Summary

In one aspect, the present disclosure refers to the use of a recombinant adeno-associated virus (rAAV) particle encapsidating a rAAV vector comprising nucleic acid encoding Factor I, or a fragment or derivative thereof that retains C3b-inactivating and iC3b-degradation activity in the manufacture of a medicament for preventing, treating, or ameliorating a complement-mediated disorder in a subject in need thereof, wherein the use comprises that the medicament is to be administered intravenously to the subject such that a therapeutically effective amount of the encoded Factor I, or the fragment or derivative thereof, is expressed from the nucleic acid in the subject, thereby increasing the level of C3b-inactivating and iC3b-degradation activity in the subject, wherein the complement-mediated disorder is a disorder associated with over-activity of the complement C3b feedback cycle. In another aspect, the present disclosure refers to a recombinant adeno-associated virus (rAAV) vector which comprises nucleic acid encoding Factor I, or a fragment or derivative thereof that retains C3b-inactivating and iC3b-degradation activity, wherein the nucleic acid encoding Factor I, or the fragment or derivative thereof, is operably linked to a liver-specific promoter. In yet another aspect, the present disclosure refers to pharmaceutical composition, which comprises: a rAAV vector as disclosed herein, or a rAAV particle as disclosed herein; and a pharmaceutically acceptable carrier, excipient, or diluent. In yet another aspect, the present disclosure refers to a kit, which comprises: a rAAV vector according to the present disclosure, or a rAAV particle according to the present disclosure; and a pharmaceutically acceptable carrier, excipient, or diluent. In still another aspect, the present disclosure refers to a kit for production of rAAV particles, which comprises: a rAAV vector according to the present disclosure; and one or more helper plasmids comprising nucleic acid encoding AAV replication and capsid proteins, and genes required for a productive AAV life cycle. In another aspect, the present disclosure refers to a rAAV vector as disclosed herein, a rAAV particle as disclosed herein, or a pharmaceutical composition as disclosed herein, for use as a medicament. In another aspect, the present disclosure refers to a rAAV vector as disclosed herein, a rAAV particle as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in the treatment of a complement-mediated disorder, wherein the complement-mediated disorder is a disorder associated with over-activity of the complement C3b feedback cycle. In yet another aspect, there is provided the use of a rAAV vector according to the present disclosure, a rAAV particle according to the present disclosure, or a pharmaceutical composition according to the present disclosure, in the manufacture of a medicament for the treatment of a complement-mediated disorder, wherein the complement-mediated disorder is a disorder associated with over-activity of the complement C3b feedback cycle.

Detailed Description

**Claims**

1. Use of a recombinant adeno-associated virus (rAAV) particle encapsidating a rAAV vector comprising nucleic acid encoding Factor I, or a fragment or derivative thereof that retains C3b-inactivating and iC3b-degradation activity in the manufacture of a medicament for preventing, treating, or ameliorating a complement-mediated disorder in a subject in need thereof, wherein the use comprises that the medicament is to be administered intravenously to the subject such that a therapeutically effective amount of the encoded Factor I, or the fragment or derivative thereof, is expressed from the nucleic acid in the subject, thereby increasing the level of C3b-inactivating and iC3b-degradation activity in the subject, wherein the complement-mediated disorder is a disorder associated with over-activity of the complement C3b feedback cycle.

2. The use according to claim 1, wherein the level of C3b-inactivating and iC3b-degradation activity in the subject is increased to a level that exceeds a normal level.

3. The use according to claim 1 or claim 2, wherein the rAAV particle infects the liver of the subject following administration, resulting in expression of the Factor I, or the fragment or derivative thereof, from the liver.

4. The use according to any preceding claim, wherein the rAAV particle is pseudotyped to confer liver tropism.

5. The use according to claim 4, wherein the rAAV particle comprises one or two AAV2 ITRs, or derivatives thereof wherein each derivative AAV2 ITR comprises nucleotide sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical over its entire length with the nucleotide sequence of a naturally occurring AAV2 ITR, and wherein the rAAV particle is pseudotyped with AAV8 capsid protein (rAAV2/8), or pseudotyped with AAV9 capsid protein (rAAV2/9), or a derivative thereof comprising amino acid sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the amino acid sequence of a naturally occurring AAV8 or AAV9 capsid protein.

6. The use according to any preceding claim, wherein the encoded Factor I, or the fragment or derivative thereof, is expressed from a liver-specific promoter, such as a human alpha-1-anti-trypsin (hAAT) promoter.

7. The use according to any preceding claim, wherein the level of C3b-inactivating and iC3b-degradation activity in the subject is increased to a level that is up to twice the normal level.

8. The use according to any preceding claim, wherein the level of C3b-inactivating and iC3b-degradation activity in the subject is increased to a level that is up to 80%, or up to 60%, above the normal level.

9. The use according to any preceding claim, wherein the level of C3b-inactivating and iC3b-degradation activity in the subject is increased to a level that is up to 40%, or up to 20% above the normal level.

10. The use according to any preceding claim, wherein the level of C3b-inactivating and iC3b-degradation activity in the subject is increased to a level that is at least 5%, 10%, 15%, 20%, or 25% above the normal level.

11. The use according to any preceding claim, wherein the level of C3b-inactivating and iC3b-degradation activity in the subject is the level in serum of the subject.

12. The use according to any preceding claim, wherein the normal level of C3b-inactivating and iC3b-degradation activity in the subject is equivalent to that provided by 30-40μg/ml Factor I in serum of the subject.

13. The use according to any preceding claim, wherein the complement-mediated disorder is age-related macular degeneration (AMD) (particularly early (dry) AMD, or geographic atrophy), dense deposit disease (DDD), atypical haemolytic uraemic syndrome (aHUS), C3 glomerulopathies, membranoproliferative glomerulonephritis Type 2 (MPGN2), atherosclerosis, chronic cardiovascular disease, Alzheimer's disease, systemic vasculitis, paroxysmal nocturnal haemoglobinuria (PNH), membranoproliferative glomerulonephritis type I (MPGN type I), membranoproliferative glomerulonephritis type III (MPGN type III), Guillain-Barré syndrome, Henoch-Schonlein purpura, IgA nephropathy, or membranous glomerulonephritis.

14. The use according to claim 13, wherein the subject is at risk of developing AMD.

15. The use according to claim 14, wherein the subject is homozygous or heterozygous susceptible for one or more SNPs associated with AMD.

16. The use according to claim 14 or 15, which further comprises determining whether the subject is at risk of developing AMD.

17. The use according to claim 16, wherein it is determined whether the subject is at risk of developing AMD by determining whether the subject is homozygous or heterozygous susceptible for one or more SNPs associated with AMD.

18. The use according to claim 15 or 17, wherein the level of C3b-inactivating and iC3b-degradation activity in the subject is increased to a level that is at least 10% above the normal level if the subject is heterozygous susceptible for one or more SNPs associated with AMD.

19. The use according to claim 15 or 17, wherein the level of C3b-inactivating and iC3b-degradation activity in the subject is increased to a level that is at least 50% above the normal level if the subject is homozygous susceptible for one or more SNPs associated with AMD.

20. The use according to any preceding claim, which further comprises determining the level of C3b-inactivating and iC3b-degradation activity in the subject at least a week after the administration, and repeating the administration if the level of activity is found to be at, or below the normal level.

21. The use according to any preceding claim, wherein the Factor I is human Factor I with an amino acid sequence of SEQ ID NO: 2 or 4.

22. The use according to any preceding claim, wherein the fragment or derivative of Factor I is a polypeptide that has at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% amino acid identity across its entire length to human Factor I with an amino acid sequence of SEQ ID NO: 2 or 4.

23. The use according to any preceding claim, wherein the subject is a human subject.

24. A recombinant adeno-associated virus (rAAV) vector which comprises nucleic acid encoding Factor I, or a fragment or derivative thereof that retains C3b-inactivating and iC3b-degradation activity, wherein the nucleic acid encoding Factor I, or the fragment or derivative thereof, is operably linked to a liver-specific promoter.

25. A rAAV vector according to claim 24, wherein the liver-specific promoter is a human alpha-1-anti-trypsin (hAAT) promoter.

26. A rAAV vector according to claim 24 or claim 25, which comprises an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises the nucleic acid encoding Factor I, or the fragment or derivative thereof, operably linked to the liver specific promoter and a polyadenylation recognition site.

27. A rAAV vector according to claim 26, wherein the ITRs are AAV2 ITRs, or derivatives thereof, wherein each derivative AAV2 ITR comprises nucleotide sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical over its entire length with the nucleotide sequence of a naturally occurring AAV2 ITR.

28. A rAAV particle, which comprises a viral capsid encapsidating a rAAV vector according to any of claims 24 to 27.

29. A rAAV particle according to claim 28 which is capable of transducing liver cells, particularly hepatocytes.

30. A rAAV particle according to claim 28 or claim 29, wherein the rAAV particle is pseudotyped to confer liver tropism.

31. A rAAV particle according to any one of claims 28 to 30, wherein the rAAV particle comprises AAV8 or AAV9 capsid protein, or a derivative thereof comprising amino acid sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the amino acid sequence of a naturally occurring AAV8 or AAV9 capsid protein.

32. A rAAV particle according to claim 31, wherein the rAAV particle comprises one or two AAV2 ITRs, or derivatives thereof wherein each derivative AAV2 ITR comprises nucleotide sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical over its entire length with the nucleotide sequence of a naturally occurring AAV2 ITR.

33. A pharmaceutical composition, which comprises: a rAAV vector according to any of claims 24 to 27, or a rAAV particle according to any of claims 28 to 32; and a pharmaceutically acceptable carrier, excipient, or diluent.

34. A pharmaceutical composition according to claim 33, which is suitable for intravenous administration.

35. A kit, which comprises: a rAAV vector according to any of claims 24 to 27, or a rAAV particle according to any of claims 28 to 32; and a pharmaceutically acceptable carrier, excipient, or diluent.

36. A kit for production of rAAV particles, which comprises: a rAAV vector according to any of claims 24 to 27; and one or more helper plasmids comprising nucleic acid encoding AAV replication and capsid proteins, and genes required for a productive AAV life cycle.

37. A kit according to claim 36, which comprises a first helper plasmid comprising the nucleic acid encoding AAV replication and capsid proteins, and a second helper plasmid comprising the nucleic acid encoding genes required for a productive AAV life cycle.

38. A rAAV vector according to any of claims 24 to 27, a rAAV particle according to any of claims 28 to 32, or a pharmaceutical composition according to claim 33 or 34, for use as a medicament.

39. A rAAV vector according to any of claims 24 to 27, a rAAV particle according to any of claims 28 to 32, or a pharmaceutical composition according to claim 33 or 34, for use in the treatment of a complement-mediated disorder, wherein the complement-mediated disorder is a disorder associated with over-activity of the complement C3b feedback cycle.

40. Use of a rAAV vector according to any of claims 24 to 27, a rAAV particle according to any of claims 28 to 32, or a pharmaceutical composition according to claim 33 or 34, in the manufacture of a medicament for the treatment of a complement-mediated disorder, wherein the complement-mediated disorder is a disorder associated with over-activity of the complement C3b feedback cycle.

41. A rAAV vector, a rAAV particle, or a pharmaceutical composition according to claim 39, or use according to claim 40, wherein the complement-mediated disorder is age-related macular degeneration (AMD) (particularly early (dry) AMD, or geographic atrophy), dense deposit disease (DDD), atypical haemolytic uraemic syndrome (aHUS), C3 glomerulopathies, membranoproliferative glomerulonephritis Type 2 (MPGN2), atherosclerosis, chronic cardiovascular disease, Alzheimer's disease, systemic vasculitis, paroxysmal nocturnal haemoglobinuria (PNH), membranoproliferative glomerulonephritis type I (MPGN type I), membranoproliferative glomerulonephritis type III (MPGN type III), Guillain-Barré syndrome, Henoch-Schonlein purpura, IgA nephropathy, or membranous glomerulonephritis.

42. A rAAV vector, a rAAV particle, or a pharmaceutical composition according to claim 39, or use according to claim 40, wherein the complement-mediated disorder is age-related macular degeneration (AMD).