CLAIMS

1. A product comprising (i) a Complement Factor I (CFI) cofactor; and (ii) Complement Factor I (CFI), or nucleotide sequences encoding therefor, as a combined preparation for simultaneous, separate or sequential use in therapy, wherein the CFI cofactor is Complement Factor H Like Protein 1 (FHL1) or Complement Factor H (CFH).

2. A product comprising (i) a Complement Factor I (CFI) cofactor; and (ii) Complement Factor I (CFI), or nucleotide sequences encoding therefor, as a combined preparation for simultaneous, separate or sequential use in treating or preventing a complement-mediated disorder, preferably a complement-mediated disorder of the eye, wherein the CFI cofactor is Complement Factor H Like Protein 1 (FHL1) or Complement Factor H (CFH).

3. The product for use according to claim 2, wherein the complement-mediated disorder is age-related macular degeneration (AMD) or diabetic retinopathy, preferably AMD.

4. The product for use according to claim 3, wherein the AMD is dry AMD.

~~5. The product for use according to any preceding claim, wherein the Complement Factor I (CFI) cofactor is selected from the group consisting of Complement Factor H Like Protein 1 (FHL1); Complement Factor H (CFH); Complement Receptor 1 (CR1) or a fragment thereof; and Membrane Cofactor Protein (MCP) or a fragment thereof.~~

~~6~~5. The product for use according to any preceding claim, wherein the product provides (i) and (ii) to a subject in a (i):(ii) molar ratio of at least 2:1, preferably at least 3:1, more preferably at least 8:1, more preferably at least 15:1.

~~7~~6. The product for use according to any preceding claim, wherein the product provides (i) and (ii) to a subject in a (i):(ii) molar ratio of between 2:1 and 12:1, preferably between 3:1 and 10:1.

~~8~~7. An isolated polynucleotide comprising nucleotide sequences encoding (i) a Complement Factor I (CFI) cofactor; and (ii) Complement Factor I (CFI), wherein the CFI cofactor is Complement Factor H Like Protein 1 (FHL1) or Complement Factor H (CFH).

~~9~~8. The isolated polynucleotide of claim ~~8~~7, wherein the polynucleotide further comprises nucleotide sequences encoding:

(a) a CMV promoter, optionally wherein the CMV promoter is upstream of the nucleotide sequences encoding the (i) and (ii);

(b) a WPRE regulatory element, optionally wherein the WPRE regulatory element is downstream of the nucleotide sequences encoding the (i) and (ii); and/or

(c) a poly-A signal, optionally a Bovine Growth Hormone poly-A signal, wherein the polyA signal is optionally downstream of the nucleotide sequences encoding the (i) and (ii).

~~10~~9. The isolated polynucleotide of claim ~~8~~ 7 or ~~9~~8, wherein the nucleotide sequence encoding (i) is upstream of the nucleotide sequence encoding (ii).

~~11~~10. The isolated polynucleotide of any one of claims ~~8~~7-~~10~~9, wherein the polynucleotide further comprises one or more adeno-associated virus (AAV) inverted terminal repeats (ITRs), preferably wherein the polynucleotide comprises an AAV ITR at its 5' end and an AAV ITR at its 3' end.

~~12~~11. The isolated polynucleotide of any one of claims ~~8~~7-~~11~~10, wherein the polynucleotide comprises:

(a) a 5' AAV ITR;

(b) a CMV promoter;

(c) a nucleotide sequence encoding ~~a~~ the Complement Factor I (CFI) cofactor;

(d) a linker, optionally wherein the linker is or is defined by a Furin cleavage site, GSG, 11aa1D sequence and an F2A sequence;

(e) a nucleotide sequence encoding CFI;

(f) a WPRE regulatory element, optionally wherein the WPRE regulatory element is a WPRE3 regulatory element;

(g) a Bovine Growth Hormone poly-A signal; and

(h) a 3' AAV ITR.

~~13. The isolated polynucleotide of any one of claims 8-12, wherein the Complement Factor~~

~~I (CFI) cofactor is selected from the group consisting of Complement Factor H Like Protein 1 (FHL1); Complement Factor H (CFH); Complement Receptor 1 (CR1) or a fragment thereof; and Membrane Cofactor Protein (MCP) or a fragment thereof.~~

~~14~~12. The isolated polynucleotide of any one of claims ~~8~~7-~~13~~11, wherein the AAV ITRs are AAV2 or AAV8 ITRs.

~~15~~13. The isolated polynucleotide of any one of claims ~~8~~7-~~14~~12, wherein the nucleotide sequences encoding the CFI cofactor, and CFI are codon optimised.

~~16~~14. The isolated polynucleotide of any one of claims ~~8~~7-~~15~~13, wherein: (a) the nucleotide sequence encoding FHL1 has at least ~~75~~85% sequence identity to SEQ ID NO: 12; and/or (b) the nucleotide sequence encoding CFI has at least ~~75~~85% sequence identity to SEQ ID NO: 10, preferably wherein: (a) the nucleotide sequence encoding FHL1 is SEQ ID NO: 12; and/or (b) the nucleotide sequence encoding CFI is SEQ ID NO: 10.

~~17~~15. The isolated polynucleotide of any one of claims ~~8~~7-~~16~~14, wherein the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 22 or 23, or a nucleotide sequence that has at least ~~75~~85% sequence identity thereto.

~~18~~16. A vector comprising the polynucleotide of any one of claims ~~8~~7-~~17~~15, preferably wherein the vector is an adeno-associated viral (AAV) vector and the CFI cofactor is Complement Factor H Like Protein 1 (FHL1).

~~19~~17. The vector of claim ~~18~~16, wherein the vector is in the form of a viral vector particle, preferably wherein the AAV vector particle comprises an AAV2 or AAV8 genome, and AAV2 or AAV8 capsid proteins.

~~20~~18. A cell comprising the polynucleotide of any one of claims ~~8~~7-~~17~~ 15 or a cell transduced with the vector of any one of claims ~~18~~ 16 or ~~19~~17.

~~21~~19. A pharmaceutical composition comprising the polynucleotide, vector or cell of any one of claims ~~8~~7-~~20~~ 18, ~~in combination with~~and a pharmaceutically acceptable carrier, diluent or excipient.

~~22~~20. The polynucleotide, vector or cell of any one of claims ~~8~~7-~~20~~ 18 for use in therapy, preferably for use in treating or preventing a complement-mediated disorder, preferably a complement-mediated disorder of the eye, more preferably wherein the complement-mediated disorder is age-related macular degeneration (AMD) or diabetic retinopathy, preferably AMD.

2321. The polynucleotide, vector or cell for use according to claim 2220, wherein the AMD is dry AMD.

2422. The polynucleotide, vector or cell for use according to any one of claims 22-20 or 2321, wherein:

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

ii) the progression of geographic atrophy is slowed; and/or

iii) 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; and/or

iv) wherein administration of the polynucleotide, vector or cell increases the level of C3b-inactivating and iC3b-degradation activity in a subject, or in an eye, such as in the retinal pigment epithelium (RPE), of a subject, optionally to a level that exceeds a normal level in a subject, or eye or RPE thereof.

2523. The polynucleotide, vector or cell for use according to any one of claims 2220-2422, wherein the polynucleotide, vector or cell is administered intraocularly, preferably wherein the polynucleotide, vector or cell is administered to the eye of a subject by subretinal, direct retinal, suprachoroidal or intravitreal injection, more preferably wherein the polynucleotide, vector or cell is administered to the eye of a subject by subretinal injection.

2624. The use of a polynucleotide, vector or cell of any one of claims 87-20 18 for the manufacture of a medicament for treating or preventing a complement-mediated disorder, preferably a complement-mediated disorder of the eye comprising administering to a subject in need thereof.

~~27. The use of a polynucleotide, vector or cell of any one of claims 8-20 for the manufacture of a medicament for providing (i) a Complement Factor I (CFI) cofactor; and (ii) Complement Factor I (CFI) to a subject, preferably to the eye of the subject.~~