

Claims

1. A fusion protein comprising:

a) an antibody or antigen-binding fragment that binds to C3b; and

b) a factor H polypeptide that binds to C3b, wherein the factor H polypeptide comprises an amino acid sequence according to SEQ ID NO: 10 or a variant thereof having at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 10;

wherein the antibody or antigen-binding fragment thereof of the fusion protein does not compete for binding to C3b with the factor H polypeptide of the fusion protein.

2. The fusion protein according to claim 1, wherein:

(i) the antibody or antigen-binding fragment thereof specifically binds to C3b and not C3;

(ii) the antibody or antigen-binding fragment thereof does not compete for binding to C3b with factor I;

(iii) the antibody or antigen-binding fragment thereof is capable of inhibiting interaction between C3b and factor B or active Bb and thereby of inhibiting assembly of C3bBb convertase complex and/or the activity of C3bBb convertase;

(iv) the antibody or antigen-binding fragment thereof competes for binding to C3b with factor B;

(v) the antibody or antigen-binding fragment thereof competes for binding to C3b with factor B, and does not compete for binding to C3b with factor I;

(vi) the antibody or antigen-binding fragment thereof binds an epitope comprised in the MG7 domain of C3b (SEQ ID NO: 20) and the N-terminus region of the C3b alpha chain (e.g., residues 1-30, 1-20 or 4-12 of SEQ ID NO:19);

(vii) the antibody or antigen-binding fragment thereof binds to an epitope consisting of the amino acids:

a) Glu759, Asn760, His918, His919, Phe920 of C3b (corresponding to Glu11, Asn12, His170, His171, Phe172 of the amino acid sequence according to SEQ ID NO: 19);

b) Glu758, Glu759, Asn760, Arg855, Val916, His918, His919, Phe920 of C3b (corresponding to Glu10, Glu11, Asn12, Arg107, Val168, His170, His171, Phe172 of the amino acid sequence according to SEQ ID NO: 19); or

c) Asp752, Asp754, Ile755, Ile756, Glu759, Asn760, His918, His919, Phe920 of C3b (corresponding to Asp4, Asp6, Ile7, Ile8, Glu11, Asn12, His170, His171, Phe172 of the amino acid sequence according to SEQ ID NO: 19); and/or
 (viii) the antibody or antigen-binding fragment thereof competes for binding to C3b with
 5 the CCP1 domain of factor H (SEQ ID NO: 21).

3. The fusion protein according to any of the preceding claims, wherein the antibody or antigen-binding fragment thereof is a single domain antibody.

(i) the single domain antibody comprises a single variable domain comprising CDR1,
 10 CDR2 and CDR3, wherein the CDR1 comprises the amino acid sequence according to SEQ ID NO: 2, the CDR2 comprises the amino acid sequence according to SEQ ID NO: 3 and the CDR3 comprises the amino acid sequence according to SEQ ID NO: 4;

(ii) the single domain antibody specifically binds to C3b and comprises or consists of:

(a) an amino acid sequence having at least 80%, 85%, 90%, 95%, 98%, or 99%
 15 sequence identity to the amino acid sequence according to SEQ ID NO: 23 and

(b) a N-terminal motif, optionally wherein the single domain antibody comprises or consists of the amino acid sequence of SEQ ID NO: 23 and a N-terminal motif; optionally wherein the N-terminal motif creates specificity towards C3b by sterically hindering binding to C3, further optionally wherein the N-terminal motif is a 3 amino acid
 20 sequence comprising or consisting of the amino acids EWE; and/or

(iii) the single domain antibody comprises or consists of the amino acid sequence of SEQ ID NO: 1.

4. The fusion protein according to any of the preceding claims, wherein the antibody or antigen-binding fragment thereof is connected to the factor H polypeptide by a first linker; optionally
 25 wherein the first linker is a glycine-serine (GS) linker, such as a GS linker comprising or consisting of an amino acid sequence according to SEQ ID NO: 6.

5. The fusion protein according to any of the preceding claims, wherein the factor H polypeptide
 30 is less than 180 amino acids, such as less than 175, 170, 165, 160, 155, 150, 145, 140, 135 or 130 amino acids, optionally wherein the factor H polypeptide is 125 amino acids long.

6. The fusion protein according to any of claims 1-4, wherein the factor H polypeptide comprises or consists of the amino acid sequence according to SEQ ID NO: 10, or a variant thereof having

at least 80%, 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence according to SEQ ID NO: 10.

7. The fusion protein according to any of claims 1-4 or 6, wherein the factor H polypeptide is less than 240 amino acids, such as less than 235, 230, 225, 220, 215, 210, 205, 200, 195, 190 or 185 amino acids, optionally wherein the factor H polypeptide is 183 amino acids long.

8. The fusion protein according to any of claims 1-4 or 6, wherein the factor H polypeptide further comprises: (i) the amino acid sequences according to SEQ ID NO: 14; and/or (ii) the amino acid sequences according to SEQ ID NO: 16.

9. The fusion protein according to any of claims 1-4, 6 or 8, wherein:

(a) the factor H polypeptide comprises:

(i) the amino acid sequences according to SEQ ID NO: 11;

(ii) the amino acid sequences according to SEQ ID NO: 12;

(iii) the amino acid sequences according to SEQ ID NO: 13;

(iv) the amino acid sequences according to SEQ ID NO: 14; and

(v) the amino acid sequences according to SEQ ID NO: 16; and/or

(b) the factor H polypeptide is less than 380 amino acids, such as less than 375, 370, 365, 360, 355, 350, 345, 340, 335, 330, 325 or 320 amino acids, optionally wherein the factor H polypeptide is 319 amino acids long.

10. The fusion protein according to any of the preceding claims, wherein:

(i) the factor H polypeptide does not comprise the CCP1 domain, such as the amino acid sequence according to SEQ ID NO: 21, or a variant thereof having at least 80%, 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence according to SEQ ID NO: 21;

(ii) the factor H polypeptide is capable of recruiting factor I, such as recruiting the amino acid sequence according to SEQ ID NO: 22;

(iii) the fusion protein inhibits the alternative pathway by preventing binding of factor B or fragments thereof to C3b and recruits factor I and/or wherein the fusion protein hinders formation of the alternative pathway C3 convertase, C3bBb and recruits factor I, such as wherein the fusion protein recruits the amino acid sequence according to SEQ ID NO: 22; and/or

(iv) the fusion protein inhibits the alternative pathway by preventing binding of factor B or fragments thereof to C3b and activates degradation of C3b by recruiting factor I.

11. A polypeptide comprising:

5 (i) a factor H polypeptide comprising a length of less than 220 amino acids, wherein the factor H polypeptide comprises an amino acid sequence according to SEQ ID NO: 10 or a variant thereof having at least 80%, 85%, 90%, 95%, 98%, or 99% sequence identity to the amino acid sequence according to SEQ ID NO: 10; or

10 (ii) a factor H polypeptide that consists of the amino acid sequence according to SEQ ID NO: 10.

12. A nucleic acid encoding the fusion protein of any of claims 1-10 or the polypeptide of claim 11.

15 13. A vector comprising the nucleic acid of claim 12.

14. A host cell comprising the nucleic acid of claim 12 or the vector of claim 13.

20 15. A pharmaceutical composition comprising the fusion protein of any of claims 1-10 or the polypeptide of claim 11, optionally comprising a pharmaceutically acceptable carrier.

16. The fusion protein of any of claims 1-10, the polypeptide of claim 11, or the pharmaceutical composition according to claim 15, for use as a medicament.

25 17. Use of the fusion protein of any of claims 1-10, the polypeptide of claim 11, or the pharmaceutical composition according to claim 15 in the manufacture of a medicament for the treatment of a disorder associated with complement activation, such as wherein the disorder is selected from the group consisting of ocular diseases, neurological diseases, autoimmune and inflammatory disorders, cancers and infectious diseases.

30