

## FACTOR H POTENTIATING ANTIBODIES AND USES THEREOF

### CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/875,309, filed July 17, 2019, the disclosures of which are incorporated by reference herein in their entirety for all purposes.

### SEQUENCE LISTING

[0001.1] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 4, 2020, is named GEM-013WO\_SL.txt and is 18,037 bytes in size.

### BACKGROUND OF THE DISCLOSURE

[0002] The complement system is an important element of innate immunity that contributes to the protection of many organisms such as mammals against invading pathogens. The complement system consists of over 30 different components which are mainly synthesized in the liver. Activation of the complement system occurs by three different pathways, the classical pathway, the lectin pathway and the alternative pathway. The three pathways converge at the formation of a C3 convertase, which are different for each pathway but have similar activity.

[0003] In the classical complement pathway, activation of the complement component (C)1 complex, consisting of C1q, C1r and C1s, occurs upon binding to antibody-antigen complexes. The C1 complex cleaves C4 and C2 leading to the formation of a C3 convertase consisting of C4bC2a. The C3 convertase cleaves C3 into the active components C3a and C3b. In the lectin pathway, mannose binding lectin binds to mannose residues on pathogenic surfaces which activates serine proteases MASP-1 and MASP-2 that are able to cleave C4 and C2. As in the classical pathway, this leads to the formation of the C4bC2a C3 convertase. This C3 convertase can bind C3b to form a C5 convertase. Contrary to the classical and lectin pathways, the alternative pathway has a low level of continuous activity due to spontaneous hydrolysis of C3 to C3(H<sub>2</sub>O) in plasma. This C3b-like C3(H<sub>2</sub>O) can form a fluid phase C3 convertase by binding factor B (FB) which in turn is activated into Bb by factor D. Similarly, when C3b binds to a surface, it may bind FB to form C3bB. This complex is cleaved by factor D to C3bBb which is the C3 convertase of the alternative

pathway that can be stabilized by properdin (factor P) to C3bBbP. This C3 convertase is able to cleave C3 into C3a and C3b. In addition to this process the alternative pathway acts as amplification loop for the classical and lectin activation pathways as C3b generated in these pathways may act as starting point for the alternative pathway. Thereby, the amplification loop results in a reinforcement of the classical and lectin pathway. The C3 convertase formed in one of the three activation pathways can bind C3b to form a C5 convertase. The C5

prevents activation of the terminal pathway and decreases the influx of immune cells. However, the use of eculizumab is associated with unwanted side effects. As it blocks C5, which is a crucial component for the initiation of the terminal pathway, patients treated with eculizumab become vulnerable to infection with encapsulated bacteria (such as *Neisseria meningitidis*), the clearance of which is very dependent on MAC formation. Therefore, vaccination against the meningococcus is required for patients prior to receiving treatment with eculizumab. Further, since eculizumab acts downstream of C3, C3 deposition is maintained, which is detrimental in several disorders involving unwanted or excessive complement activation. In addition, high costs are involved with eculizumab treatment and the availability of the antibody is limited.

[0011] A mouse monoclonal antibody that binds CCP18 is described by Cheng et al. (Clinical Chemistry, 2005). It is described that this antibody, called X52.1, increases binding of FH to C3b and C3d which is thought to be caused by dimerization of FH. The increased binding of FH to C3b and C3d induced by X52.1 results in an increased complement mediated lysis of cells, including RBCs and several types of cancer cells as shown by Corey et al. (J Biol Chem. 2000). This demonstrates that antibody X52.1 inhibits the complement inhibitory activity of FH. Indeed, Corey et al. suggests that the antibody can be used in the treatment of cancer by enhancing complement-mediated lysis of cancer cells.

[0012] There is a continuous need for novel and improved therapeutic agents that bind FH, such as agent that are useful in the treatment of disorders associated with unwanted or excessive complement activation.

## SUMMARY OF THE DISCLOSURE

[0013] The present ~~invention~~disclosure provides antibodies or antigen binding fragments thereof, for example, isolated, synthetic or recombinant antibodies or antigen binding fragments thereof, that specifically bind complement control protein domain 18 (CCP18) of factor H (FH). Such antibodies and antigen binding fragments are useful for potentiating the activity of FH, for example, increasing the binding affinity of FH to C3b, increasing the ability of FH to inhibit C3 deposition, and/or increasing the ability of FH to inhibit hemolytic activity. In one aspect, the present disclosure provides an isolated, synthetic or recombinant antibody or an antigen binding fragment thereof that specifically binds to complement control protein domain 18 (CCP18) of factor H (FH) comprising:

- a light chain CDR1 sequence comprising the sequence SSVTY (SEQ ID NO: 1) or the sequence TSVTY (SEQ ID NO: 13).

- a light chain CDR2 sequence comprising the sequence ATS (SEQ ID NO: 2) or the sequence ASS (SEQ ID NO: 14),
- a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3),
- a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5),
- a heavy chain CDR2 sequence comprising the sequence VWSGGTT (SEQ ID NO: 6) or the sequence of IWSGGTT (SEQ ID NO: 10), and
- a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDY (SEQ ID NO: 7) or the sequence ARNFGNYAMDF (SEQ ID NO: 11).

**[0013a]** In some embodiment examples, the antibody or fragment comprises: a light chain CDR1 sequence comprising the sequence SSVTY (SEQ ID NO: 1) or the sequence TSVTY (SEQ ID NO: 13); a light chain CDR2 sequence comprising the sequence ATS (SEQ ID NO: 2) or the sequence ASS (SEQ ID NO: 14); a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3); a heavy chain CDR1 sequence comprising the sequence

GFSLTNYG (SEQ ID NO: 5); a heavy chain CDR2 sequence comprising the sequence VWSGGTT (SEQ ID NO: 6) or the sequence of IWSGGTT (SEQ ID NO: 10); and a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDY (SEQ ID NO: 7) or the sequence ARNFGNYAMDF (SEQ ID NO: 11).

**[0014]** In some embodimentexamples, the antibody or fragment comprises: a light chain CDR1 sequence comprising the sequence SSVTY (SEQ ID NO: 1); a light chain CDR2 sequence comprising the sequence ATS (SEQ ID NO: 2); a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3); a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5); a heavy chain CDR2 sequence comprising the sequence IWSGGTT (SEQ ID NO: 10); and a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDF (SEQ ID NO: 11). In some

embodimentexamples, the antibody or fragment comprises: a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 4 or 16, and a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 8 or 12. In some

embodimentexamples, the antibody or fragment comprises a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 4, and a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 12.

**[0015]** In some embodimentexamples, the antibody or fragment comprises: a light chain CDR1 sequence comprising the sequence SSVTY (SEQ ID NO: 1); a light chain CDR2 sequence comprising the sequence ATS (SEQ ID NO: 2); a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3); a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5); a heavy chain CDR2 sequence comprising the sequence VWSGGTT (SEQ ID NO: 6); and a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDY (SEQ ID NO: 7). In some

embodimentexamples, the antibody or fragment comprises a variable light chain sequence comprising a sequence which

has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 4, and a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 8.

**[0016]** In some embodimentexamples, the antibody or fragment comprises: a light chain CDR1 sequence comprising the sequence TSVTY (SEQ ID NO: 13); a light chain CDR2 sequence comprising the sequence ASS (SEQ ID NO: 14); a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3); a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5); a heavy chain CDR2 sequence comprising the sequence VWSGGTT (SEQ ID NO: 6); and a heavy chain CDR3 sequence having the sequence ARNFGNYAMDY (SEQ ID NO: 7). In some

embodimentexamples, the antibody or fragment comprises a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 16, and a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 8.

**[0017]** In some embodimentexamples, the antibody or fragment comprises: a light chain CDR1 sequence comprising the sequence TSVTY (SEQ ID NO: 13); a light chain CDR2 sequence comprising the sequence ASS (SEQ ID NO: 14); a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3); a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5); a heavy chain CDR2 sequence comprising the sequence IWSGGTT (SEQ ID NO: 10); and a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDF (SEQ ID NO: 11). In some

embodimentexamples, the antibody or fragment comprises a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 16, and a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at

least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 12.

**[0018]** In some [embodimentexamples](#), the antibody or fragment has a binding affinity for FH with a  $K_D$  of  $2.5 \times 10^{-8}$  M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a  $K_D$  of  $0.1 \times 10^{-9}$  M or less, or wherein the antibody or fragment has a binding affinity for FH with a  $K_D$  of  $1.25 \times 10^{-8}$  M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a  $K_D$  of  $0.04 \times 10^{-9}$  M or less. In some [embodimentexamples](#), the antibody or fragment has a binding affinity for FH with a  $K_D$  of  $2.5 \times 10^{-8}$  M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a  $K_D$  of  $0.1 \times 10^{-9}$  M or less, or wherein the antibody or fragment has a binding affinity for FH with a  $K_D$  of  $0.6 \times 10^{-8}$  M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a  $K_D$  of  $0.6 \times 10^{-11}$  M or less. In some [embodimentexamples](#), the antibody or fragment of the present disclosure: inhibits C3 deposition on lipopolysaccharide (LPS) *in vitro* in the presence of 10% (v/v) serum with an  $IC_{50}$  value of 38 nM or less, such as with an  $IC_{50}$  value of 30 nM or less, and/or inhibits hemolytic activity *in vitro* in the presence of 10% (v/v) serum with an  $IC_{50}$  value of 150 nM or less, such as with an  $IC_{50}$  value of 130 nM or less, and/or decreases the  $K_D$  value (increases binding affinity) of FH for C3b *in vitro* in the presence of 10% (v/v) serum to 2  $\mu$ M or less, and/or increases binding affinity of FH for C3b *in vitro* in the presence of 10% (v/v) serum by at least 3-fold. In certain [embodimentexamples](#), serum is normal human serum.

**[0019]** In some [embodimentexamples](#), the antibody or fragment potentiates FH activity, optionally wherein FH activity is inhibition of alternative complement activation, further optionally wherein inhibition of alternative complement activation comprises: an inhibition of hemolytic activity; an inhibition of complement component 3 (C3) deposition, and/or an increase in binding of FH to C3b, iC3b and/or C3d. In some [embodimentexamples](#), the antibody or fragment comprises an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region, and wherein the antibody or fragment further comprises an immunoglobulin heavy chain constant region and an immunoglobulin light chain constant region. In some [embodimentexamples](#), the antibody or fragment comprises the constant region of an IgG. In some [embodimentexamples](#), the constant region of the IgG is IgG1, IgG2, IgG3, or IgG4 (*e.g.*, human IgG1, IgG2, IgG3, or IgG4). In some [embodimentexamples](#), the antibody or fragment comprises the constant region of IgG4 (*e.g.*, human IgG4). In some [embodimentexamples](#), the constant region of IgG4 comprises a mutation at position 297. In certain [embodimentexamples](#), the

constant region of IgG4 comprises amino acid residue Q at position 297. In certain embodimentexamples, the constant region of IgG4 comprises amino acid residue A at position 297.

[0020] In some embodimentexamples, the fragment comprises at least a Fab fragment. In some embodimentexamples, the antibody or fragment is a monoclonal antibody or fragment thereof. In some embodimentexamples, the antibody or fragment is a chimeric or humanized antibody or fragment thereof, comprising human light chain and heavy chain constant regions. In some embodimentexamples, the antibody or fragment is PEGylated. In some embodimentexamples, the antibody or fragment is a PEGylated Fab fragment.

[0021] In another aspect~~some embodiments~~, the disclosure provides for an isolated, synthetic or recombinant nucleic acid comprising a nucleic acid sequence encoding any of the antibodies or fragments disclosed herein. In another aspect, the disclosure provides a vector comprising the nucleic acid as described herein, optionally wherein the vector is an AAV vector, further optionally wherein the AAV vector is selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, and AAV12. In some embodimentexamples, the disclosure provides for a vector comprising any of the nucleic acids disclosed herein. In some embodimentexamples, the vector is an AAV vector. In some embodimentexamples, the AAV vector is selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, and AAV12.

[0022] In ~~some embodiments~~ yet another aspect, the disclosure provides for a recombinant cell comprising any of the nucleic acids disclosed herein or any of the vectors disclosed herein.

[0023] In yet another aspect~~some embodiments~~, the disclosure provides for a pharmaceutical composition comprising any of the antibodies or fragments disclosed herein, any of the nucleic acids disclosed herein, any of the vectors disclosed herein or any of the recombinant cells disclosed herein, and a pharmaceutically acceptable carrier, diluent and/or excipient.

[0024] In a further aspect, the disclosure provides for the antibody or fragment as described herein, the nucleic acid as described herein, the vector as described herein, the recombinant cell as described herein, or the pharmaceutical composition as described herein for use in therapy. In some embodimentexamples, the disclosure provides for any of the antibodies or fragments disclosed herein, any of the nucleic acids disclosed herein, any of the vectors disclosed herein for use in therapy. In some embodimentexamples, the disclosure

provides for any of the antibodies or fragments disclosed herein, any of the nucleic acids disclosed herein, or any of the vectors disclosed herein for use in inhibiting alternative complement activation. In some embodiment examples, the disclosure provides for any of the antibodies or fragments disclosed herein, any of the nucleic acids disclosed herein, or any of the vectors disclosed herein for use in the treatment, alleviation or prevention of a disorder associated with alternative pathway complement activation. In some embodiment examples, the disorder is selected from the group consisting of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), membranoproliferative glomerulonephritis (MPGN), and IgA Nephropathy.

**[0025]** In a further aspect, the disclosure provides for a use of the antibody or fragment as described herein, the nucleic acid as described herein, the vector as described herein, the recombinant cell as described herein, or the pharmaceutical composition as described herein in the preparation of a medicament for the treatment, alleviation or prevention of a disorder associated with alternative pathway complement activation. In some **embodimentexamples**, the disclosure provides for a use of any of the antibodies or fragments disclosed herein, any of the nucleic acids disclosed herein, or any of the vectors disclosed herein for the preparation of a medicament for the treatment, alleviation or prevention of a disorder associated with alternative pathway complement activation. In some **embodimentexamples**, the disorder is selected from the group consisting of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), membranoproliferative glomerulonephritis (MPGN) and IgA Nephropathy.

**[0026]** In a further aspect, the disclosure provides for a use of the antibody or fragment as described herein, the nucleic acid as described herein, the vector as described herein, the recombinant cell as described herein, or the pharmaceutical composition as described herein in the preparation of a medicament for inhibiting alternative complement activation. In some **embodimentexamples**, the disclosure provides for a method for treating, alleviating, or preventing a disorder associated with alternative pathway complement activation comprising administering to an individual in need thereof a therapeutically effective amount of any of the antibodies or fragments disclosed herein, any of the nucleic acids disclosed herein, any of the vectors disclosed herein, or any of the pharmaceutical compositions disclosed herein. In some **embodimentexamples**, the disorder is selected from the group consisting of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), membranoproliferative glomerulonephritis (MPGN), and IgA Nephropathy.

**[0027]** In some **embodimentexamples**, the disclosure provides for a method for inhibiting alternative complement activation comprising administering to a subject any of the antibodies or fragments disclosed herein, any of the nucleic acids disclosed herein, any of the vectors disclosed herein, or any of the pharmaceutical compositions disclosed herein.

**[0028]** In a further aspect, the disclosure provides for a method for producing an isolated, synthetic or recombinant antibody or an antigen binding fragment thereof, the method comprising providing a cell with the nucleic acid as described herein or the vector as described herein, and allowing the cell to translate the nucleic acid sequence comprised by

the nucleic acid or vector, thereby producing the antibody or fragment. In some embodimentexamples, the disclosure provides for a method for producing any of the antibodies or fragments disclosed herein, the method comprising providing a cell with any of the nucleic acids disclosed herein or any of the vectors disclosed herein, and allowing the cell to translate the nucleic acid sequence comprised by the nucleic acid or vector, thereby producing the antibody or fragment. In some embodimentexamples, the method further comprises harvesting, purifying and/or isolating the antibody or fragment.

## **DETAILED DESCRIPTION OF THE DISCLOSURE**

### **A. General Techniques and Definitions**

**[0029]** Unless otherwise defined herein, scientific and technical terms recited herein shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, pharmacology, cell and

## CLAIMS

### WHAT IS CLAIMED IS:

1. An isolated, synthetic or recombinant antibody or an antigen binding fragment thereof that specifically binds to complement control protein domain 18 (CCP18) of factor H (FH) comprising:

- a light chain CDR1 sequence comprising the sequence SSVTY (SEQ ID NO: 1) or the sequence TSVTY (SEQ ID NO: 13),
- a light chain CDR2 sequence comprising the sequence ATS (SEQ ID NO: 2) or the sequence ASS (SEQ ID NO: 14),
- a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3),
- a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5),
- a heavy chain CDR2 sequence comprising the sequence VWSGGTT (SEQ ID NO: 6) or the sequence of IWSGGTT (SEQ ID NO: 10), and
- a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDY (SEQ ID NO: 7) or the sequence ARNFGNYAMDF (SEQ ID NO: 11).

2. The antibody or fragment according to claim 1, comprising:

- a light chain CDR1 sequence comprising the sequence SSVTY (SEQ ID NO: 1),
- a light chain CDR2 sequence comprising the sequence ATS (SEQ ID NO: 2),
- a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3),
- a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5),
- a heavy chain CDR2 sequence comprising the sequence IWSGGTT (SEQ ID NO: 10), and
- a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDF (SEQ ID NO: 11).

3. The antibody or fragment according to claim 1, comprising:

- a light chain CDR1 sequence comprising the sequence SSVTY (SEQ ID NO: 1),
- a light chain CDR2 sequence comprising the sequence ATS (SEQ ID NO: 2),
- a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO:

- 3),
- a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5),
  - a heavy chain CDR2 sequence comprising the sequence VWSGGTT (SEQ ID NO: 6),
  - and
  - a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDY (SEQ ID NO: 7).
4. The antibody or fragment according to claim 1, comprising:
- a light chain CDR1 sequence comprising the sequence TSVTY (SEQ ID NO: 13),
  - a light chain CDR2 sequence comprising the sequence ASS (SEQ ID NO: 14),
  - a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3),
  - a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5),
  - a heavy chain CDR2 sequence comprising the sequence VWSGGTT (SEQ ID NO: 6),
  - and
  - a heavy chain CDR3 sequence having the sequence ARNFGNYAMDY (SEQ ID NO: 7).
5. The antibody or fragment according to claim 1, comprising:
- a light chain CDR1 sequence comprising the sequence TSVTY (SEQ ID NO: 13),
  - a light chain CDR2 sequence comprising the sequence ASS (SEQ ID NO: 14),
  - a light chain CDR3 sequence comprising the sequence QHRSSSNPLT (SEQ ID NO: 3),
  - a heavy chain CDR1 sequence comprising the sequence GFSLTNYG (SEQ ID NO: 5),
  - a heavy chain CDR2 sequence comprising the sequence IWSGGTT (SEQ ID NO: 10),
  - and
  - a heavy chain CDR3 sequence comprising the sequence ARNFGNYAMDF (SEQ ID NO: 11).
6. The antibody or fragment according to any one of claims 1-5, wherein:
- (a) the antibody or fragment has a binding affinity for FH with a  $K_D$  of  $2.5 \times 10^{-8}$  M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a  $K_D$  of  $0.1 \times 10^{-9}$  M or less, or wherein the antibody or fragment has a binding affinity for FH with a

K<sub>D</sub> of 1.25 x 10<sup>-8</sup> M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a K<sub>D</sub> of 0.04 x 10<sup>-9</sup> M or less; and/or

(b) the antibody or fragment has a binding affinity for FH with a K<sub>D</sub> of 2.5 x 10<sup>-8</sup> M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a K<sub>D</sub> of 0.1 x 10<sup>-9</sup> M or less, or wherein the antibody or fragment has a binding affinity for FH with a K<sub>D</sub> of 0.6 x 10<sup>-8</sup> M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a K<sub>D</sub> of 0.6 x 10<sup>-11</sup> M or less.

~~7. — The antibody or fragment according to any one of claims 1-5, wherein the antibody or fragment has a binding affinity for FH with a K<sub>D</sub> of 2.5 x 10<sup>-8</sup> M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a K<sub>D</sub> of 0.1 x 10<sup>-9</sup> M or less, or wherein the antibody or fragment has a binding affinity for FH with a K<sub>D</sub> of 0.6 x 10<sup>-8</sup> M or less and/or a binding affinity for a FH fragment comprised of CCP18-20 with a K<sub>D</sub> of 0.6 x 10<sup>-11</sup> M or less.~~

87. The antibody or fragment according to any one of claims 1-~~76~~, wherein the antibody or fragment:

- inhibits C3 deposition on lipopolysaccharide *in vitro* with an IC<sub>50</sub> value of 38 nM or less, such as with an IC<sub>50</sub> value of 30 nM or less, in the presence of 10% (v/v) serum; and/or
- inhibits hemolytic activity *in vitro* with an IC<sub>50</sub> value of 150 nM or less, such as with an IC<sub>50</sub> value of 130 nM or less, in the presence of 10% (v/v) serum; and/or
- decreases K<sub>D</sub> (increases binding affinity) of FH for C3b *in vitro* to at most 2 μM and/or increases binding affinity of FH for C3b *in vitro* by at least 3-fold.

98. The antibody or fragment according to any one of claims 1-~~87~~, comprising:

- a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 4 or SEQ ID NO: 16, and
- a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 8 or SEQ ID NO: 12.

~~10. The antibody or fragment according to any one of claims 1-9, comprising a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 4 and a variable heavy chain sequence comprising a sequence which has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to 8.~~

~~11. The antibody or fragment according to any one of claims 1-9, comprising a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 4, and a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 12.~~

~~12. The antibody or fragment according to any one of claims 1-9, comprising a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 16, and a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 8.~~

~~13. The antibody or fragment according to any one of claims 1-9, comprising a variable light chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 16, and a variable heavy chain sequence comprising a sequence which has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 12.~~

**149.** The antibody or fragment according to any one of claims 1 to **138**, wherein the antibody or fragment potentiates FH activity, optionally wherein the FH activity is inhibition

of alternative complement activation, further optionally wherein inhibition of alternative complement activation comprises:

- an inhibition of hemolytic activity,
- an inhibition of ~~complement component 3~~ (C3b) deposition, and/or
- an increase of binding of FH to C3b, iC3b and/or C3d.

~~1510.~~ The antibody or fragment according to any one of claims 1 to ~~149~~, wherein the antibody or fragment comprises:

      (a)       an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region, and further comprises an immunoglobulin heavy chain constant region and an immunoglobulin light chain constant region; and/or

      (b)       a Fab fragment.

~~16. The antibody or fragment according to any one of claims 1 to 15, wherein the antibody or fragment comprises a Fab fragment.~~

~~1711.~~ The antibody or fragment according to any one of claims 1 to ~~1610~~, wherein the antibody or fragment is monoclonal.

~~1812.~~ The antibody or fragment according to any one of claims 1 to ~~1711~~, wherein the antibody or fragment comprises human light chain and heavy chain constant regions.

13. The antibody or fragment according to claim 12, wherein the constant regions comprise the Fc domain of human IgG4.

14. The antibody or fragment according to claim 13, wherein the Fc domain of human IgG4 comprises amino acid residue Ala or Gln at position 297.

~~1915.~~ The antibody or fragment according to any one of claims 1-~~1814~~, wherein the antibody or fragment is PEGylated, optionally the antibody or fragment is a PEGylated Fab fragment.

~~20. The antibody or fragment according to claim 19, wherein the antibody or fragment is~~

~~a PEGylated Fab fragment.~~

~~2416.~~ An isolated, synthetic or recombinant nucleic acid comprising a nucleic acid sequence encoding the antibody or fragment according to any one of claims 1 to ~~2015~~.

~~2217.~~ A vector comprising ~~a the~~ nucleic acid according to claim ~~2416~~, ~~optionally wherein the vector is an AAV vector, further optionally wherein the AAV vector is selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, and AAV12.~~

~~23.~~ ~~The vector of claim 22, wherein the vector is an AAV vector.~~

~~24.~~ ~~The vector of claim 23, wherein the AAV vector is selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, and AAV12.~~

~~2518.~~ A recombinant cell comprising the nucleic acid according to claim ~~2416~~ or the vector according to ~~any one of claims 22-24~~~~claim 17~~.

~~2619.~~ A pharmaceutical composition comprising the antibody or fragment according to any one of claims 1 to ~~2015~~, the nucleic acid according to claim ~~2416~~, the vector according to ~~any one of claims 22-24~~~~claim 17~~, or the recombinant cell according to claim ~~2518~~, and a pharmaceutically acceptable carrier, diluent and/or excipient.

~~2720.~~ The antibody or fragment according to any one of claims 1 to ~~2015~~, the nucleic acid according to claim ~~2416~~, the vector according to ~~any one of claims 22-24~~~~17~~, the recombinant cell according to claim ~~2518~~, or the pharmaceutical composition according to claim ~~2619~~ for use in therapy.

~~28.~~ ~~The antibody or fragment according to any one of claims 1 to 20, the nucleic acid according to claim 21, the vector according to any one of claims 22-24, the recombinant cell according to claim 25, or the pharmaceutical composition according to claim 26 for use in inhibiting alternative complement activation.~~

~~29.—The antibody or fragment according to any one of claims 1 to 20, the nucleic acid according to claim 21, the vector according to any one of claims 22–24, the recombinant cell according to claim 25, or the pharmaceutical composition according to claim 26 for use in the treatment, alleviation or prevention of a disorder associated with alternative pathway complement activation.~~

~~30.—The antibody or fragment, nucleic acid, recombinant cell, or pharmaceutical composition for use according to claim 29, wherein the disorder is selected from the group consisting of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), membranoproliferative glomerulonephritis (MPGN), and IgA Nephropathy.~~

~~31~~21. Use of the antibody or fragment according to any one of claims 1 to ~~20~~15, the nucleic acid according to claim ~~21~~16, the vector according to ~~any one of claims 22–24~~claim 17, the recombinant cell according to claim ~~25~~18, or the pharmaceutical composition according to claim ~~26–19~~for in the preparation of a medicament for the treatment, alleviation or prevention of a disorder associated with alternative pathway complement activation.

~~32~~22. The use according to claim ~~31–20~~20, wherein the disorder is selected from the group consisting of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), membranoproliferative glomerulonephritis (MPGN) and IgA Nephropathy.

~~33.—A method for treating, alleviating, or preventing a disorder associated with alternative pathway complement activation, the method comprising administering to a subject in need thereof a therapeutically effective amount of the antibody or fragment according to any one of claims 1 to 20, the nucleic acid according to claim 21, the vector according to any one of claims 22–24, the recombinant cell according to claim 25, or the pharmaceutical composition according to claim 26.~~

~~34.—The method according to claim 33, wherein the disorder is selected from the group consisting of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), membranoproliferative~~

~~glomerulonephritis (MPGN), and IgA Nephropathy.~~

~~3523. Use of the antibody or fragment according to any one of claims 1 to 15, the nucleic acid according to claim 16, the vector according to claim 17, the recombinant cell according to claim 18, or the pharmaceutical composition according to claim 19 in the preparation of a medicament~~ A method for inhibiting alternative complement activation ~~comprising administering to a subject the antibody or fragment according to any one of claims 1 to 20, the nucleic acid according to claim 21, the vector according to any one of claims 22-24, the recombinant cell according to claim 25, or the pharmaceutical composition according to claim 26.~~

~~3624. A method for producing an isolated, synthetic or recombinant antibody or an antigen binding fragment thereof, the method comprising providing a cell with the nucleic acid according to claim 21-16 or the vector according to any one of claims 22-24~~ claim 17, and allowing the cell to translate the nucleic acid sequence comprised by the nucleic acid or vector, thereby producing the antibody or fragment ~~according to any one of claims 1 to 20.~~

~~3725. The method according to claim 3624,~~ further comprising harvesting, purifying and/or isolating the antibody or fragment.