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— *with international search report (Art. 21(3))*

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(88) **Date of publication of the international search report**:
4 October 2012

(54) **Title**: CHIMERIC FACTOR H BINDING PROTEINS (FHBP) AND METHODS OF USE

Fig. 1A: Table 7, Source strains and characteristics of unique factor H binding protein variants.

			MLST		Por A	fHbp Characteristics						fHbp Variable Segment[1]				
Strain (reference)	Country	Capsular Group	ST	Clonal Cpx.	Variable Region ST	Variant Group	Sub-family	Peptide ID	Modular Group[2]	GenBank Acc. No.	N-term Element[3]	A	B	C	D	E
MC58 (Tettelin *et al.*, 2000)	UK	B	74	32	7,16-2	1	B	1	I	NP 274866	G	A.α.2	B.α.1	C.α.5	D.α.5	E.α.8
M2197	US	C	11	11	7,1	1	B	2	I	None*	G	A.α.3	B.α.1	C.α.2	D.α.2	E.α.1
4243 (Welsch et al., 2004)	US	C	11	11	5,2	1	B	3	I	AAS569 16	G	A.α.3	B.α.1	C.α.6	D.α.1	E.α.1
M4105 (Welsch et al., 2004)	US	B	154	41/44	7,4	1	B	4	I	AAS569 20	G	A.α.1	B.α.1	C.α.2	D.α.4	E.α.2
Z2491 (Parkhill *et al.*, 2000)	Gambia	A	4	4	7,13-1	1	B	5	I	NP 283399	G	A.α.13	B.α.1	C.α.2	D.α.4	E.α.2
M6190 (Welsch et al., 2004)	US	B	1988	11	5,2	1	B	6	I	AAS569 17	G	A.α.2	B.α.7	C.α.14	D.α.3	E.α.17
M2937	US	B	35	35	23,14	1	B	7	I	None*	G	A.α.12	B.α.1	C.α.10	D.α.3	E.α.12

[1] For each variable segment, distinct sequence variants were assigned a unique identifier beginning with a letter, A through E, to represent the segment; followed by an α or β to indicate the presence of residues with the respective types described above, followed by a number for each distinct sequence
[2] Modular group see Figure 8.
[3] The mature fHbp begins with a cysteine residue that is lipidated, which is followed by three invariant amino acid residues, SSG. This invariant sequence is followed by a repetitive variable sequence consisting of 1 to 6 glycine and/or serine residues and then by two invariant glycine residues

(57) **Abstract**: Provided are chimeric factor H binding proteins (fHbps) that can elicit antibodies that are bactericidal for different fHbp variant strains of N. meningitidis, and methods of use fHbps. More specifically, the disclosure provides unique sequences in fHbp variable segment A through E, each assigned with a unique identifier beginning with a letter, A through E, to represent the segment. Further disclosed are chimeric fHbps including operably linked amino acid sequences derived from different variants. Methods of using the fHbps for treating Neisseria infection, especially N. meningitidis, are further disclosed.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/33048

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/02; A61K 39/00; A61K 39/116; A61K 39/095 (2012.01)
USPC - 424/190.1; 424/192.1; 424/203.1; 424/250.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/02; A61K 39/00; A61K 39/116; A61K 39/095; C07K 1/00; C07H 21/04 (2012.01)
USPC - 424/190.1; 424/192.1; 424/203.1; 424/250.1; 530/350; 536/23.4, 435/69.7; 530/324; 530/330

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 39/02; A61K 39/00; A61K 39/116; A61K 39/095; C07K 1/00; C07H 21/04 (2012.01) - see keyword below
USPC - 424/190.1; 424/192.1; 424/203.1; 424/250.1; 530/350; 536/23.4, 435/69.7; 530/324; 530/330 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: Factor H Binding Protein, fHbp, GNA1870, Neisseria meningitidis, domain, A B C D E meningococcal, chimeric, fusion, combination, vaccine, peptide, polypeptide, five, variable, region epitope, fragment, linker, Asp-Asp, DD, alpha, beta, variant

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0251670 A1 (COMANDUCCI et al.) 09 November 2006 (09.11.2006), Abstract, para [0014], [0040], [0047], [0064], [0067], [0068], [0331], SEQ ID NO: 24, SEQ ID NO: 81 (a.a 1-66 and 154-172), SEQ ID NO: 25 (a.a 98-159), SEQ ID NO: 31 (a.a.186-253), SEQ ID NO: 84 (a.a. 1-69)	1-2
Y	US 2005/0222385 A1 (Pizza) 06 October 2005 (06.10.2005), para [0001], [0050], [0057], [0159], Fig 1, SEQ ID NO: 8 (a.a 52-66), and SEQ ID NO: 11 (a.a. 49-63)	1-2
Y	US 2007/0148729 A1 (FARLEY et al.) 28 June 2007 (28.06.2007), para [0119], SEQ ID NO: 29 (a.a 13-17), SEQ ID NO: 30(a.a. 2-5), and SEQ ID NO: 31(a.a. 1-5)	1-2
Y	US 2009/0104150 A1 (PEPINSKY et al.) 23 April 2009 (23.04.2009), para [0032]	1-2
A	WO 2008/125985 A2 (Rappuoli) 23 October 2008 (23.10.2008), Abstract; and pg 1, ln 15-16	1-2
A	BEERNINK et al. Bactericidal Antibody Responses Induced by Meningococcal Recombinant Chimeric Factor H-Binding Protein Vaccines. Infect Immun. 2008, Vol. 76(6), p. 2568-75. Entire documentation, especially Abstract	1-2
Y,P	US 2009/0285845 A1 (MASIGNANI et al.) 19 November 2009 (19.11.2009), para [0004], [0022], [0023], SEQ ID NO: 13 (a.a. 79-93), and SEQ ID NO: 10 (a.a.32-100)	1-2
Y,P	BEERNINK et al. The modular architecture of meningococcal factor H-binding protein. Microbiology. 2009 Sep, Vol. 155(Pt 9), p. 2873-83. Epub 2009 Jul 2. Entire documentation, especially, Abstract; pg 2879, Fig 2; pg 2877, Fig 3; and pg 2879, Fig 6	1-2

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2012 (13.07.2012)	27 JUL 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/33048

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: claims 1-8, drawn to a non-naturally occurring fHbp, comprising, from N-terminus to C-terminus: VA-I3-VB-I4-VC-I5-VD-I6-VE, wherein the combination of alleles for each of VA, VB, VC, VD, and VE variable segments is not found in nature. The first named invention (claims 1-2) is limited to wherein each of said variable segments is an alpha progenitor sequence. Applicant is invited to elect (an) additional feature(s) including wherein each of said variable segments is a beta progenitor sequence (claim 3), wherein at least one of VA, VB, VC, VD, and VE is of an a progenitor fHbp amino acid sequence and at least one of VA, VB, VC, VD, and VE is of a beta progenitor fHbp amino acid sequence (claims 4-5, 7), wherein said non-naturally occurring fHbp comprises, from N-terminus to C-terminus: I1-Nte-I2-VA-I3-VB-I4-VC-I5-VD-I6-VE-I7, or/and wherein said fHbp comprises an epitope that is bound by a monoclonal antibody set forth in Table 1, by paying additional fee for each election. The exact number of extra claims to be searched will depend upon the election. Note: Claims 3-8 are excluded from the search because they require a search of nonelected subject matter.

**********Continued in the extra sheet**********

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-2, limited to wherein each of said variable segments is an alpha progenitor sequence

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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Continuation of:
Box No III (unity of invention is lacking)

Group II, claims 9-14, drawn to a method of eliciting an antibody response in a mammal, the method comprising administering to a mammal a composition comprising a first non-naturally occurring fHbp according to claim 1

Group III, claims 15-21, drawn to an immunogenic composition comprising a first non-naturally occurring fHbp according to claim 1, and a pharmaceutically acceptable excipient.

Group IV, claims 22-23, drawn to a nucleic acid encoding the non-naturally occurring fHbp of claim 1.

The inventions listed as Groups I+-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I+-III do not include the inventive concept of a nucleic acid encoding the non-naturally occurring fHbp, as required by Group IV.

Groups I+-II and IV do not include the inventive concept of an immunogenic composition comprising a first non-naturally occurring fHbp and a pharmaceutically acceptable excipient, as required by Group III.

Groups I+ and III-IV do not include the inventive concept of administering to a mammal a composition comprising a first non-naturally occurring fHbp, as required by Group II.

Furthermore, among Group I+, claims 2-7 do not include the inventive concept of a non-naturally occurring fHbp comprising an epitope that is bound by a monoclonal antibody set forth in Table 1, as required by claim 8; claims 2-5 and 7-8 do not include the inventive concept of a non-naturally occurring fHbp comprising N-terminal 'I1-Nte-I2-', as required by claim 6; claims 2-3, 6, and 8 do not include the inventive concept of a non-naturally occurring fHbp comprising at least one alpha progenitor sequence and at least one beta progenitor sequence, as required by claims 4-5 and 7; claims 2 and 4-8 do not include the inventive concept of a non-naturally occurring fHbp comprising all beta progenitor sequences, as required by claim 3; and claims 3-8 do not include the inventive concept of a non-naturally occurring fHbp comprising all alpha progenitor sequences, as required by claim 2.

The inventions of Groups I+ through IV share the technical feature of a non-naturally occurring fHbp of claim 1, comprising, from N-terminus to C-terminus: VA-I3-VB-I4-VC-I5-VD-I6-VE, wherein the combination of alleles for each of VA, VB, VC, VD, and VE variable segments is not found in nature. Claims 2 and 4-5 and 7 further share the technical feature of wherein at least one of VA, VB, V C, VD, and VE is of an alpha progenitor fHbp amino acid; and claims 3-5 and 7 further share the technical feature of wherein at least one of VA, VB, VC, VD, and VE is of a beta progenitor fHbp amino acid sequence. However, these shared technical features do not represent a contribution over prior art as being obvious over US 2006/0251670 A1 to COMANDUCCI et al. (hereinafter 'Comanducci'), in view of US 2005/0222385 A1 to Pizza, and further in view of US 2007/0148729 A1 to FARLEY et al. (hereinafter 'Farley'), and US 2009/0104150 A1 to PEPINSKY et al. (hereinafter 'Pepinsky') as follows:

Comanducci discloses a non-naturally occurring fHbp (para [0064] - 'fusion protein is disclosed ... in which two or more ... 5, 6 or more..Neisserial proteins are joined', wherein 'fusion protein' is 'a non-naturally occurring protein, and 'Neisserial proteins' comprising 'fHbp' para [0014] - 'the use of NMB1870 for providing immunity against multiple (e.g. 2, 3, 4, 5 or more) strains and/or serogroups of N. meningitidis', wherein 'NMB1870' protein is 'fHbp'; Abstract - 'Meningococcal protein NMB 1870'; please see WO 2008/125985 A2 to Rappuoli: Abstract; and pg 1, ln 15-16 - 'Meningococcal protein 'NMB1870' has been reported...to bind to the human complement protein Factor H ("fH")'; Please also see: BEERNINK et al.: Abstract; Specification: para [0005] - 'Factor H Binding Protein (fHbp, ... is an N. meningitidis protein ... An important function of fHbp is to bind human complement fH'; para [0041] - '"Non-naturally occurring",... fHbp...is not normally found in nature ... made via chemical synthesis or recombinant methods'), comprising,
--- from N-terminus to C-terminus a formula equivalent to: VA-I3-VB-I4-VC-I5-VD-I6-VE (para [0064] - ' fusion protein is disclosed ... in which ... 5, 6 or more...Neisserial proteins are joined.... by the formula: NH.sub.2-A-[-X-L-].sub.n-B--COOH wherein X is... a Neisserial sequence, L is an optional linker amino acid sequence, A is an optional N-terminal amino acid sequence, B is an optional C-terminal amino acid sequence, and n is an integer greater than 1. ... between 2 and x, and the value of x is.. 5, 6, 7', wherein '[-X-L-].sub.n is equivalent to 'VA-I3-VB-I4-VC-I5-VD-I6-VE' and 'X' is equivalent to 'VA, VB, VC, VD, or VE' when n=5, and 'L' is equivalent to 'I3, I4, I5, or I6' when n=4; para [0068] - 'Linker amino acid sequence(s) -L- will typically be short ... fewer amino acids ... 5, 4, 3, 2', without both optional A and B), and wherein
---VA comprising an amino acid sequence that is about 89-100% identical to SEQ ID NO: 15 (para [0067] - 'NMB1870 sequences include SEQ ID NO..., 81', wherein SEQ ID NO: 81 comprises a region between amino acid 1-66, that is 100% identical to the claimed SEQ ID NO: 15; para [0047] - 'NMB1870 proteins... at least ... 90%,..99.5% or more... sequence identity to one or more of SEQ ID NO.sup.s 1 to 252 ...or comprising an amino acid sequence consisting of a fragment of at least 7...60, 70'; para [0064]; Specification: para [0059] - 'VA of an a progenitor (VA alpha) comprises an amino acid sequence that is about 89 to 100% identical to....SEQ ID NO: 15');
---VC comprising an amino acid sequence that is about 85-100% identical to SEQ ID NO:96 (para [0040] - 'amino acid sequence ...at least .. 85% ...99.5% or more.. identity to ...fragment of at least 7 ...60, 70... contiguous amino acids from one or more of SEQ IDs...preferably SEQ IDs 25', wherein SEQ ID NO: 25 comprising a region between amino acid residues 98-159, that is 100% identical to the claimed SEQ ID NO: 96; para [0064]; Specification: para [0063] - 'VC of an a progenitor (VCa) comprises an amino acid sequence that is about 85 to 100% identitical to ...SEQ ID NO:96');
---VD comprising an amino acid sequence that is about 89-100% identical to SEQ ID NO: 174' (para [0067] - 'NMB1870 sequences include SEQ ID NO..., 81', wherein SEQ ID NO: 81 comprises a region between amino acid 154-172, that is 100% identical to the claimed SEQ ID NO: 174; para [0047] - 'NMB1870 proteins... at least ... 90%,..99.5% or more... sequence identity to one or more of SEQ ID NO.sup.s 1 to 252 ...or comprising an amino acid sequence consisting of a fragment of at least 7 ...19'; para [0064]; Specification: para [0065] - 'VD of an a progenitor (VDa) comprises an amino acid sequence that is about 89 to 100% identitical to...SEQ ID NO: 174')

**********Continued in the next extra sheet**********

INTERNATIONAL SEARCH REPORT

International application No.
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Continuation of:
The previous extra sheet - Box No III (unity of invention is lacking)

(Continuation of the discussion for Groups I+ through IV)
---VE comprising an amino acid sequence that is about 86 to 100% identitical to SEQ ID NO:195 (para [0040] - ' amino acid sequence ...at least .. 90% ...99.5% or more.. identity to ...fragment of at least 7 ...60, 70... contiguous amino acids from one or more of SEQ IDs...preferably SEQ IDs 25 to 45', wherein SEQ ID NO: 31 comprising a region between amino acid residues 186-253, that is 100% identical to the claimed SEQ ID NO: 195'; para [0064]; Specification: para [0067] - 'VE of an a progenitor (VEa) comprises an amino acid sequence that is about 86 to 100% identitical to...SEQ ID NO:195'), and
--- wherein the combination of alleles for each variable segments is not found in nature (para [0064] - 'fusion protein is disclosed ... in which two or more ... 5, 6 or more..Neisserial proteins are joined'; Abstract; Specification: para [0041]).
Comanducci does not specifically teach wherein
---VB comprising an amino acid sequence that is about 80-100% identical to SEQ ID NO:85 (Specification: para [0061] - 'VB of an a progenitor (VBa) comprises an amino acid sequence that is about 80% to 100% identical to...SEQ ID NO:85');
---I3 is defined by the amino acid sequence of SEQ ID NO:3 (Specification: para [0050] - 'I3, is defined by the amino acid sequence of SRFDF (SEQ ID NO:3)')
---I4 is defined by the amino acid sequence of SEQ ID NO: 4 (Specification: para [0050] - 'I4, ...is defined by the amino acid sequence GEFQ (SEQ ID NO:4)')
---I5 is defined by the amino acid sequence DD (Specification: para [0050] - 'I5 is defined by the amino acid sequence DD')
---I6 is defined by the amino acid sequence of SEQ ID NO: 5 (Specification: para [0050] - 'I6, positioned C-terminal to I5, is defined by IEHLK (SEQ ID NO:5)').
Pizza discloses polymorphic forms of proteins 741 expressed in different Neisseria strains including Neisseria meningitidis, which comprises SEQ ID NO: 85 (VB) (para [0001] - 'proteins from Neisseria... preferably, N. meningitidis'; para [0057] - ' Stains are indicated as a subscript e.g. 741.sub.MC58 is protein 741 from strain MC58'; para [0050] - 'polymorphic forms of proteins 741 (SEQ IDs 1-22)', wherein SEQ ID NO: 8 comprises a region between amino acid residues 52-66, that is 100% identical to the claimed ID 85; and SEQ ID NO: 11 comprises a region between amino acid residues 49-63, that is also 100% identical to the claimed SEQ ID NO: 85). Pizza further discloses wherein SEQ ID NO: 85 is shared by different polymorphic forms of proteins 741 (para [0159] - 'FIG. 1 shows an alignment of twenty-three sequences for protein 741. These are SEQ IDs 1 to 22'; Fig 1, wherein form 312294 comprises a region between amino acid 104-118, that is 100% identical to the claimed SEQ ID NO: 85, which is shared by 18 polymorphic peptides in the alignment).
Pizza also does not specifically teach SEQ ID NOs: 3-5 (I3-I4, I6) and I5. Farley discloses a mixture of protein antigens that against different Neisseria meningitidis serosubtypes (para [0119] - 'purified ORF2086 protein antigen exhibited bactericidal activity against at least six of the Neisseria meningitidis serosubtypes'), wherein the antigens comprising fragments of SEQ ID NOs: 3-5 (I3, I4, I6, respectively) (para [0120] - 'an ORF2086 protein comprises any of the following amino acid sequences: ...SLNTGKLKNDKxSRFDF (SEQ ID NO:29), ...SGEFQxYKQ (SEQ ID NO:30),... IEHLKxPE (SEQ ID NO:31)', wherein SEQ ID NO: 29 comprising a region between amino acid residues 13-17, that is 100% identical to the claimed SEQ ID NO: 3 (I3); SEQ ID NO: 30 comprising a region between amino acid residues 2-5, that is 100% identical to the claimed SEQ ID NO: 4 (I4); and SEQ ID NO: 31 comprising a region between amino acid residues 1-5, that is 100% identical to the claimed SEQ ID NO: 5 (I6)). Although Farley does not specifically teaches using the sequence as linker sequences, one of ordinary skill in the art at the time the invention was made would have been motivated to do so for increasing a chimeric peptide for eliciting serum antibodies production for against different Neisseria meningitidis serosubtypes based on the combination of Farley and Comanducci (para [0068] - 'Linker amino acid sequence(s) -L- will typically be short ... fewer amino acids ... 5, 4, 3, 2'; Abstract).
Farley also does not specifically teach I5. Pepinsky discloses a linker sequence comprising I5 (para [0032] - 'The enterokinase linker sequence (AspAspAspAspLys)', which comprising DD (AspAsp) sequence; Specification: para [0050] - 'I5 is defined by the amino acid sequence DD'), one of ordinary skill in the art at the time the invention was made would have known to use a select length of amino acid sequence from an existing linker sequence for a linker based on the combination of Pepinsky and Comanducci (para [0068]).
It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Comanducci, Pizza, Farley, and Pepinsky, to obtain a non-naturally occurring fHbp, comprising, from N-terminus to C-terminus a formula equivalent to: VA-I3-VB-I4-VC-I5-VD-I6-VE , wherein VA comprising an amino acid sequence that is about 89-100% identical to SEQ ID NO: 15, VC comprising an amino acid sequence that is about 85-100% identical to SEQ ID NO:96, VD comprising an amino acid sequence that is about 89-100% identical to SEQ ID NO: 174, and VE comprising an amino acid sequence that is about 86 to 100% identical to SEQ ID NO:195, and wherein the combination of alleles for each variable segments is not found in nature, based on the teaching of Comanducci, and further wherein VB comprising an amino acid sequence that is about 80-100% identical to SEQ ID NO:85, based on the combination of Pizza and Comanducci, and I3 is defined by the amino acid sequence of SRFDF (SEQ ID NO:3), I4 is defined by the amino acid sequence of GEFQ (SEQ ID NO:4), I6 is defined by the amino acid sequence of IEHLK (SEQ ID NO:5), based on the combination of Farley and Comanducci, and I5 is defined by the amino acid sequence DD, based on the combination of Pepinsky and Comanducci, in order to include fragments of different meningococcal proteins and linker(s) known in the art for facilitating generating a non-naturally occurring fHbp protein for vaccine production for facilitating preventing and treating infections from different strains of N. meningitidis.

In addition, although the combination of Comanducci, Pizza, Farley, and Pepinsky does not specifically teach VA, VB, VC, VD, and VE, represented by SEQ ID NOs: 15, 85, 96, 174, and 195, respectively, each is an alpha progenitor fHbp amino acid, this limitation is determined by the inherent property of amino acid sequence (please see Specification: para [0059], [0061],[0063], [0065], [0067]). Furthermore Comanducci further discloses a fHbp protein sequence comprises a peptide from different variant (para [0064] - 'fusion protein is disclosed ... in which two or more ... 5, 6 or more..Neisserial proteins are joined'; para [0331] - 'Hybrid and tandem proteins can be represented by the formula: NH.sub.2-A-[-X-L-].sub.n-B-COOH.... various proteins ...M1239 (SEQ ID 84)'), which comprises a region between amino acid 1-69, that is 100% identical to the VA beta segments having SEQ ID NO: 67 (Specification: para [0060] - 'VA of a beta progenitor (VA beta) comprises an amino acid sequence that is about 89 to 100% identitical to...SEQ ID NO:67'). Without a shared special technical feature, the inventions lack unity with one another.

Groups I+-IV therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note: Claim 1 is self-referring. For the purposes of this ISR, 'A non-naturally occurring fHbp of claim 1' is read as 'A non-naturally occurring fHbp'.