

CLAIMS

1. An isolated polynucleotide comprising nucleotide sequences encoding (i) an anti-VEGF entity and (ii) a negative complement regulator.
2. The isolated polynucleotide according to claim 1 wherein the anti-VEGF entity is selected from an Ig fusion protein, an antibody, a polypeptide, a peptide, a non-antibody scaffold, an antisense oligonucleotide, siRNA, shRNA, CRISPR-guide strand and an aptamer.
3. The isolated polynucleotide according to claim 2 wherein the anti-VEGF entity is selected from aflibercept, ranibizumab, bevacizumab, brolucizumab and pegaptanib.
4. The isolated polynucleotide according to claim 3 wherein the anti-VEGF entity is aflibercept, for example wherein the aflibercept is encoded by a polynucleotide sequence ~~comprising any one of SEQ ID NO: 3 to 11~~ having at least 75% identity to any of SEQ ID NO: 2 to 11.
5. The isolated polynucleotide according to any preceding claim wherein the negative complement regulator is selected from Complement Factor I (CFI), Complement Factor H Like Protein 1 (FHL1), Complement Factor H (CFH), Complement receptor type 1 (CR1), Membrane Cofactor Protein (MCP), Complement decay-accelerating factor (DAF), MAC-inhibitory protein (MAC-IP), C1-inhibitor, anaphylatoxins inhibitor, C4b binding protein (C4BP), clusterin, vitronectin or a variant or fragment thereof.
6. The isolated polynucleotide according to claim 5 wherein the negative complement regulator is selected from CFI and FHL1 or a variant or fragment thereof.
7. The isolated polynucleotide according to any of claims 3 to 6, wherein the nucleotide sequence encoding aflibercept has at least 75% sequence identity to SEQ ID NO: 11.
8. The isolated polynucleotide according to claim 6 or 7, wherein the nucleotide sequence encoding CFI has at least 75% sequence identity to SEQ ID NO: 35 or 36.
9. The isolated polynucleotide according to claim 6 or 7, wherein ~~or~~ the nucleotide sequence encoding FHL-1 has at least 75% sequence identity to SEQ ID NO: 41.
10. The isolated polynucleotide according to any of claims 3 to ~~8~~ 9, wherein the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 45 to 54, or a nucleotide sequence that has at least 75% sequence identity thereto.

11. The isolated polynucleotide according to any preceding claim, wherein the polynucleotide comprises two AAV ITRs, preferably wherein the AAV ITRs are AAV2 ITRs.
- 5 12. The isolated polynucleotide according to any preceding claim, wherein the nucleotide sequence encoding the anti-VEGF entity is upstream of the nucleotide sequence encoding the negative complement regulator.
13. The isolated polynucleotide according to any of claims 1 to 11, wherein the nucleotide sequence encoding the negative complement regulator is upstream of the nucleotide sequence encoding the anti-VEGF entity.
- 10 14. The isolated polynucleotide according to any preceding claim, wherein the polynucleotide comprises a 5' AAV ITR with the nucleotide sequence of SEQ ID NO: 55 or SEQ ID NO: 65, or a nucleotide sequence that has at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 55 or SEQ ID NO: 65.
- 15 15. The isolated polynucleotide according to any preceding claim, wherein the polynucleotide comprises a 3' AAV ITR with the nucleotide sequence of SEQ ID NO: 57 or SEQ ID NO: 66, or a nucleotide sequence that has at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 57 or SEQ ID NO: 66.
- 20 16. The isolated polynucleotide according to any preceding claim, wherein the polynucleotide comprises a promoter sequence, wherein the promoter sequence is SEQ ID NO: 59 or SEQ ID NO: 60 or a sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 59 or SEQ ID NO: 60.
- 25 17. The isolated polynucleotide according to any preceding claim, wherein the polynucleotide comprises a Bovine Growth Hormone poly-A (bGH poly-A) signal.
18. The isolated polynucleotide according to claim 17, wherein the Bovine Growth Hormone poly-A (bGH poly-A) signal has the nucleotide sequence of SEQ ID NO: 61 or 62, or a nucleotide sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 61 or 62.
- 30 10. ~~The isolated polynucleotide according to any of claims 1 to 9, wherein the polynucleotide is less than or equal to 4.7 kb.~~

4119. A vector comprising the isolated polynucleotide of any one of claims 1 to 4018.

4220. The vector of claim 4119, wherein the vector is an adeno-associated viral (AAV) vector, optionally in the form of a viral vector particle.

21. The vector of claim 20 having ~~a serotype that has natural tropism for or a high~~
efficiency of infection of target cells within the eye.

22. The vector of claim 20, wherein the AAV is an AAV2 or AAV8 serotype, ~~preferably an~~
~~AAV vector particle comprising an AAV2 genome and AAV2 or AAV8 capsid proteins.~~

2343. A pharmaceutical composition comprising the isolated polynucleotide or vector of any one of claims 1 to 4222 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

4424. The isolated polynucleotide, vector or pharmaceutical composition of any one of claims 1 to 4323 for use in therapy.

~~2545. Use of the~~ The isolated polynucleotide, vector or pharmaceutical composition of any one of claims 1 to 4423 ~~for use in the manufacture of a medicament for the~~
treatment or prevention of a complement-mediated disorder of the eye, for example age-related macular degeneration (AMD), diabetic retinopathy, glaucoma, Stargardt's disease, central serous chorioretinopathy, retinitis pigmentosa, polypoidal choroidal vasculopathy, diabetic macular edema, branch retinal vein occlusion or uveitis, preferably AMD.

~~4626. The isolated polynucleotide, vector or pharmaceutical composition for use according to claim 4525, wherein the AMD is wet AMD and/or dry AMD.~~

~~4727. The isolated polynucleotide, vector or pharmaceutical composition for use according to claim 4525, wherein i) the AMD is wet AMD and the use medicament is for further~~
preventions and/or treatments of onset of dry AMD in a subject, or ii) the AMD is dry
AMD and the medicament is use for further ~~preventions and/or treatments of onset of~~
wet AMD in a subject, or iii) the medicament is for use ~~preventions and/or treatments~~
of dry AMD and wet AMD simultaneously.

~~2848. The isolated polynucleotide, vector or pharmaceutical composition for use according to claim 4727, wherein the AMD is wet AMD and the medicament is use for further~~
~~prevents prevention and/or treats treatment of onset of dry AMD in a subject.~~

5 | 1929. The ~~isolated polynucleotide, vector or pharmaceutical composition~~ for use according to any of claims ~~2545~~ to ~~4828~~, wherein:

(i) the formation of geographic atrophy is prevented or reduced, and/or the amount of geographic atrophy is reduced or wherein the progression of geographic atrophy is slowed;

(ii) there is at least a 10% reduction in the increase in geographic atrophy area over the 12 months following administration to a treated eye of a subject, relative to an untreated eye over the same period; or

10 | (iii) the medicament is to be administered to a subject, and administration of the isolated polynucleotide, vector or pharmaceutical composition increases the level of C3b-inactivating and iC3b-degradation activity in thea subject, or in an eye, such as in the retinal pigment epithelium (RPE), of a the subject, is increased, optionally to a level that exceeds a normal level in a subject, or eye or RPE thereof.

15 | 2030. The ~~isolated polynucleotide, vector or pharmaceutical composition~~ for use according to any of claims ~~45-25~~ to ~~4929~~, wherein i) neovascularization is prevented or reduced, ii) vascular leakage is prevented or reduced and/or iii) retina edema is prevented or reduced.

20 | 2131. The ~~isolated polynucleotide, vector or pharmaceutical composition~~ for use according to any one of claims ~~45-25~~ to ~~2030~~, wherein the polynucleotide, vector, cell or pharmaceutical composition is administered intraocularly, for example by subretinal, direct retinal, suprachoroidal or intravitreal injection.

25 | 2232. A product comprising (i) an anti-VEGF entity; and (ii) a negative complement regulator, or nucleotide sequences encoding therefor, as a combined preparation for i) simultaneous, separate or sequential use in treating wet AMD and wherein the use further prevents and/or treats onset of dry AMD in a subject; or ii) simultaneous, separate or sequential use in treating dry AMD and wherein the use further prevents and/or treats onset of wet AMD in a subject, or iii) simultaneous, separate or sequential use for simultaneously treating and/or preventing dry AMD and wet AMD.

30 | 2333. Use of a The product comprising (i) an anti-VEGF entity; and (ii) a negative complement regulator, or nucleotide sequences encoding therefor, in the manufacture of a medicament ~~for use according to claim 22~~for simultaneous, separate or sequential

use in the treatment of treating-wet AMD and wherein the use medicament is for further prevents-prevention and/or treats-treatment of onset of dry AMD in a subject.

2434. The ~~product for use~~ according to claim ~~22 or 23~~33 wherein the anti-VEGF entity is selected from an Ig fusion protein, an antibody, a polypeptide, a peptide, a non-antibody scaffold, an antisense oligonucleotide, siRNA, shRNA, CRISPR-guide strand and an aptamer, preferably wherein the anti-VEGF entity is selected from aflibercept, ranibizumab, bevacizumab, brolucizumab and pegaptanib.

2535. The ~~product for use~~ according to any of claims ~~22-33 to 24 or -34~~ wherein the negative complement regulator is selected from Complement Factor I (CFI), Complement Factor H Like Protein 1 (FHL1), Complement Factor H (CFH), Complement receptor type 1 (CR1), Membrane Cofactor Protein (MCP), Complement decay-accelerating factor (DAF), MAC-inhibitory protein (MAC-IP), C1-inhibitor, anaphylatoxins inhibitor, C4b binding protein (C4BP), clusterin, vitronectin or a variant or fragment thereof, preferably wherein the negative complement regulator is selected from CFI or FHL1 or a variant or fragment thereof.

2636. A product comprising (i) an anti-VEGF entity; and (ii) Factor I, or nucleotide sequences encoding therefor, as a combined preparation for simultaneous, separate or sequential use as a medicament.

2737. ~~Use of a~~ The product comprising (i) an anti-VEGF entity; and (ii) Factor I, or nucleotide sequences encoding therefor, in the manufacture of a medicament for simultaneous, separate or sequential use in the treatment ~~for use according to claim 26-36 for use in treating or preventing-prevention of~~ a complement-mediated ocular disorder, such as age-related macular degeneration (AMD), diabetic retinopathy, glaucoma, Stargardt's disease, central serous chorioretinopathy, retinitis pigmentosa, polypoidal choroidal vasculopathy, diabetic macular edema, branch retinal vein occlusion or uveitis, preferably AMD.

28 38. The ~~product for use~~ according to any of claims ~~22-33-35 and to 27-37~~33-35 and to 27-37, wherein:

(i) the formation of geographic atrophy is prevented or reduced, and/or the amount of geographic atrophy is reduced or wherein the progression of geographic atrophy is slowed;

(ii) there is at least a 10% reduction in the increase in geographic atrophy area over the 12 months following administration to a treated eye of a subject, relative to an untreated eye over the same period; or

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(iii) ~~the medicament is to be administered to a subject, and administration of the isolated polynucleotide, vector or pharmaceutical composition increases~~ the level of C3b-inactivating and iC3b-degradation activity in ~~a~~the subject, or in an eye, such as in the retinal pigment epithelium (RPE), of ~~a~~the subject, is increased, optionally to a level that exceeds a normal level in a subject, or eye or RPE thereof.

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~~2939.~~ The product for use according to any of claims ~~22-33-35 and 37- to 28~~33-35 and 37- to 28~~38~~, wherein i) neovascularization is prevented or reduced, ii) vascular leakage is prevented or reduced and/or iii) retina edema is prevented or reduced.