

CLAIMS

1. A polynucleotide comprising a Complement Factor I (CFI) nucleotide sequence,
wherein the CFI nucleotide sequence encodes a CFI polypeptide or a fragment
5 thereof, wherein at least a portion of the CFI nucleotide sequence is not wild-type,
wherein the CFI polypeptide or the fragment thereof encoded by the CFI nucleotide
sequence is expressed at a higher level in a human liver cell compared to
expression of a CFI polypeptide encoded by a reference CFI nucleotide sequence.
- 10 2. The polynucleotide of claim 1, wherein:
- (i) the reference CFI nucleotide sequence is a wild type CFI nucleotide
sequence;
 - (ii) the CFI polypeptide or the fragment thereof encoded by the CFI nucleotide
15 sequence is expressed at a higher level on transfection of the
polynucleotide comprising the CFI nucleotide sequence into a human liver
cell compared to expression of the CFI polypeptide encoded by the
reference CFI nucleotide sequence on transfection with an equivalent
polynucleotide comprising the reference CFI nucleotide sequence;
 - (iii) the human liver cell is a Huh-7 cell; and/or
 - 20 (iv) the expression of the CFI polypeptide or the fragment thereof encoded by
the CFI nucleotide sequence is at least 1.5x, at least 2x, at least 3x, at least
5x, at least 8x, at least 10x, at least 20x, at least 30x, at least 40x, or at
least 50x higher compared to the CFI polypeptide encoded by the
reference CFI nucleotide sequence.
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3. The polynucleotide of claim 1 or 2, wherein:
- (a) the portion of the CFI nucleotide sequence that is not wild type is codon-
optimised, and wherein the portion of the CFI nucleotide sequence that is codon-
optimised is codon-optimised for expression in human liver cells; or
 - 30 (b) the portion of the CFI nucleotide sequence that is not wild type is codon-
optimised, and wherein the portion of the CFI nucleotide sequence that is codon-
optimised is codon-optimised for expression in human liver cells, and-

4. ~~The polynucleotide of claim 3,~~ wherein the portion of the CFI nucleotide sequence that is codon-optimised:
- (i) is a contiguous portion;
 - 5 (ii) is at least 1000, at least 1200, at least 1300, at least 1400, at least 1500, at least 1600, at least 1700, 1752 or fewer, between 1300 and 1752, between 1500 and 1752, between 1600 and 1752, or around 1752 nucleotides in length;
 - 10 (iii) is at least 1000, at least 1200, at least 1300, at least 1400, at least 1500, 1698 or fewer, between 1300 and 1698, between 1500 and 1698, or around 1698 nucleotides in length; and/or
 - (iv) encodes a mature CFI polypeptide.
- 15 ~~54.~~ The polynucleotide of any one of the preceding claims, wherein the CFI nucleotide sequence is codon-optimised for expression in human liver cells.
- 20 ~~65.~~ The polynucleotide of ~~any one of claims 3 to 5~~claim 3 or 4, wherein, in the CFI nucleotide sequence or the portion of the CFI nucleotide sequence that is codon-optimised, at least 70%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, or at least 81%, at least 82%, at least 83%, or at least 84% of the codons are selected from the group consisting of: GCT, GCC, TGC, GAC, GAG, TTC, GGA, GGC, CAC, ATC, AAG, CTG, AAT, AAC, CCT, CCC, CAG, AGG, AGA, AGT, AGC, ACC, GTG and TAC.
- 25 ~~76.~~ The polynucleotide of any one of claims 3 to ~~65~~, wherein the CFI nucleotide sequence or the portion of the CFI nucleotide sequence that is codon-optimised:
- (i) comprises a reduced number of CpGs compared to a corresponding portion of a reference CFI nucleotide sequence; and/or
 - (ii) comprises a reduced number of CpGs compared to a corresponding portion
 - 30 of a reference CFI nucleotide sequence, and:
 - (a) comprises 40 or fewer, 20 or fewer, 15 or fewer, 10 or fewer, or 5 or fewer CpGs;

- (b) comprises 40 or fewer, 20 or fewer, 15 or fewer, 10 or fewer, or 5 or fewer CpGs, and wherein the CFI nucleotide sequence or the portion of the CFI nucleotide sequence that is codon-optimised comprises 5 or fewer, 4 or fewer, 3 or fewer, or 2 or fewer CpGs per 100 nucleotides; and/or
- 5 (c) is CpG-free.

87. The polynucleotide of claim 76, wherein the reference CFI nucleotide sequence is a wild-type CFI nucleotide sequence.

- 10 98. The polynucleotide of any one of claims 3, 4 or 6 to 8 or 5 to 7, wherein the portion of the CFI nucleotide sequence that is codon-optimised is:
- (i) at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.5%, at least 99.8%, or 100% identical to any one of SEQ ID NOs: 5, 10, and 17;
- 15 (ii) at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.5%, at least 99.8%, or 100% identical to any one of SEQ ID NOs: 1-20; and/or
- (iii) at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.5%, at least 99.8%, or 100% identical to SEQ ID NO: 5.

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409. The polynucleotide of any one of the preceding claims, wherein:
(a) the CFI nucleotide sequence encodes a signal peptide; and/or

11. The polynucleotide of any one of the preceding claims, (b) wherein the
25 polynucleotide further comprises a transcription regulatory element.

12. The polynucleotide of claim 11, wherein the transcription regulatory element comprises a liver specific promoter.

30 13. The polynucleotide of claim 11 or 12, wherein the transcription regulatory element comprises a nucleotide sequence having at least 98% identity to SEQ ID NO: 74.

410. A polynucleotide comprising a Complement Factor I (CFI) nucleotide sequence,
wherein:
(a) the CFI nucleotide sequence encodes a CFI polypeptide or a fragment thereof
and wherein at least a portion of the CFI nucleotide sequence is not wild-type; or
5 (b) the CFI nucleotide sequence encodes a CFI polypeptide or a fragment thereof
and the CFI nucleotide sequence comprises a sequence that is at least 95%, at least
96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.8%, or
100% identical to a fragment of at least 1200, at least 1400, at least 1500, 1698 or
fewer, 1752 or fewer, between 1200 and 1698, between 1200 and 1752, between
10 1500 and 1698, between 1500 and 1752, around 1698, or around 1752 nucleotides
of any one of SEQ ID NOs: 1-40.
411. The polynucleotide of ~~any one of the preceding claims~~any one of claims 1 to 9 or
10(a), wherein the CFI nucleotide sequence comprises a sequence that is at least
15 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least
99.8%, or 100% identical to a fragment of at least 1200, at least 1400, at least 1500,
1698 or fewer, 1752 or fewer, between 1200 and 1698, between 1200 and 1752,
between 1500 and 1698, between 1500 and 1752, around 1698, or around 1752
nucleotides of any one of SEQ ID NOs: 1-40.
16. ~~A polynucleotide comprising a CFI nucleotide sequence, wherein the CFI
nucleotide sequence encodes a CFI polypeptide or a fragment thereof and the CFI
nucleotide sequence comprises a sequence that is at least 95%, at least 96%, at least
97%, at least 98%, at least 99%, at least 99.5%, at least 99.8%, or 100% identical to
25 a fragment of at least 1200, at least 1400, at least 1500, 1698 or fewer, 1752 or
fewer, between 1200 and 1698, between 1200 and 1752, between 1500 and 1698,
between 1500 and 1752, around 1698, or around 1752 nucleotides of any one of
SEQ ID NOs: 1-40.~~
412. The polynucleotide of any one of the preceding claims, wherein the CFI nucleotide
sequence comprises:

- 5 (i) a sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.8%, or 100% identical to a fragment of at least 1200, at least 1400, at least 1500, 1698 or fewer, 1752 or fewer, between 1200 and 1698, between 1200 and 1752, between 1500 and 1698, between 1500 and 1752, around 1698, or around 1752 nucleotides of any one of SEQ ID NO: 5 or 25;
- (ii) a sequence of any one of SEQ ID NOs: 1-20, or a variant thereof encoding a CFI polypeptide comprising a sequence at least 95% identical to the wild type CFI amino acid sequence of SEQ ID NO: 44; and/or
- 10 (iii) a sequence of any one of SEQ ID NOs: 1-20, or a variant thereof encoding a CFI polypeptide comprising a sequence at least 95% identical to the wild type CFI amino acid sequence of SEQ ID NO: 44, wherein the variant is a variant of SEQ ID NO: 5, and wherein the variant of SEQ ID NO: 5 is identical to SEQ ID NO: 5 except that it comprises nucleotide substitutions
- 15 such that the CFI polypeptide has 1, 2 or fewer, 3 or fewer, 4 or fewer, 5 or fewer, 6 or fewer, 7 or fewer, 8 or fewer, 9 or fewer, or 10 or fewer amino acid substitutions relative to the wild type CFI amino acid sequence of SEQ ID NO:44.

20 ~~18~~13. A viral particle comprising a recombinant genome comprising the polynucleotide of any one of the preceding claims.

~~19~~14. The viral particle of claim ~~18~~13, wherein the viral particle:

25 (a) which is an AAV viral particle; or
(b) is an AAV viral particle and comprises a capsid.

~~20. The viral particle of claim 19, wherein the viral particle comprises:~~

30 ~~(i) a capsid;~~
~~(ii) a liver tropic capsid; and/or~~
~~(iii) a liver tropic capsid, wherein the liver tropic capsid comprises a sequence at least 98%, at least 99%, or at least 99.5% identical to a fragment of at least 600, at least 650, at least 700, between 600 and 734, between 600 and~~

~~736, between 650 and 734, between 650 and 736, between 700 and 734,
between 700 and 736, around 734, or around 736 amino acids of any one of
SEQ ID NOs: 56-59.~~

5 ~~24~~15. A composition comprising the polynucleotide or viral particle of any one of the
preceding claims, and a pharmaceutically acceptable excipient.

10 ~~22~~16. The polynucleotide according to any one of claims 1 to ~~17~~12, the viral particle
according to ~~any one of claims 18 to 20~~claim 13 or 14, or the composition
according to claim ~~24-15~~ for use in ~~a method of treatment~~therapy.

15 ~~23. A method of treatment comprising administering an effective amount of the
polynucleotide according to any one of claims 1 to 17, the viral particle according
to any one of claims 18 to 20, or the composition according to claim 21.~~

20 ~~24~~17. Use of the polynucleotide according to any one of claims 1 to ~~17~~12, the viral
particle according to ~~any one of claims 18 to 20~~claim 13 or 14, or the composition
according to claim ~~24-15~~ in the manufacture of a medicament for treating a
complement-mediated disorder~~use in a method of treatment~~.

25 ~~25. The polynucleotide, viral particle or composition for use, or use of any one of
claims 22 to 24, wherein the method of treatment comprises administering an
effective amount of the polynucleotide, viral particle or composition to a patient.~~

30 ~~26. A polynucleotide comprising a Complement Factor I (CFI) nucleotide sequence, a
viral particle comprising a recombinant genome comprising the polynucleotide, or
a composition comprising the polynucleotide or viral particle for use in a method of
treatment, wherein the method of treatment is a method of treating a complement-
mediated disorder, and the CFI nucleotide sequence encodes a CFI polypeptide or a
fragment thereof.~~

27. — ~~A method of treatment comprising administering an effective amount of a polynucleotide comprising a CFI nucleotide sequence, a viral particle comprising a recombinant genome comprising the polynucleotide, or a composition comprising the polynucleotide or viral particle, wherein the method of treatment is a method of treating a complement mediated disorder, and the CFI nucleotide sequence encodes a CFI polypeptide or a fragment thereof.~~

2818. Use of a polynucleotide comprising a CFI nucleotide sequence, a viral particle comprising a recombinant genome comprising the polynucleotide, or a composition comprising the polynucleotide or viral particle in the manufacture of a medicament for use in a method of treatment, wherein the method of treatment is a method of treating a complement-mediated disorder, and the CFI nucleotide sequence encodes a CFI polypeptide or a fragment thereof.

29. — ~~The polynucleotide, viral particle or composition for use, or use of any one of claims 26 to 28, wherein the method of treatment comprises administering an effective amount of the polynucleotide, viral particle or composition to a patient.~~

30. — ~~The polynucleotide, viral particle or composition for use, or use of any one of claims 22 to 25, wherein the method of treatment is a method of treating a complement mediated disorder.~~

3119. ~~The polynucleotide, viral particle, or composition for use, use, or method use of any one of claims 26 to 30~~claim 17 or 18, wherein the disorder:

- (i) is a C3-mediated disorder;
- (ii) is a kidney disorder;
- (iii) is associated with over-activity of the complement C3b feedback cycle;
- (iv) is selected from C3 glomerulopathy, IgA nephropathy, lupus nephritis, systemic lupus erythematosus, membranous nephropathy, membranoproliferative glomerulonephritis, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, autoimmune

- 5 haemolytic anemia, ANCA-associated vasculitis, Gaucher disease, peritonitis, age-related macular degeneration, diabetic retinopathy, dense deposit disease, age-related inflammatory or autoinflammatory diseases, autoimmune arthritis such as rheumatoid arthritis, atherosclerosis, chronic cardiovascular disease, Alzheimer's disease, systemic vasculitis, Guillain-Barre syndrome, and Henoch-Schonlein purpura;
- (v) is selected from C3 glomerulopathy, C3 glomerulonephritis and dense deposit disease;
- 10 (vi) is atypical hemolytic uremic syndrome with monoallelic CFH mutation; and/or
- (vii) is a kidney glomerular or tubular disorder; ~~and/or~~
- (vii) ~~is not an ocular disorder.~~
- 15 ~~3220.~~ The polynucleotide, the viral particle, or the composition according to claim 16 ~~for use, use, or method of any one of claims 22 to 31 or the use of any one of claims 17 to 19,~~ wherein the polynucleotide, viral particle, or composition:
- (i) ~~is not administered intraocularly;~~
- 20 (ii) is to be administered: intravenously; systemically; to the liver via peripheral vein infusion; to the liver via hepatic vessels such as hepatic vein infusion or hepatic artery infusion; or via intraparenchymal administration direct to the liver;
- (iii) is to be administered by injection into the renal artery;
- (~~iv~~iii) is to be administered by retrograde administration; and/or
- 25 (iv) is to be administered by retrograde administration, wherein the administration is via the ureters using a urinary catheter.