

CLAIMS

1. An inhibitor of expression and / or function of CFHR4/FHR-4, wherein said inhibitor is conjugated to one or more ligand moieties, preferably wherein the ligand moiety allows targeting of hepatocytes.
2. An inhibitor according to claim 1, wherein said inhibitor is an siRNA oligomer.
3. An inhibitor of expression and / or function of CFHR4/FHR-4, wherein said inhibitor is an siRNA oligomer.
4. An inhibitor according to claim 3, wherein said inhibitor comprises an siRNA oligomer conjugated to one or more ligand moieties, preferably wherein the ligand moiety allows targeting of hepatocytes.
5. An inhibitor according to claim 1, 2 or 4, wherein said one or more ligand moieties comprise one or more GalNAc ligands or comprise one more GalNAc ligand derivatives.
6. An inhibitor according to one or more preceding claims, wherein the target of the inhibitor is CFHR4/FHR-4.
7. An inhibitor according to one or more preceding claims, wherein the inhibitor is a nucleic acid for inhibiting expression of CFHR4 comprising a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein
 - (i) at least partially complementary to a portion of RNA transcribed from the CFHR4 gene, and
 - (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.
8. An inhibitor according to one or more preceding claims, wherein the inhibitor is a nucleic acid for inhibiting expression of CFHR4 comprising a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is:
 - (i) at least partially complementary to a portion of RNA transcribed from the CFHR4 gene, and

- (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand modified sequences as listed in Table 3.
9. An inhibitor according to claim 7, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.
 10. An inhibitor according to claim 8, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.
 11. An inhibitor according to one or more preceding claims, formulated as a pharmaceutical composition with an excipient and / or carrier.
 12. A pharmaceutical composition comprising an inhibitor according to one or more preceding claims, in combination with a pharmaceutically acceptable excipient or carrier.
 13. An inhibitor according to any one of claims 1 to 11 or a pharmaceutical composition according to claim 12, for use in therapy.
 14. An inhibitor according to any one of claims 1 to 11 or a pharmaceutical composition according to claim 12 for use in treating a disease or disorder associated with alterations in complement pathway protein levels and/or function in a patient, in particular wherein the disease or disorder is associated with elevated levels of complement factor H-related protein 4 (FHR-4), optionally wherein the disease or disorder associated with alterations in complement pathway protein levels and/or function is a) age-related macular degeneration (AMD), preferably dry age-related macular degeneration, or b) a kidney disease, such as atypical haemolytic uraemic syndrome (aHUS), C3 glomeruloneuropathy (C3G), IgA nephropathy (IgAN), or membranous (glomerulo) nephropathy (MN).
 15. An inhibitor or a pharmaceutical composition for use according to claim 14, wherein the inhibitor of expression and/or function of CFHR4/FHR-4 slows the progression of the disease or disorder associated with alterations in complement pathway protein levels and/or function.
 16. An inhibitor according to any one of claims 1 to 11 or a pharmaceutical composition according to claim 12, for use in the treatment of age-related macular degeneration (AMD) in a patient, preferably dry age-related macular degeneration.

17. An inhibitor or pharmaceutical composition for use according to any one of claims 14 to 16, wherein the patient has elevated levels of FHR-4, optionally wherein the patient having elevated levels of FHR-4 is a carrier of:

(a) diplotype alleles rs61818956TT and/or rs10494745GG and/or rs7531555CC;

(b) diplotype alleles (i) rs61818956TT and rs10494745GG; (ii) rs61818956TT and rs10494745GA; (iii) rs61818956TT and rs10494745AA; (iv) rs61818956CT and rs10494745GG; (v) rs61818956CT and rs10494745GA; (vi) rs61818956CT and rs10494745AA; (vii) rs61818956CC and rs10494745GG; or (viii) rs61818956CC or rs10494745GA;

(c) diplotype alleles (i) rs61818956TT and rs10494745GG; (ii) rs61818956TT and rs10494745GA; (iii) rs61818956TT and rs10494745AA; (iv) rs61818956CT and rs10494745GG; or (v) rs61818956CT and rs10494745GA;

(d) diplotype alleles (i) rs61818956TT and rs10494745GG or (ii) rs61818956TT and rs10494745GA; or (iii) rs61818956CT and rs10494745GG;

(e) diplotype alleles (i) rs61818956TT and rs10494745GG or (ii) rs61818956TT and rs10494745GA;

(f) diplotype alleles (i) rs61818956TT, rs10494745GG, rs7531555CC; (ii) rs61818956CT, rs10494745GG, rs7531555CC; (iii) rs61818956TT, rs10494745GA, rs7531555CT; (iv) rs61818956TT, rs10494745GA, rs7531555CC; (v) rs61818956CC, rs10494745GG, rs7531555CC; (vi) rs61818956TC, rs10494745GA, rs7531555CC; (vii) rs61818956TC, rs10494745GG, rs7531555CT; (viii) rs61818956CT, rs10494745GA, rs7531555CT; (ix) rs61818956CT, rs10494745GA, rs7531555CC; (x) rs61818956TT, rs10494745GG, rs7531555CT; (xi) rs61818956TT, rs10494745AA, rs7531555TT; (xii) rs61818956TT, rs10494745AA, rs7531555TC; or (xiii) rs61818956TT, rs10494745AA, rs7531555CC;

(g) diplotype alleles (i) rs61818956TT, rs10494745GG, rs7531555CC; (ii) rs61818956CT, rs10494745GG, rs7531555CC; (iii) rs61818956TT, rs10494745GA, rs7531555CT; or (iv) rs61818956TT, rs10494745GA, rs7531555CC;

(h) diplotype alleles (i) rs61818956TT, rs10494745GG, rs7531555CC; (ii) rs61818956CT, rs10494745GG, rs7531555CC; (iii) rs61818956CC, rs10494745GG, rs7531555CC; (iv) rs61818956TC, rs10494745GA, rs7531555CC; (v) rs61818956TC, rs10494745GG, rs7531555CT; or

(i) diplotype alleles (i) rs61818956TT, rs10494745GG, rs7531555CC; or (ii) rs61818956CT, rs10494745GG, rs7531555CC.

18. Use of CFHR4/FHR-4 as a target for identifying one or more therapeutic agents for the treatment of age-related macular degeneration (AMD).

19. CFHR4/FHR-4 for use as a biomarker of age-related macular degeneration (AMD).

20. CFHR4/FHR-4 for use in an *in vivo* method of predicting susceptibility to age-related macular degeneration (AMD), typically by monitoring the sequence and/ or level of expression and / or function of CFHR4 in a sample obtained from a patient.

21. A method of predicting susceptibility to age-related macular degeneration (AMD), and optionally treating age-related macular degeneration (AMD), in a patient, said method comprising:

- (a) obtaining a sample from the patient,
- (b) detecting the sequence and / or expression and / or function of CFHR4/FHR-4 in said sample obtained from the patient,
- (c) predicting susceptibility to age-related macular degeneration (AMD), based on the sequence and / or expression and / or function of CFHR4/FHR-4 in said sample obtained from the patient,
- (d) preferably administering to the diagnosed patient an effective amount of an inhibitor of CFHR4/FHR-4, preferably an inhibitor of CFHR4/FHR-4 according to any one of claims 1 to 43, or of a pharmaceutical composition comprising an inhibitor of CFHR4/FHR-4, such as a composition as defined according to claim 44.

22. A method of selecting a patient having a disease or disorder associated with alterations in complement pathway protein levels, in particular age-related macular degeneration (AMD), for a treatment with the inhibitor according to the invention, and optionally treating the disease or disorder associated with alterations in complement pathway protein levels, in particular age-related macular degeneration (AMD), in said patient, said method comprising:

- (a) providing a sample from the patient,

- (b) detecting the sequence and / or expression and / or function of CFHR4/FHR-4 in said sample obtained from the patient,
- (c) selecting the patient having the disease or disorder associated with alterations in complement pathway protein levels, in particular age-related macular degeneration (AMD), for a treatment with the inhibitor according to the invention based on the sequence and / or expression and / or function of CFHR4/FHR-4 in said sample obtained from the patient,
- (d) preferably administering to the diagnosed patient an effective amount of an inhibitor of CFHR4/FHR-4.

23. A method according to claim 22, wherein the patient is selected for a treatment with the inhibitor according to the invention, if the protein levels of FHR-4 and/or the activity of FHR-4 in the sample obtained from said patient are elevated compared to a suitable control, preferably wherein the suitable control is a comparable sample from a healthy donor.

24. A method according to claim 22 or 23, wherein the method comprises a step of determining the presence of a single nucleotide polymorphism (SNP) at positions rs61818956, rs10494745, and/or rs7531555 in the sample obtained from said patient.

25. A method according to claim 23 or 24, wherein the patient is determined to have elevated levels of FHR-4, if the patient is a carrier of diplotype alleles rs61818956TT and/or rs10494745GG and/or rs7531555CC; preferably of diplotype alleles (i) rs61818956TT and rs10494745GG; (ii) rs61818956TT and rs10494745GA; (iii) rs61818956TT and rs10494745AA; (iv) rs61818956CT and rs10494745GG; (v) rs61818956CT and rs10494745GA; (vi) rs61818956CT and rs10494745AA; (vii) rs61818956CC and rs10494745GG; or (viii) rs61818956CC or rs10494745GA; more preferably of diplotype alleles (i) rs61818956TT, rs10494745GG, and rs7531555CC; (ii) rs61818956CT, rs10494745GG, and rs7531555CC; (iii) rs61818956TT, rs10494745GA, and rs7531555CT; (iv) rs61818956TT, rs10494745GA, and rs7531555CC; (v) rs61818956CC, rs10494745GG, and rs7531555CC; (vi) rs61818956TC, rs10494745GA, and rs7531555CC; (vii) rs61818956TC, rs10494745GG, and rs7531555CT; (viii) rs61818956CT, rs10494745GA, and rs7531555CT; (ix) rs61818956CT, rs10494745GA, and rs7531555CC; (x) rs61818956TT, rs10494745GG, and rs7531555CT; (xi) rs61818956TT, rs10494745AA, and rs7531555TT; (xii) rs61818956TT, rs10494745AA, and rs7531555TC; or (xiii) rs61818956TT, rs10494745AA, and rs7531555CC; even more preferably of diplotype alleles (i) rs61818956TT, rs10494745GG, and rs7531555CC; (ii) rs61818956CT,

rs10494745GG, and rs7531555CC; (iii) rs61818956TT, rs10494745GA, and rs7531555CT; or (iv) rs61818956TT, rs10494745GA, and rs7531555CC or of alleles (i) rs61818956TT, rs10494745GG, and rs7531555CC; (ii) rs61818956CT, rs10494745GG, and rs7531555CC; (iii) rs61818956CC, rs10494745GG, and rs7531555CC; (iv) rs61818956TC, rs10494745GA, and rs7531555CC; (v) rs61818956TC, rs10494745GG, and rs7531555CT; most preferably of diplotype alleles (i) rs61818956TT, rs10494745GG, and rs7531555CC; or (ii) rs61818956CT, rs10494745GG, and rs7531555CC.