serum or blood and evades innate host defenses. Recently, genetic variation in the human factor H gene cluster was found to affect susceptibility to developing meningococcal disease (Davila S et al. (2010) Nat Genetics doi:10.1038/ng.640). Binding of fH to fHbp is specific for human fH and could account for why *Neisseria meningitidis* is strictly a human pathogen.

[0005] There remains a need for a fHbp polypeptide that can elicit effective bactericidal antibody responses.

SUMMARY

[0006] Non-naturally occurring factor H binding proteins derived from variant 3 fHbp that can elicit antibodies that are bactericidal for at least one strain of *N. meningitidis*, and methods of use of such proteins, are provided.

[0006a] In one aspect of the present disclosure, there is provided a non-naturally occurring factor H binding protein (fHbp) derived from a naturally occurring variant 3 fHbp, the non-naturally fHbp comprising:

a substitution of the histidine at position 223 of the naturally occurring variant 3 fHbp with an amino acid selected from the group consisting of arginine, lysine, phenylalanine, tyrosine, or tryptophan, wherein the numbering of position 223 is based on the numbering of the mature fHbp ID 1,

wherein the non-naturally occurring fHbp has lower affinity for human factor H (fH) than fHbp ID 79.

[0006b] In another aspect of the present disclosure, there is provided an immunogenic composition comprising:

a) the non-naturally occurring fHbp as disclosed herein; and

b) a pharmaceutically acceptable excipient.

[0006c] In a further aspect of the present disclosure, there is provided a use of the non-naturally occurring fHbp as disclosed herein, or the immunogenic composition as disclosed herein, in the manufacture of a medicament for eliciting an antibody response in a mammal.

[0006d] In another aspect of the present disclosure, there is provided a nucleic acid encoding the fHbp as disclosed herein.

[0006e] In a further aspect of the present disclosure, there is provided a recombinant expression vector comprising the nucleic acid as disclosed herein.

[0006f] In another aspect of the present disclosure, there is provided a genetically modified host cell comprising the nucleic acid as disclosed herein or the recombinant expression vector as disclosed herein.

[0006g] In a further aspect of the present disclosure, there is provided an immunogenic composition comprising:

a) a vesicle obtained from a genetically modified *Neisseria* host cell that is genetically modified with a nucleic acid encoding the non-naturally occurring fHbp as disclosed herein, such that the encoded non-naturally occurring fHbp is produced by the genetically modified host cell, wherein the vesicle comprises the encoded non-naturally occurring fHbp; and

b) a pharmaceutically acceptable excipient.

[0006h] In another aspect of the present disclosure, there is provided a use of the immunogenic composition as disclosed herein in the manufacture of a medicament for eliciting an antibody response in a mammal.

[0006i] In a further aspect of the present disclosure, there is provided the non-naturally occurring fHbp as disclosed herein, or the immunogenic composition as disclosed herein, for use in eliciting an antibody response in a mammal.

[0007] In certain embodiments, a non-naturally occurring factor H binding protein (fHbp) derived from a naturally occurring variant 3 fHbp is disclosed. The non-naturally fHbp may include a substitution of the histidine at position 223 of the naturally occurring variant 3 fHbp with an amino acid selected from the group consisting of arginine, lysine, phenylalanine, tyrosine, or tryptophan, wherein the numbering of position 223 is based on the numbering of the mature fHbp ID 1. The non-naturally occurring fHbp may have a lower affinity for human factor H (fH) than fHbp ID 79.

[0008] In certain embodiments, the histidine may be substituted with arginine.

[0009] In certain cases, the variant 3 fHbp may be a modular group V fHbp. In other cases, the variant 3 fHbp may be a modular group II fHbp.

[0010] Exemplary non-naturally occurring fHbp may include an amino acid sequence having at least 90% sequence identity to the amino acid sequence of the fHbp ID 79.

[0011] In certain cases, the non-naturally occurring fHbp may include the amino acid sequence of fHbp ID 28 with the amino acid substitution H223R.

[0012] In certain cases, the non-naturally occurring fHbp may include the amino acid sequence of fHbp ID 67 with the amino acid substitution H223R.

[0013] In certain cases, the non-naturally occurring fHbp may include the amino acid sequence of fHbp ID 175 with the amino acid substitution H223R.

[0014] In certain cases, the non-naturally occurring fHbp may include the amino acid sequence of fHbp ID 79 with the amino acid substitution H223R.

8. The non-naturally occurring fHbp of any one of claims 1-5, wherein the non-naturally occurring fHbp comprises fHbp ID 79 comprising the amino acid substitution H223R.

9. The non-naturally occurring fHbp of any one of claims 1-5, wherein the non-naturally occurring fHbp comprises fHbp ID 45 comprising the amino acid substitution H223R.

10. An immunogenic composition comprising:
a) the non-naturally occurring fHbp according to any of claims 1-9; and
b) a pharmaceutically acceptable excipient.

11. The immunogenic composition of claim 10, wherein the non-naturally occurring fHbp is expressed on surface of a vesicle preparation prepared from a *Neisseria meningitidis* strain expressing the fHbp.

12. The immunogenic composition of claim 10, wherein the non-naturally occurring fHbp is present as an isolated polypeptide.

13. The immunogenic composition of any one of claims 11-12, wherein said pharmaceutically acceptable excipient comprises an adjuvant.

14. The immunogenic composition of any one of claims 10-13, further comprising an additional *N. meningitidis* antigen.

15. Use of the non-naturally occurring fHbp according to any of claims 1-9, or the immunogenic composition of any of claims 10-14, in the manufacture of a medicament for ~~A method of~~ eliciting an antibody response in a mammal~~, the method comprising administering to a mammal the non-naturally occurring fHbp according to any of claims 1-9, or the immunogenic composition of any of claims 10-14~~.

16. The ~~method~~ use of claim 15, wherein the medicament is to be administered to the mammal, and wherein the administration~~said administering~~ provides for production of bactericidal antibodies to *N. meningitidis*.

17. A nucleic acid encoding the fHbp according to any of claims 1-10.

18. A recombinant expression vector comprising the nucleic acid of claim 17.

19. A genetically modified host cell comprising the nucleic acid of claim 17 or the recombinant expression vector of claim 18.

20. An immunogenic composition comprising:

a) a vesicle obtained from a genetically modified *Neisseria* host cell that is genetically modified with a nucleic acid encoding the non-naturally occurring fHbp according to any of claims 1-9, such that the encoded non-naturally occurring fHbp is produced by the genetically modified host cell, wherein the vesicle comprises the encoded non-naturally occurring fHbp; and

b) a pharmaceutically acceptable excipient.

21. The immunogenic composition of claim 20, wherein the vesicle is a native outer membrane vesicle.

22. The immunogenic composition of any one of claims 20-21, wherein the host cell is genetically modified to provide for decreased or no activity of a polypeptide product of the *lpxL1* gene and/or the *lpxL2* gene.

23. The immunogenic composition of any one of claims 20-22, wherein the host cell is genetically modified to provide for increased expression of a *Neisserial* antigen.

24. Use of the immunogenic composition of any one of claims 20-23 in the manufacture of a medicament for ~~A method of~~ eliciting an antibody response in a mammal~~, the method comprising administering to a mammal the immunogenic composition of any one of claims 20-23~~.

25. The non-naturally occurring fHbp according to any of claims 1-9, or the immunogenic composition of any of claims 10-14 or 20-23, for use in eliciting an antibody response in a mammal.