were also identified. For example, the majority of AAV8.VR-IV and AAV8.VR-VIII variants that showed a greater than 10-fold increase in retinal transduction yet did not transduce liver, heart, or kidney to a greater degree than AAV8.

[0319] Protein (TP) levels were measured from AH (A), VH (B), Retina lysates (C) and RPE-Choroid lysates (D) from a macular punch, distal and proximal tissue strips harvested from eyes 29 days post administration of AAV8 and AAV8.2 vectors (**FIGs. 37A-37D**).

[0320] Additionally, down-selection of AAV3B.455 capsids from a library of AAV3B variants was performed. Cynomolgus monkeys ("NHPs"; n=3 per test article group (6 eyes)) were administered pooled AAV3B.455 capsids carrying a CAG.TdTomato transgene, 1E12 GC/eye SCS administration per animal. Following 4 weeks (29 days), animals were sacrificed and eyes and several peripheral tissues were collected. Ophthalmic exams, IOP, OCT, fundus photography were performed. Aqueous humor taps were performed at pre-dose, Day (D)15, and D29. Serum, plasma, and whole blood were collected: Pre-dose, D3, D8, D15, D29. Samples were collected at certain additional early timepoints for pharmacokinetic studies. Extensive frozen ocular (n=5/group) tissue collection was performed, whereas one fixed eye per group was also collected, as well as CNS and peripheral tissue collection.

[0321] TdTomato genome (cDNA) and transcripts (mRNA) were detected by digital PCR and plotted against a reference gene. Results show that relative abundance adjusted for input (RAAFI) (DNA and mRNA) was increased in retina and RPE-choroid for several AAV3B.455 vectors in the pool compared to parental AAV3B or wtAAV8 vector. Three capsids/vector with high abundance are shown in Table 31.

Table 31.

Capsid	**Average AAV3B fold change RNA: retina**	**Average AAV3B fold change RNA: RPE-C**	**Average AAV8 fold change RNA: retina**	**Average AAV8 fold change RNA: RPE-C**
AAV3B.455.DLMLPGS^	19	3	19	0.8
AAV3B.455.DVTPLLS	11	3	39	3
AAV3B.455.LVSVSLP	5	2	12	0.6

^ Also evaluated in the single vector mini-pig cohort

[0322] All variants expressed transgene mRNA in retina more efficiently than parental serotypes as measured by average RNA relative abundance across multiple samples per eye. AAV3B.VR-IV insertion variants were up to >30-fold improved when compared to the parental serotype or wtAAV8.

B. Mini-pig study:

[0323] A variant capsid library and a subset of single vectors was assessed via SCS delivery in Yucatan minipigs.

[0324] Briefly, Yucatan pigs ("mini-pigs"; n=3 per test article group) were administered as a single AAV8.456 or AAV8.590 capsids or AAV3B.455 capsids carrying an antibody (mAb) transgene, formatted as an scFv, at a low dose 3E11 and high dose 3E12 GC/eye SCS administration per animal. Also, pooled capsids (vectors) were administered to one cohort (2 animals, 2 eyes collected each). Following 4 weeks, animals were sacrificed and eyes and several peripheral tissues were collected (Day 15 and Day 29).

[0325] The scFv genome (cDNA) and transcripts (mRNA) were detected by digital PCR and plotted against a reference gene following administration of AAV8 variants (8.1, 8.2 and 8.4). Retina and RPE tissues as well as aqueous humor (AH) and vitreous humor (VH) were tested for transgene product and DNA biodistribution (BD) at Day 29 (TP measured as ng/mL protein, DNA genome copies (GC)/μg) (**FIGS. 31A-D)**.

[0326] Several novel AAV8 variants from the libraries outperform AAV8 following single vector SCS delivery of scFv01 transgene in minipigs in a dose-dependent manner. AAV8 variants achieve TP concentrations up to 344ng/mg in retina, consistent with biodistribution. (**FIG. 32A-32B**). AAV8.3 achieves >153X AAV8 expression levels if transgene product in AAV8 in AH.

Table 32A

	Max. AAV8 TP fold change	
Variant	retina	RPE-C
AAV3B-3.1	+++	28
AAV8.1	+++	29
AAV8.2	+++	20
AAV8.4	++	11

Table 32B

	Max. AAV8 TP fold change	
Variant	AH	VH
AAV3B-3.1	93	+++
AAV8.1	60	+++

AAV8.2	153	+++
AAV8.4	7	++

[0327] Results show that transgene product (TP) in aqueous humor for the AAV8.456.RIQMGTK (8.1), AAV8.456.RQKNAMV (8.2), AAV8.590.GDNTTFRRA (8.3), and AAV8.590.GRTIRGDLA (8.4) vectors were increased relative to wildtype AAV8 vector. AAV8.456.RIQMGTK (8.1) and AAV8.456.RQKNAMV (8.2) vectors exhibited about 50-fold and 150-fold change, respectively, in TP concentration relative to wtAAV8 vector at the high dose at Day 15.

[0328] Findings from the AAV8 insertion variants, were largely translatable from NHP to minipigs, with top hits achieving improvement relative to AAV8 of >60-fold and >100-fold transduction in RPE-choroid and retina, respectively. Variants evaluated as single vectors achieved up to 150-fold higher secreted transgene protein expression in the aqueous humor as compared to the AAV8 control. Transduction of iCell RPE cells and an ARPE-AAVR cell line with either the 63-member library (SCS5, 6, 7 pools) or a subset of top hits as single vectors established that most variants exhibit superior transduction efficiency compared to AAV8 with top variants achieving >20-fold improvement in both the library and single vector settings (**FIGs. 34A-34B**).

[0329] The scFv genome (cDNA) and transcripts (mRNA) were detected by digital PCR and plotted against a reference gene following delivered via AAV3B-3.1 variant. Retina and RPE tissues as well as aqueous humor (AH) and vitreous humor (VH) were tested for transgene product and DNA biodistribution (BD) at Day 29 (TP measured as ng/mL protein, DNA genome copies (GC)/μg) (**FIGs. 35A-35D)**.

[0330] Novel AAV3B variants from the library screen outperformed wild-type AAV8 (wtAAV8) following single vector SCS delivery of scFv01 transgene in minipigs in a dose-dependent manner. These findings were supported by the DNA biodistribution, where variants with the highest BD to retina also resulted in highest tissue protein levels.

[0331] The AAV3B-3.1 (AAV3B.455.DLMLPGS) variant achieved significantly higher transgene product (TP) concentrations (+++) in retina, consistent with biodistribution and dose-dependent, compared to wtAAV8 (**FIGs. 35A** and **35C**). AAV3B-3.1 also achieved significantly higher transgene product (TP) concentrations, calculated to 28-fold higher than wtAAV8 at its

maximum concentration, in RPE-choroid (RPE-C). TP production in RPE-C appears consistent with biodistribution and is dose-dependent. (**FIGs. 35B** and **35D**.)

[0332] AAV3B-3.1 also achieved higher expression levels of transgene product in VH (+++, TP >10μg/mL in VH) compared to wtAAV8 (which was non-detectable in VH in this minipig study) (**FIG. 36**).

[0333] Results also showed that transgene product (TP) in aqueous humor for the single AAV3B.455 vector (capsid AAV3B.455.DLMLPGS / AAV3B-3.1) was increased (++) compared to parental capsid or an AAV8 wildtype capsid. The AAV3B.455 capsid exhibited over 50-fold change (up to 93 fold at the maximum concentration) in TP concentration in AH compared to wtAAV8 vector at the high dose.

[0334] Findings from the AAV3B insertion variants in a library setting, showed that the improvement of AAV3B variants over parental AAV3B appeared to be species-limited. Transduction of iCell RPE cells and an ARPE-AAVR cell line with either the 63-member library or a subset of top hits as single vectors was also tested.

Examples 25A and 25B: $NaIO_3$ Induction Mouse Models

[0335] A. The NaIO3 induced model in mice, commonly used as a model for human geographic atrophy (GA) or dry age-related macular degeneration (AMD), was used to assess AAV8-anti-hC5-scFv01 vector and AAV8.2-anti-hC5-scFv01 vector, each administered by tail vein (intravenous) injection in methods analogous to Examples 14A, 14B and 20. The vectors carrying anti-C5 transgene were compared to an AAV8.2.null vector (control), a vector carrying a transgene that does not encode for any protein. Briefly, male C57BL/6J mice were dosed via tail vein with AAV at 3E13 vg/kg body weight (dose volume 5 mL/kg). Four weeks later, sodium iodate (SI) was dosed at 20 mg/kg via tail vein. At week 5, mice were euthanized and eyes collected for either measurement of transgene product levels via ELISA, analysis of AAV biodistribution via ddPCR, or histology following fixation in Davidson's fixative. Study groups were masked, and measurements of photoreceptor layer and total retina thickness were taken from Optical Coherence Tomography (OCT) scans or H&E images using FIJI/ImageJ. Animals were assessed by dark-adapted electroretinogram (ERG) to assess rod function, since rods are a type of photoreceptor cell in the retina that are sensitive to light levels and are concentrated in the outer areas of the retina. Preserving rod function is important to provide vision in low light as well as peripheral vision.

[0336] All AAVs encoding the anti-hC5-scFv01 transgene demonstrated disease rescue relative to the negative control as determined using ERG, OCT imaging, and histological analyses. Retinal function assessed via ERG three days after disease induction was significantly higher in groups treated with anti-hC5-scFv01 vectors compared to the negative control group. OCT imaging performed seven days post sodium iodate induction demonstrated significant preservation of photoreceptor layers in anti-C5 groups compared to the negative control group. Preservation of retina and photoreceptor nuclear layers (outer nuclear layer; ONL) was further demonstrated in anti-C5 groups using Hematoxylin/Eosin (H&E)-stained ocular sections.

[0337] This study demonstrated that either AAV8 or AAV8.2 encoding anti-hC5-scFv01 were sufficient to produce high and sustained levels of C5 inhibitor at the target site in the eye when dosed at 3E13 vg/kg.

[0338] B. This study evaluated the pharmacology of AAV8.2.CAG.anti-hC5-scFv01 vectors. Four dose levels (DLs) (DL1, DL2, DL3 and DL4 vg/kg) were tested analogously to the above methods in the mouse sodium iodate retinal disease model of GA/dry AMD. Male C57BL/6J mice (6 per cohort), 6-8 weeks of age at study enrollment, were sourced from Jackson Laboratories (Bar Harbor, ME) and randomly divided into six study groups following baseline optical coherence tomography (OCT) imaging. Mice in each group were treated prophylactically with a single intravenous (IV) injection via the tail vein with either vehicle or one of four doses of AAV8.2.CAG.anti-hC5 on Day 0. AAV8.2.CAG.anti-hC5-scFv01 encodes a human-specific single-chain fragment variable antibody (scFv) with high affinity for human C5 and lower affinity for mouse C5. The transgene cassette is packaged in an AAV8-derived variant capsid.

[0339] Retinal degeneration was induced on Day 28 by intravenous administration of NaIO3 in Groups 1-5 only, and Group 6 served as a control. Disease progression was assessed in all groups over the next 7 days. Electroretinography (ERG) was performed on all animals on Day 24 and Day 31, four days before and three days after sodium iodate administration. OCT was performed on Day 35 prior to termination. Blood was collected for isolation of serum at baseline prior to dosing, and on Days 7, 21, and 35. At scheduled euthanasia, the right eye (OD) from each animal and biopsies from liver, heart, kidney, brain, lung, and spleen from each animal were collected, fixed, and processed to H&E sections for microscopic evaluation and image analysis (eyes only). The left eye (OS) and additional biopsies from liver, heart, kidney, brain, lung, and spleen were also flash frozen for either

transgene product (TP) quantitation (subset of eyes only) or vector biodistribution (subset of eyes and all collected systemic tissues). Morbidity or mortality was observed in dose Group 1 (highest dose AAV group; 4/6 animals). One animal each in Groups 4 (low dose AAV) and 5 (vehicle) died during delivery of NaIO3 on D28. All other animals survived to the date of scheduled necropsy. In the surviving animals, NaIO3-induced retinal degeneration was similarly prevented at all received doses of AAV8.2.CAG.anti-hC5-scFv01. Preservation of retinal function was confirmed by ERG, and retinal thickness by OCT and histological analyses.

[0340] In Groups 1-4, increasing doses of AAV8.2.CAG.anti-hC5-scFv01 resulted in increasing TP levels in both serum and ocular tissues. A subset of eyes collected for analysis of vector biodistribution demonstrated dose-dependent transduction for all AAV-treated groups analyzed (Group 2-4). Biopsies of all peripheral tissues collected at necropsy also demonstrated dose-dependent vector transduction for all four AAV doses tested (Groups 1-4).

[0341] Three days after sodium iodate delivery, a-wave and b-wave amplitudes of groups treated with AAV8.2.CAG.anti-hC5-scFv01 (Groups 1-4) were significantly higher relative to the negative control (Group 5) for all doses delivered, most notably at the highest light intensities tested (10 cd.s/m2). The difference in both a-wave and b-wave amplitudes from D24 to D31 per animal was also generally preserved in AAV8.2.CAG.anti-hC5-scFv01 groups. All groups treated with intravenous AAV8.2.CAG.anti-hC5-scFv01 demonstrated significantly preserved ONL and retina layers compared to the negative control group. This study demonstrated that DL1, DL2 and DL3 of AAV8.2 vectors encoding an scFv inhibitor of human C5 were well tolerated, and exhibited dose-dependent vector transduction and sufficient inhibition of C5 to improve the survival and function of retinal photoreceptors at each dose in the mouse NaIO3-induced disease model of GA.

EQUIVALENTS

[0342] Although the invention is described in detail with reference to specific embodiments thereof, it will be understood that variations which are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended

claims. 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.

[0343] All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference in their entireties.

What is claimed is:

1. A recombinant adeno-associated virus (rAAV) vector comprising

   (a) an AAV capsid comprising viral capsid protein; wherein the viral capsid protein comprises a 7 amino acid peptide inserted into a AAV3B or AAV8 capsid protein as a parental capsid protein and is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249); and

   (b) an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene comprising a nucleotide sequence encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197), and wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

   wherein the rAAV vector has enhanced tropism to ocular tissue compared to an rAAV vector prepared from the parental capsid protein.
2. The rAAV vector of claim 1, wherein said ocular tissue with enhanced tropism is retina, RPE choroid or sclera tissue.
3. The rAAV vector of claim 2, wherein the rAAV vector exhibits an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, or 25 fold greater transduction of ocular tissue than an rAAV vector comprising the parental capsid.
4. The rAAV vector of any one of claims 1 to 3, wherein the rAAV vector has reduced transduction of liver, heart or astrocytes than an rAAV vector comprising parental capsid protein.
5. The rAAV vector of claim 4, wherein the rAAV vector has an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, 25 fold or 40 fold lower transduction of liver than an rAAV vector comprising the parental capsid protein.
6. The rAAV vector any one of claims 1 to 5, wherein the viral capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243).
7. The rAAV vector any one of claims 1 to 5, wherein the viral capsid protein is AAV3B.455.DVTPLLS (SEQ ID NO: 244).
8. The rAAV vector any one of claims 1 to 5, wherein the viral capsid protein is AAV3B.455.LVSVSLP (SEQ ID NO: 245).

9. The rAAV vector of any one of claims 6 to 8, wherein the parental capsid is AAV3B (SEQ ID NO: 254).
10. The rAAV vector any one of claims 1 to 5, wherein the viral capsid protein is AAV8.456.RIQMGTK (SEQ ID NO: 246).
11. The rAAV vector any one of claims 1 to 5, wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247).
12. The rAAV vector any one of claims 1 to 5, wherein the viral capsid protein is AAV8.590.GDNTTFRRA (SEQ ID NO: 248).
13. The rAAV vector any one of claims 1 to 5, wherein the viral capsid protein is AAV8.590.GRTIRGDLA (SEQ ID NO: 249).
14. The rAAV vector of any one of claims 10 to 13, wherein the parental capsid is AAV8 (SEQ ID NO: 260).
15. The rAAV vector any one of claims 1 to 14, wherein the transgene encodes a signal sequence at the N-terminus of the scFv that directs secretion and post-translational modification in said human ocular tissue cells.
16. The rAAV vector of claim 15, wherein the transgene comprises a signal sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 55) or a signal sequence from Table 2.
17. The rAAV vector of any one of claims 1 to 16, wherein the regulatory sequence comprises a regulatory sequence from Table 1 or Table 1a.
18. The rAAV vector of any one of claims 1 to 17, wherein the regulatory sequence is a CAG promoter (SEQ ID NO: 2), a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), a CB promoter (SEQ ID NO: 24 or 25), a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS: 5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), a human red opsin (RedO) promoter (SEQ ID NO: 14) or a Best1/GRK1 tandem promoter (SEQ ID NO: 26).
19. The rAAV vector of claim 18, wherein the regulatory sequence is a mutated CAG promoter (SEQ ID NO: 29).
20. The rAAV vector of any one of claims 1 to 19, wherein the nucleotide sequence encoding C5-D-mab.scFv is the nucleotide sequence of SEQ ID NO:224, SEQ ID NO: 227, or SEQ ID NO: 230.
21. The rAAV vector of any one of claims 1 to 19, wherein the expression cassette comprises SEQ

ID NO: 226, 228, 231, 233, 235, 237, 239, 241, 278 or 279.

22. The rAAV vector of any one of claims 1 to 21, wherein the rAAV vector comprises a nucleotide sequence of SEQ ID NO: 225, 229, 232, 234, 236. 238. 240, 242, 276 or 277.
23. An rAAV vector comprising (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247) and (b) an artificial genome comprising a transgene encoding an anti-C5 scFv having an amino acid sequence of SEQ ID NO: 195, 197 or 203 operatively linked to a regulatory sequence which promotes expression in ocular tissue and flanked by ITR sequences.
24. The rAAV vector of claim 23, wherein the artificial genome comprises a nucleotide sequence of SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240 SEQ ID NO: 242, SEQ ID NO: 276 or SEQ ID NO: 277.
25. A pharmaceutical composition comprising the rAAV vector of any one of claims 1 to 24 and a pharmaceutically acceptable carrier.
26. The pharmaceutical composition according to claim 25, wherein said composition is formulated for subretinal, intravitreal, intranasal, intracameral, or suprachoroidal administration.
27. The pharmaceutical composition according to claim 26, wherein said composition is formulated for suprachoroidal administration.
28. The pharmaceutical composition according to claim 26, wherein said composition is formulated for suprachoroidal administration with a microneedle.
29. A method of delivering a transgene to a cell, said method comprising contacting said cell with the rAAV vector of any one of claims 1-24.
30. A method of delivering a transgene to a target tissue of a subject in need thereof, said method comprising administering to said subject the rAAV vector of any one of claims 1-24.
31. A pharmaceutical composition comprising a recombinant adeno-associated virus (rAAV) vector comprising

    (a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein comprises a 7 amino acid peptide inserted into a AAV3B or AAV8 capsid protein as a parental capsid protein and is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 345), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249); and

(b) an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197), and wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

wherein the rAAV vector has enhanced tropism to ocular tissue compared to an rAAV vector prepared from the parental capsid protein.

32. The composition of claim 31, wherein said ocular tissue with enhanced tropism is retina, RPE choroid or sclera tissue.
33. The composition of claim 32, wherein the rAAV vector exhibits an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, or 25 fold greater transduction of ocular tissue than an rAAV vector comprising the parental capsid.
34. The composition of any one of claims 31 to 33, wherein the rAAV vector has reduced transduction of liver, heart or astrocytes than an rAAV vector comprising parental capsid protein.
35. The composition of claim 34, wherein the rAAV vector has an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, 25 fold or 40 fold lower transduction of liver than an rAAV vector comprising the parental capsid protein.
36. The composition any one of claims 31 to 35, wherein the viral capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243).
37. The composition any one of claims 31 to 35, wherein the viral capsid protein is AAV3B.455.DVTPLLS (SEQ ID NO: 244).
38. The composition any one of claims 31 to 35, wherein the viral capsid protein is AAV3B.455.LVSVSLP (SEQ ID NO: 245).
39. The composition of any one of claims 33 to 35, wherein the parental capsid is AAV3B (SEQ ID NO: 254).
40. The composition any one of claims 31 to 39, wherein the viral capsid protein is AAV8.456.RIQMGTK (SEQ ID NO: 246).
41. The composition any one of claims 31 to 39, wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247).
42. The composition any one of claims 31 to 39, wherein the viral capsid protein is AAV8.590.GDNTTFRRA (SEQ ID NO: 248).

43. The composition any one of claims 31 to 39, wherein the viral capsid protein is AAV8.590.GRTIRGDLA (SEQ ID NO: 249).
44. The composition of any one of claims 33 to 35, wherein the parental capsid is AAV8 (SEQ ID NO: 260).
45. The composition any one of claims 31 to 44, wherein the transgene encodes a signal sequence at the N-terminus of the scFv that directs secretion and post-translational modification in said human ocular tissue cells.
46. The composition of claim 45, wherein the transgene comprises a signal sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 55) or a signal sequence from Table 2.
47. The composition of any one of claims 31 to 46, wherein the regulatory sequence comprises a regulatory sequence from Table 1 or Table 1a.
48. The composition of any one of claims 31 to 47, wherein the regulatory sequence is a CAG promoter (SEQ ID NO: 2), a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), a CB promoter (SEQ ID NO: 24 or 25), a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS: 5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), a human red opsin (RedO) promoter (SEQ ID NO: 14) or a Best1/GRK1 tandem promoter (SEQ ID NO: 26).
49. The composition of claim 44, wherein the regulatory sequence is a mutated CAG promoter (SEQ ID NO: 29).
50. The composition of any one of claims 31 to 49, wherein the artificial genome comprises the nucleotide sequence of SEQ ID NO: 225, SEQ ID NO: 229, SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, SEQ ID NO: 242, SEQ ID NO: 276, or SEQ ID NO: 277.
51. A pharmaceutical composition for use in treating Age-Related Macular Degeneration in a subject comprising or a method for treating Age-Related Macular Degeneration (AMD) in a human subject in need thereof comprising administering a therapeutically effective amount of recombinant adeno-associated virus (rAAV) vector to the eye comprising

(a) an AAV capsid comprising a viral capsid protein; wherein the viral capsid protein comprises a 7 amino acid peptide inserted into a AAV3B or AAV8 capsid protein as a parental capsid protein and is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO:

246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249); and

(b) an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197), and wherein the transgene is operably linked to one or more regulatory sequences;

wherein the rAAV vector has enhanced tropism to ocular tissue compared to an rAAV vector prepared from the parental capsid protein.

52. The pharmaceutical composition or method for treating according to claim 51, wherein said ocular tissue with enhanced tropism is retina, RPE choroid or sclera tissue.
53. The pharmaceutical composition or method for treating according to claim 52, wherein the rAAV vector exhibits an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, or 25 fold greater transduction of ocular tissue than an rAAV vector comprising the parental capsid protein.
54. The pharmaceutical composition or method for treating according to any one of claims 51 to 53, wherein the rAAV vector has reduced transduction of liver or peripheral tissue compared to rAAV vector comprising the parental capsid protein.
55. The pharmaceutical composition or method for treating according to claim 54, wherein the rAAV vector has an at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, 25 fold or 40 fold lower transduction of liver than an rAAV vector comprising the parental capsid protein.
56. The pharmaceutical composition or method for treating according to any one of claims 51 to 55, wherein the viral capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243).
57. The pharmaceutical composition or method for treating according to any one of claims 51 to 55, wherein the viral capsid protein is AAV3B.455.DVTPLLS (SEQ ID NO: 244).
58. The pharmaceutical composition or method for treating according to any one of claims 51 to 55, wherein the viral capsid protein is AAV3B.455.LVSVSLP (SEQ ID NO: 245).
59. The pharmaceutical composition or method for treating according to any one of claims 51 to 55, wherein the viral capsid protein is AAV8.456.RIQMGTK (SEQ ID NO: 246).
60. The pharmaceutical composition or method for treating according to any one of claims 51 to 55, wherein the viral capsid protein is AAV8.456.RQKNAMV (SEQ ID NO: 247).
61. The pharmaceutical composition or method for treating according to any one of claims 51 to 55, wherein the viral capsid protein is AAV8.590.GDNTTFRRA (SEQ ID NO: 248).

62. The pharmaceutical composition or method for treating according to any one of claims 51 to 55, wherein the viral capsid protein is AAV8.590.GRTIRGDLA (SEQ ID NO: 249).
63. The pharmaceutical composition or method for treating according to any one of claims 51 to 62, wherein the transgene encodes a signal sequence at the N-terminus (SEQ ID NO: 203) that directs secretion and post-translational modification in said human ocular tissue cells.
64. The pharmaceutical composition or method for treating according to claim 63, wherein the transgene comprises a signal sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 55) or a signal sequence from Table 2.
65. The pharmaceutical composition or method for treating according to any one of claims 51 to 64, wherein the regulatory sequence comprises a regulatory sequence from Table 1 or Table 1a.
66. The pharmaceutical composition or method for treating according to any one of claims 51 to 65, wherein the regulatory sequence is a CAG promoter (SEQ ID NO: 2), a mutated CAG promoter (SEQ ID NO: 29, SEQ ID NO: 30 or SEQ ID NO: 31), a CB promoter (SEQ ID NO: 24 or 25), a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS: 5 or 19), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 16-18), a human red opsin (RedO) promoter (SEQ ID NO: 14) or a Best1/GRK1 tandem promoter (SEQ ID NO: 26).
67. The pharmaceutical composition or method for treating according to claim 66, wherein the regulatory sequence is a mutated CAG promoter (SEQ ID NO: 29).
68. The pharmaceutical composition or method for treating according to any one of claims 51 to 67, wherein the artificial genome comprises the nucleotide sequence of SEQ ID NO: 225, SEQ ID NO: 229, SEQ ID NO: 232, SEQ ID NO: 234, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 240, SEQ ID NO: 242, SEQ ID NO: 276, or SEQ ID NO: 277.
69. The pharmaceutical composition or method for treating according to any one of claims 51 to 68, wherein the AAV vector is formulated for subretinal, intravitreal, intranasal, intracameral, or suprachoroidal, administration to said human subject.
70. The pharmaceutical composition or method for treating according to claim 69, wherein the AAV vector is formulated for suprachoroidal administration to said human subject.
71. The pharmaceutical composition or method for treating according to claim 70, wherein the AAV vector is formulated for suprachoroidal administration with a microneedle or microinjector.
72. The pharmaceutical composition or method for treating according to any one of claims 51 to 71, wherein the therapeutically effective amount is determined to be sufficient to maintain a

concentration of at least 10 ng/ml in RPE, retina, aqueous humor or vitreous humor.

73. The pharmaceutical composition of method for treating according to any one of claims 51 to 72, which results in a therapeutic or prophylactic levels in ocular tissues of the antibody within 20 days, 30 days, 40 days, 50 days, 60 days, or 90 days of administration of the rAAV composition.
74. The pharmaceutical composition of method for treating according to any one of claims 51 to 73, wherein the AMD is dry AMD with geographic atrophy or geographic atrophy secondary to AMD.
75. The pharmaceutical composition or method for treatment according to of any one of claims 51 to 74, wherein the therapeutically effective amount is determined to be sufficient to improve best corrected visual acuity (BCVA) by >= 2 ETDRS lines; to decrease the mean rate of change in geographic atrophy as measured by fundus autofluorescence (FAF); to improve visual function as measured by dark adaptation methodology; to improve contrast sensitivity by the Pelli-Robson test or reduce the drusen area within 10 weeks, 20 weeks, 6 months or 1 year of administration.
76. The pharmaceutical composition of any one of claims 25 to 50 or the composition for use in treatment of AMD of any one of claims 51 to 77 wherein the pharmaceutical composition or composition or composition for use in the treatment of AMD comprises between about 0.5% to about 1.0% w/v hyaluronic acid.
77. The pharmaceutical composition of any one of claims 25 to 50 or the composition for use in treatment of AMD of any one of claims 51 to 76 wherein the pharmaceutical composition or composition or composition for use in the treatment of AMD comprises about (2.5% w/v) sucrose and between about 0.5% to about 1.0% w/v hyaluronic acid.
78. The pharmaceutical composition of any one of claims 25 to 50 or the composition for use in treatment of AMD of any one of claims 51 to 77 wherein the pharmaceutical composition or composition or composition for use in the treatment of AMD comprises about 0.2 mg/mL potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 25.0 mg/mL (2.5% w/v) sucrose, about 0.002% (0.02 mg/mL) poloxamer 188 and about 0.7% w/v hyaluronic acid.
79. The pharmaceutical composition of any one of claims 25 to 50 or the composition for use in treatment of AMD of any one of claims 51 to 78 wherein the pharmaceutical composition or composition or composition for use in the treatment of AMD comprises about 0.2 mg/mL

potassium chloride, about 0.2 mg/mL potassium phosphate monobasic, about 5.84 mg/mL sodium chloride, about 1.15 mg/mL sodium phosphate dibasic anhydrous, about 40.0 mg/mL (4% w/v) sucrose, about 0.001% (0.01 mg/mL) poloxamer 188, and about 1% carboxymethylcellulose (CMC) high viscosity grade.

80. A method of producing recombinant AAVs comprising:

(c) culturing a host cell containing:

(i) an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197), and wherein the transgene is operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

(ii) a *trans* expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and an AAV capsid protein operably linked to expression control elements that drive expression of the AAV rep and the AAV capsid protein in the host cell in culture and supply the AAV rep and the AAV capsid protein in *trans,* wherein the capsid has ocular tissue cell tropism, wherein the AAV capsid protein is AAV3B.455.DLMLPGS (SEQ ID NO: 243), AAV3B.455.DVTPLLS (SEQ ID NO: 244), AAV3B.455.LVSVSLP (SEQ ID NO: 245), AAV8.456.RIQMGTK (SEQ ID NO: 246), AAV8.456.RQKNAMV (SEQ ID NO: 247), AAV8.590.GDNTTFRRA (SEQ ID NO: 248), or AAV8.590.GRTIRGDLA (SEQ ID NO: 249);

(iii) sufficient adenovirus helper genes to permit replication and packaging of the artificial genome by the AAV capsid protein; and

(d) recovering recombinant AAV encapsidating the artificial genome from the cell culture.

81. A host cell comprising:

a plasmid comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197) operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells.

82. A method for treating a human subject diagnosed with age-related macular degeneration (AMD), comprising delivering to an eye of the human subject a therapeutically effective amount of an

anti-C5 scFv antibody produced by the human subject's ocular cells transduced with a recombinant adeno-associated virus (rAAV) vector carrying an artificial genome containing an expression cassette comprising a transgene encoding an anti-C5 scFv antibody, by a single dose administration of the rAAV vector via suprachoroidal (SC) injection or subretinal (SR) injection to the eye of the human subject.

83. A pharmaceutical composition for use in treating a human subject diagnosted with age-related macular degeneration (AMD), comprising delivering to an eye of the human subject a therapeutically effective amount of an anti-C5 scFv antibody produced by the human subject's ocular cells transduced with a recombinant adeno-associated virus (rAAV) vector comprising an artificial genome comprising an expression cassette comprising a transgene encoding an anti-C5 scFv, by a single dose administration of the rAAV vector via suprachoroidal (SC) injection or subretinal (SR) injection to the eye of the human subject.
84. The method of claim 82 or the pharmaceutical composition of claim 83, wherein the amount of an anti-C5 scFv antibody in the eye of the human subject is effective to enhance the survival and/or the function of the photoreceptors of the eye.
85. The method or pharmaceutical composition of any one of claims 82 to 84, wherein the human subject is diagnosed with geographic atrophy (GA) secondary to AMD.
86. The method or pharmaceutical composition of any one of claims 82 to 85, wherein the amount of an anti-C5 scFv antibody delivered to the eye of the human subject is effective to slow progression of geographic atrophy.
87. The method or pharmaceutical composition of any one of claims 82 to 86, wherein the rAAV vector comprises an engineered AAV8 capsid protein AAV8.456.RQKNAMV (SEQ ID NO: 247).
88. The method or pharmaceutical composition of any one of claims 82 to 87, wherein the expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197).
89. The method or pharmaceutical composition of any one of claims 82 to 88, wherein the single dose is from about 1×10^{9} genome copies (GC) to about 3×10^{13} GC per eye.
90. A method for enhancing the survival and/or the function of the photoreceptors of the eye, comprising delivering to an eye of a mammal a therapeutically effective amount of an anti-C5 scFv antibody produced by the mammal's ocular cells transduced with a recombinant adeno-

associated virus (rAAV) vector carrying an expression cassette encoding the anti-C5 scFv antibody, by a single dose administration of the rAAV vector via suprachoroidal (SC) injection or subretinal (SR) injection to the mammal's eye.

91. The method of claim 90, wherein the mammal is a human, non-human primate, mouse or a pig.
92. The method of claim 90 or 91, wherein the rAAV vector comprises an engineered AAV8 capsid protein AAV8.456.RQKNAMV (SEQ ID NO: 247).
93. The method of any one of claims 90 to 92, wherein the expression cassette comprises a transgene encoding C5-D-mab.ScFv.HL (SEQ ID NO: 195 or 203) or C5-A-mab.ScFv.HL (SEQ ID NO: 197).
94. The method of any one of claims 90 to 93, wherein the single dose is from about 1×10^{10} genome copies (GC) to about 3×10^{13} GC per eye.