To prevent excess complement activation, the system also comprises a number of regulators. One of these regulators, factor H, is a fluid phase regulator that interacts with host cells and inhibits the complement progression in two ways. Firstly, factor H is a cofactor for the serine protease factor I that degrades and irreversibly inactivates the activation product of the central complement C3b. Secondly, factor H accelerates the decay of the alternative pathway C3 convertase (C3bBb). Factor H comprises 20 CCP domains.

Different minimized versions of factor H have previously been described, including the mini-FH comprising CCP1-4 and CCP19-20 joined by a polypeptide linker (Fig 1) (WO 2013/142362 A1). CCP1-3 is believed to be the minimal unit with cofactor activity for C3b proteolysis by factor I (Hocking et al. 2008).

The single domain antibody named hC3Nb1 capable of binding C3 and C3b is disclosed in Jensen et al. 2018. A C3b specific recombinant version of this single domain antibody named EWE-hC3Nb1 is described in WO 2019/238674 A1. This single domain antibody EWE-hC3Nb1 inhibits the alternative pathway (AP) by preventing the binding of factor B (FB) to C3b. hC3Nb1 binds at the interface between MG6 and MG7 domains of C3b and C3 (Fig 2). In complex with C3, the N-terminus is in close proximity to the MG6 domain (Fig 2D). The inventors rationalized that an extension of the N-terminus of hC3Nb1 might render it specific towards C3b. The inventors hence extended the N-terminus of hC3Nb1 by a Glu-Trp-Glu motif, which conferred specificity of the resulting EWE-hC3Nb1 toward C3b (Fig 3). The EWE-hC3Nb1 binds close to, but does not overlap with CCP2 of factor H.

Summary

In one aspect, provided herein is 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.

In another aspect, provided herein is a polypeptide comprising: (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 (ii) a factor H polypeptide that consists of the amino acid sequence according to SEQ ID NO: 10.

In another aspect, provided herein is the fusion protein as described herein, the polypeptide as described herein, or the pharmaceutical composition as described herein, for use as a medicament.

In another aspect, provided herein is use of the fusion protein as described herein, the polypeptide as described herein, or the pharmaceutical composition as described herein 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.

Regulators of the complement system have long been sought for, since overactivation of the complement system induces tissue damage and sustains chronic inflammation. The inventors of the present disclosure made the surprising discovery that a recombinant linkage of a single domain antibody capable of binding C3b (EWE-hC3Nb1) to a novel minimized version of factor H comprising the CCP2-4 and CCP19-20 domains of factor H, results in an alternative pathway (AP) inhibitor that mediates cleavage of C3b by factor I. As shown in the examples, this novel fusion protein retains both its capabilities from the single domain antibody moiety and surprisingly also the