

A therapy for the treatment of geographic atrophy has been developed and is currently in a phase III clinical study (MAHALO study by Genentech/Roche). Lampalizumab is a humanised monoclonal inhibitory antibody to complement Factor D, administered by intravitreal injection to stop the rate of progression of geographic atrophy. As show in Figure 1, Factor D is part of the C3b feedback ('amplification') cycle. Factor D is present in very low serum concentrations and is an essential factor for the alternative pathway. Nevertheless, due to its small size (27 kDa), Factor D is rapidly cleared out by the kidneys and quickly re-synthesised. The therapy requires monthly intravitreal injections.

There is a need in the art for new approaches to treat AMD.

10 SUMMARY

The present inventors now provide an approach for modulating the complement system which is useful, for example, in the treatment of AMD. The inventors provide Factor I delivered by gene therapy with the aim of negatively regulating the complement C3b feedback cycle through targeting of the breakdown cycle (Figure 1). The resulting re-balancing of the feedback loop of the alternative pathway will promote C3b and iC3b breakdown and thus remove major disease factors in complement-mediated disorders, particularly disorders that have an underlying defect in alternative pathway regulation. Alternatively, Factor H may instead be used.

In one aspect, the present disclosure refers to an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I or a fragment thereof, wherein the Factor I or fragment thereof is capable of cleaving C3b into iC3b. In another aspect, the present disclosure refers to an isolated cell transfected with the AAV vector as disclosed herein. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the AAV vector or the cell as disclosed herein in combination with a pharmaceutically acceptable carrier, diluent or excipient. In yet another aspect, there is provided an AAV vector, cell or pharmaceutical composition of the present disclosure for use in treating or preventing a complement-mediated disorder of the eye, wherein the disorder is age-related macular degeneration (AMD), and wherein the AAV vector, cell or pharmaceutical composition is to be administered intraocularly. In yet another aspect, there is provided the use of the AAV vector, cell or pharmaceutical composition of the present disclosure in the manufacture of a medicament for treating or preventing a complement-mediated disorder of the eye, wherein the disorder is age-related macular degeneration (AMD), and wherein the AAV vector, cell or pharmaceutical composition is to be administered intraocularly. In one aspect, the present disclosure refers to a use of an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I, wherein the Factor I is capable of cleaving C3b into iC3b, in the manufacture of a medicament for treating age-related macular degeneration (AMD), wherein the AAV vector is to be

administered intraocularly. In another aspect, the present disclosure refers to a use of an isolated cell transfected with an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I, wherein the Factor I is capable of cleaving C3b into iC3b, in the manufacture of a medicament for treating age-related macular degeneration (AMD), wherein the cell is to be administered intraocularly. In yet another aspect, the present invention refers to a use of a pharmaceutical composition comprising an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I, wherein the Factor I is capable of cleaving C3b into iC3b, in combination with a pharmaceutically acceptable carrier, diluent or excipient, in the manufacture of a medicament for treating age-related macular degeneration (AMD), wherein the pharmaceutical composition is to be administered intraocularly. In one aspect, the present disclosure refers to a use of a pharmaceutical composition comprising an isolated cell transfected with an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I, wherein the Factor I is capable of cleaving C3b into iC3b, in combination with a pharmaceutically acceptable carrier, diluent or excipient, in the manufacture of a medicament for in treating age-related macular degeneration (AMD), wherein the pharmaceutical composition is to be administered intraocularly.

In one example, the disclosure provides an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I or a fragment or derivative thereof. In another

CLAIMS

1. ~~An adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I or a fragment thereof, wherein the Factor I or fragment thereof is capable of cleaving C3b into iC3b.~~
- 5 2. ~~The AAV vector of claim 1, wherein the nucleotide sequence encoding Factor I or fragment thereof comprises a sequence selected from the group consisting of:
 - (a) ~~a nucleotide sequence encoding an amino acid sequence that has at least 70% identity to SEQ ID NO: 1;~~
 - 10 (b) ~~a nucleotide sequence that has at least 70% identity to SEQ ID NO: 2;~~
~~and~~
 - (c) ~~the nucleotide sequence of SEQ ID NO: 2.~~~~
3. ~~The AAV vector of claim 1 or 2, wherein the viral vector is in the form of a viral particle.~~
- 15 4. ~~The AAV vector of claim 3, wherein the AAV viral particle comprises an AAV2 genome and AAV2 capsid proteins.~~
5. ~~The AAV vector of any preceding claim, wherein the nucleotide sequence encoding Factor I or fragment thereof is operably linked to a CAG promoter, preferably a promoter with the nucleotide sequence of SEQ ID NO: 5.~~
6. ~~An isolated cell transfected with the AAV vector of any one of claims 1-5.~~
- 20 7. ~~A pharmaceutical composition comprising the AAV vector of any one of claims 1-5 or the cell of claim 6 in combination with a pharmaceutically acceptable carrier, diluent or excipient.~~
8. ~~The AAV vector, cell or pharmaceutical composition of any one of claims 1-7 for use in treating or preventing a complement mediated disorder of the eye, wherein the disorder is age-related macular degeneration (AMD), and wherein the AAV vector, cell or pharmaceutical composition is to be administered intraocularly.~~
- 25 9. ~~The AAV vector, cell or pharmaceutical composition for use according to claim 8, wherein the AMD is dry AMD.~~

- 5 10. ~~The AAV vector, cell or pharmaceutical composition for use according to claim 8 or 9, wherein the AAV vector, cell or pharmaceutical composition to be administered increases the level of C3b-inactivating and iC3b-degradation activity in an eye, such as in the retinal pigment epithelium (RPE), of a subject, optionally to a level that exceeds a normal level in an eye or RPE of a subject.~~
11. ~~The AAV vector, cell or pharmaceutical composition for use according to any one of claims 8-10, wherein the AAV vector, cell or pharmaceutical composition is to be administered to the eye of a subject by subretinal, direct retinal, suprachoroidal or intravitreal injection.~~
- 10 12. ~~The AAV vector, cell or pharmaceutical composition for use according to any one of claims 8-11, wherein the AAV vector, cell or pharmaceutical composition is to be administered to the eye of a subject by subretinal injection.~~
- 15 ~~13.1. Use of the an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I, wherein the Factor I is capable of cleaving C3b into iC3b, cell or pharmaceutical composition of any one of claims 1-7 in the manufacture of a medicament for treating or preventing a complement-mediated disorder of the eye, wherein the disorder is age-related macular degeneration (AMD), and wherein the AAV vector, cell or pharmaceutical composition is to be administered intraocularly.~~
- 20 2. Use of an isolated cell transfected with an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I, wherein the Factor I is capable of cleaving C3b into iC3b, in the manufacture of a medicament for treating age-related macular degeneration (AMD), wherein the cell is to be administered intraocularly.
- 25 3. Use of a pharmaceutical composition comprising an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I, wherein the Factor I is capable of cleaving C3b into iC3b, in combination with a pharmaceutically acceptable carrier, diluent or excipient, in the manufacture of a medicament for treating age-related macular degeneration (AMD), wherein the pharmaceutical composition is to be administered intraocularly.
- 30 4. Use of a pharmaceutical composition comprising an isolated cell transfected with an adeno-associated viral (AAV) vector comprising a nucleotide sequence encoding Factor I, wherein the Factor I is capable of cleaving C3b into iC3b, in combination with a pharmaceutically acceptable carrier, diluent or excipient, in the manufacture of

- a medicament for in treating age-related macular degeneration (AMD), wherein the pharmaceutical composition is to be administered intraocularly.
5. The use of any preceding claim, wherein the nucleotide sequence encoding Factor I comprises a sequence selected from the group consisting of:
- 5 (a) a nucleotide sequence encoding an amino acid sequence that has at least 70% identity to SEQ ID NO: 1;
- (b) a nucleotide sequence that has at least 70% identity to SEQ ID NO: 2;
 and
- (c) the nucleotide sequence of SEQ ID NO: 2.
- 10 6. The use of any preceding claim, wherein the AAV vector is in the form of an AAV viral particle.
7. The use of claim 6, wherein the AAV viral particle is an AAV2, AAV5, or AAV8 serotype.
- 15 8. The use of claim 6 or 7, wherein the AAV viral particle comprises an AAV2 genome and AAV2 capsid proteins, an AAV2 genome and AAV5 capsid proteins, or an AAV2 genome and AAV8 capsid proteins.
9. The use of claim 6 or 7, wherein the AAV viral particle comprises an AAV2 genome and AAV2 capsid proteins.
- 20 10. The use of any preceding claim, wherein the nucleotide sequence encoding Factor I or is operably linked to a CAG promoter, preferably a promoter with the nucleotide sequence of SEQ ID NO: 5.
11. The use of any preceding claim, wherein the nucleotide sequence encoding Factor I is operably linked to a Bovine Growth Hormone poly-A signal.
- 25 12. The use of any preceding claim, wherein the nucleotide sequence encoding Factor I is operably linked to a woodchuck hepatitis post-transcriptional regulatory element (WPRE).
- ~~14.~~13. The use of any one of the preceding claimsclaim 13, wherein the AMD is dry AMD.
- ~~15.~~14. The use of any one of the preceding claimsclaim 13 or 14, wherein the AAV vector, cell or pharmaceutical composition to be administered increases the level of C3b-

inactivating and iC3b-degradation activity in an eye, such as in the retinal pigment epithelium (RPE), of a subject, optionally to a level that exceeds a normal level in an eye or RPE of a subject.

5 | ~~16.15.~~ The use of any one of the preceding claims~~claims 13-15~~, wherein the AAV vector, cell or pharmaceutical composition is to be administered to the eye of a subject by subretinal, direct retinal, suprachoroidal or intravitreal injection.

| ~~17.16.~~ The use of any one of the preceding claims~~claims 13-16~~, wherein the AAV vector, cell or pharmaceutical composition is to be administered to the eye of a subject by subretinal injection.

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