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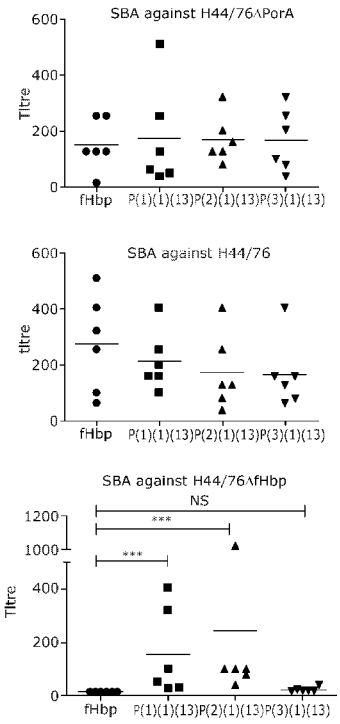

Figure 7

(57) Abstract: The invention relates to a modified factor H binding protein (fHbp), comprising fHbp, or a variant thereof, modified with the addition of at least one exogenous peptide loop; and associated nucleic acid, compositions, and uses. The invention further relates to treatment or prevention of a pathogenic infection or colonisation of a subject using the modified factor H binding protein (fHbp).

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MODIFIED FACTOR H BINDING PROTEIN

This invention relates to a modified factor H binding protein (fHbp) and its use to elicit an immune response against pathogenic infection or colonisation, such as against *Neisseria meningitidis* or *Neisseria gonorrhoeae*.

Neisseria meningitidis (*Nm*) remains a leading cause of sepsis and bacterial meningitis in children and young adults. The onset of disease can be extremely rapid, with fatality rates of around 10% for septicaemic disease[1], while those that survive can suffer significant disabilities including loss of limbs and neurological deficits[1]. Therefore prophylactic immunisation is the best way to protect individuals from meningococcal infection. Vaccines are available based on the bacterial capsule[2], but there are only partially effective vaccines available for endemic serogroup B infection, which causes over 80% of cases in the UK currently[3]; the polysaccharide of serogroup B capsule *Nm* is poorly immunogenic as it has structural identity with a human glycoprotein in neural tissue and could induce autoimmunity if used as a vaccine[4]. Therefore there is an urgent need to generate novel vaccines, and there are intense efforts in academia and industry to achieve this important goal.

The major target of the immune response elicited against meningococcal outer membrane vesicles (OMVs) is PorA[16,17,18], an integral outer membrane protein (OMP) in the meningococcus[19]. However, the sequence of this protein is diverse and the prevalence of particular variants differs by geographic region, and OMV vaccines are largely PorA-specific. Variants of PorA are identified by sequences in the variable-regions (VR) of the protein, which are located in the surface-exposed loops of the protein and are the target of immune responses[17]. PorA has seven extracellular loops; the fourth loop is variable region 2 (VR2) and is the target of most serum bactericidal activity (SBA) generated by PorA following natural infection and after immunisation with OMVs[16,18]. SBA is a known correlate of protection against meningococcal disease. Despite sequence

diversity, around 70 % of UK isolates would be covered by vaccines containing six PorA proteins (http://pubmlst.org/neisseria/PorA/).

A major obstacle for bacterial vaccine development is the difficulty in producing quantities of integral OMPs, such as PorA, in their native conformation. This is because OMPs contain hydrophobic domains which span the membrane and do not fold correctly when expressed as soluble recombinant proteins. Correct folding is critical for PorA as SBA is elicited by conformational, and not linear, epitopes of the protein[20]. Previous attempts to use PorA peptides as vaccines have not been successful because they have not been sufficiently immunogenic and do not present the immunogenic portion of PorA in its correct conformation. Consequently, the only PorA-based vaccines under development are OMVs, which have limited efficacy in infants[2], are reactogenic[21], and poorly defined providing regulatory issues. OMVs as immunogens are not favoured because consistency and toxicity can be problematic during manufacture. For example, OMVs may contain toxic lipopolysaccharide (LPS).

Meningococcal factor H binding protein (fHbp) is a surface-exposed lipoprotein that consists of two β-barrels[5] (Fig. 1A). The N-terminal β-barrel of fHbp has a relatively open structure, while the C-terminal β-barrel is stabilised by extensive hydrogen bonding between the seven β-strands, which form this barrel[5].

Importantly, fHbp is a key antigen in vaccines against serogroup B *Nm* under development by pharmaceutical companies such as Pfizer, GSK, and others, and is included in next generation OMV vaccines[6,7,8]. The Pfizer vaccine consists of two fHbps, while the GSK vaccine has a single fHbp in a cocktail of other antigens which includes an OMV. fHbp binds human, but not murine, factor H (fH)[9,10], an abundant plasma protein that down regulates the complement system[11], a critical aspect of immunity against *Nm*[12]. Immunisation of adolescents and adults with fHbp elicits SBA[13].

fHbp has been categorised into different schemes based on its predicted amino acid sequence. In the present application, three variant groups (v1, v2 and v3[7]) and peptide numbers (www.mlst.org) are recognised. Importantly, serum raised against v1 fHbp does not mediate SBA against *Nm* expressing v2 and v3 proteins, and *vice versa*. The GSK vaccine contains a single v1 protein (v1.1), while the Pfizer formulation includes a v1 and v3 fHbp[13,14]. Therefore no current vaccine includes a v2 fHbp even though between a significant proportion of disease in the UK is currently caused by strains expressing fHbp from this variant group[3,15].

WO2011024072 is a patent application that describes the use of fHbp which is selected or engineered to have a sequence which can elicit broad-spectrum bactericidal anti-meningococcal antibodies after administration to a host animal. This document teaches that additional meningococcal antigens may be provided with the engineered fHbp in the form of a N- or C-terminal fusion protein. However, such a proposal is unlikely to produce a protein that would present the immunogenic portion of many meningococcal antigens, such as PorA, in correct conformation and they would not be sufficiently immunogenic.

The present invention provides alternative and improved immunogenic molecules for vaccination against pathogenic organisms, particularly to prevent or reduce meningococcal or gonococcal infection or colonisation.

According to a first aspect of the invention, there is provided a modified factor H binding protein (fHbp), comprising wild-type fHbp or the wild-type gonococcal orthologue of fHbp (Ghfp), or a variant thereof having at least 75% identity with any of the sequences of SEQ ID NOs: 1-13, which is further modified with the addition of an exogenous peptide loop, wherein the exogenous peptide loop is between 8 and 20 amino acids in length and wherein the exogenous peptide loop is inserted at an amino acid position that is corresponding to any one of the amino acid residue numbers 49-54, 83-88, 114-124, 199-206, 227-233, and 240-246 of SEQ ID NO: 1, or equivalent residues in any of SEQ ID NOs: 2 to 13.

It has been shown herein that immunogenic peptides, such as those from PorA, can be introduced into factor H binding protein (fHbp), which acts as a

molecular scaffold. The peptides that are introduced into fHbp are presented to the immune system and are able to elicit protective responses such as SBA. Advantageously, the fHbp molecule provides an ideal molecular scaffold for stable inclusion of peptide loops for the display of epitopes, particularly for epitopes that are difficult to stabilise and display in their native conformation, for example loops from integral OMPs such as PorA. This is in contrast to teachings such as in WO2011024072, where simple N- or C- terminal fusions of fHbp and additional antigen would not solve inherent stability and solubility difficulties with some antigens. In particular, many OMPs, such as PorA, are difficult to express because of the insolubility of their membrane spanning domains. PorA has a 16-beta stranded barrel structure with the surface-exposed loops between strands 1 and 2 (loop 1), strands 7 and 8 (loop 4), strands 9 and 10 (loop 5) and strands 11 and 12 (loop 7) demonstrated to be the most effective antigens. fHbp contains two beta barrels, therefore the peptide loop sequences from OMPs can be inserted into the tips of the loops between beta-strands of fHbp to present the extra-cellular loop fragments from integral OMPs, in their native conformations for immunisation. Therefore, the modified fHbp scaffold molecule of the invention may be used as a prophylactic or a therapeutic vaccine directed to *Nm* or the gonococcus in which a single protein presents key epitopes from two different antigens.

In one embodiment, the fHbp is meningococcal fHbp. In another embodiment, the fHbp is gonococcal fHbp. The fHbp may comprise any one of variants v1, v2 and v3. In one embodiment, the fHbp may comprise fHbp v1. In another embodiment, the fHbp may comprise fHbp v2. In another embodiment, the fHbp may comprise fHbp v3.

In one embodiment, the fHbp variant v1 may be variant v1.1, v1.13, v1.14, v1.15, v1.4, or v1.55. In one embodiment, the fHbp variant v1 may not be v1.1. In one embodiment, the fHbp variant v1 may not be v1.55. In one embodiment, the fHbp variant v1 may not be v1.1 or v1.55. In one embodiment, the fHbp variant v2 may be variant v2.16, v2.19, v2.22, or v2.25. In one embodiment, the

fHbp variant v3 may be variant v3.45. In one embodiment, the fHbp comprises any one of fHbp variants v1.4, v2.25 or v3.45.

A variant of fHbp may comprise an orthologue of fHbp. For example, a variant of fHbp may comprise Ghfp, the Gonococcal homologue of fHbp. Ghfp is non-functional and closely related to V3 fHbps (>95% aa identity, dissociation constant KD > 100 μM with factor H).

In one embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTAFQ TEQIQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA TYRGTAFGSD DAGGKLTYTI DFAAKQGNGK IEHLKSPELN VDLAAADIKP DGKRHAVISG SVLYNQAEKG SYSLGIFGGK AQEVAGSAEV KTVNGIRHIG LAAKQ (SEQ ID NO: 1, fHbp V1.1 GI:316985482).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTALQ TEQVQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA TYRGTAFGSD DASGKLTYTI DFAAKQGHGK IEHLKSPELN VDLAASDIKP DKKRHAVISG SVLYNQAEKG SYSLGIFGGQ AQEVAGSAEV ETANGIRHIG LAAKQ (SEQ ID NO: 2, fHbp V1.4 GI:989557230).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGKLIT LESGEFQVYK QSHSALTALQ TEQVQDSEDS GKMVAKRQFR IGDIAGEHTS FDKLPKGGSA TYRGTAFGSD DAGGKLTYTI DFAAKQGHGK IEHLKSPELN VELATAYIKP DEKRHAVISG SVLYNQDEKG SYSLGIFGGQ AQEVAGSAEV ETANGIHHIG LAAKQ (SEQ ID NO: 3, fHbp V1.13 GI:752774533).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTALQ TEQEQDPEHS GKMVAKRRFK IGDIAGEHTS FDKLPKDVMA TYRGTAFGSD DAGGKLTYTI DFAAKQGHGK IEHLKSPELN VELATAYIKP DEKHHAVISG SVLYNQDEKG SYSLGIFGGQ AQEVAGSAEV ETANGIHHIG LAAKQ (SEQ ID NO: 4, fHbp V1.14 GI:630057376).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGSGG GGVAADIGAG LADALTAPLD HKDKGLKSLT LEDSISQNGT LTLSAQGAER TFKAGDKDNS LNTGKLKNDK ISRFDFIRQI EVDGQLITLE SGEFQVYKQS HSALTALQTE QVQDSEHSGK MVAKRQFRIG DIVGEHTSFG KLPKDVMATY RGTAFGSDDA GGKLTYTIDF AAKQGHGKIE HLKSPELNVD LAAADIKPDE KHHAVISGSV LYNQAEKGSY SLGIFGGQAQ EVAGSAEVET ANGIRHIGLA AKQ (SEQ ID NO: 5, fHbp V1.15 GI:504394462).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGSGG GGVTADIGTG LADALTAPLD HKDKGLKSLT LEDSISQNGT LTLSAQGAEK TYGNGDSLNT GKLKNDKVSR FDFIRQIEVD GQLITLESGE FQVYKQSHSA LTALQTEQEQ DPEHSEKMVA KRRFRIGDIA GEHTSFDKLP KDVMATYRGT AFGSDDAGGK LTYTIDFAAK QGHGKIEHLK SPELNVDLAV AYIKPDEKHH AVISGSVLYN QDEKGSYSLG IFGEKAQEVA GSAEVETANG IHHIGLAAKQ (SEQ ID NO: 6, fHbpV 1.55 GI:40353481).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPDGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELAAAELKAD

EKSHAVILGD TRYGSEEKGT YHLALFGDRA QEIAGSATVK IGEKVHEIGI AGKQ (SEQ ID NO: 7, fHbp V2.16 GI:488155511).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGGEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 8, fHbp V2.19 GI:488148626).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD PNGRLHYSID FTKKQGYGRI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGGEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 9, fHbp V2.22 GI:120865922).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TTPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQTIT LASGEFQIYK QNHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPDGKAE YHGKAFSSDD PNGRLHYSID FTKKQGYGRI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGGEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 10, fHbp 2.25 GI:488158712).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGSGSGGG GVAADIGTGL ADALTAPLDH KDKGLKSLTL EDSISQNGTL TLSAQGAEKT FKVGDKDNSL NTGKLKNDKI SRFDFVQKIE VDGQTITLAS GEFQIYKQDH SAVVALQIEK INNPDKIDSL INQRSFLVSG LGGEHTAFNQ

LPSGKAEYHG KAFSSDDAGG KLTYTIDFAA KQGHGKIEHL KTPEQNVELA SAELKADEKS HAVILGDTRY GSEEKGTYHL ALFGDRAQEI AGSATVKIRE KVHEIGIAGK Q (SEQ ID NO: 11, fHbp V3.45 GI:284466869).

In another embodiment, the fHbp which is to be further modified with the at least one exogenous peptide loop may comprise or consist of the sequence of CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LKSLTLEDSI SQNGTLTLSA QGAEKTFKVG DKDNSLNTGK LKNDKISRFD FVQKIEVDGQ TITLASGEFQ IYKQNHSAVV ALQIEKINNP DKIDSLINQR SFLVSGLGGE HTAFNQLPGG KAEYHGKAFS SDDAGGKLTY TIDFAAKQGH GKIEHLKTPE QNVELAAAEL KADEKSHAVI LGDTRYGSEE KGTYHLALFG DRAQEIAGSA TVKIGEKVHE ISIAGKQ (SEQ ID NO: 12, fHbp V3.47 GI:284466897).

In another embodiment the Ghfp which is to be further modified with the at least one exogenous peptide loop, may comprise or consist of the sequence of MTRSKPVNRT TFCCLSLTAG PDSDRLQQRR GGGGGVAADI GTGLADALTA PLDHKDKGLK SLTLEASIPQ NGTLTLSAQG AEKTFKAGGK DNSLNTGKLK NDKISRFDFV QKIEVDGQTI TLASGEFQIY KQDHSAVVAL RIEKINNPDK IDSLINQRSF LVSDLGGEHT AFNQLPDGKA EYHGKAFSSD DADGKLTYTI DFAAKQGHGK IEHLKTPEQN VELASAELKA DEKSHAVILG DTRYGGEEKG TYRLALFGDR AQEIAGSATV KIGEKVHEIG IADKQ (SEQ ID NO: 13, GHFP).

A variant of fHbp may comprise one or more amino acid residue mutations, including additions, deletions or substitutions, relative to wild type fHbp in addition to the exogenous peptide loop(s) provided on the modified fHbp. For example, the fHbp may act as a scaffold upon which exogenous peptide loops are provided and the variants relative to wild-type may comprise amino acid mutations in the scaffold framework in regions outside of the exogenous peptide loop(s) attachment points. Reference to wild-type fHbp may refer to any one of the variants of fHbp discussed herein, for example any one of SEQ ID NOs: 1 to 13).

A variant of fHbp may comprise at least one amino acid change compared to the amino acid in the wild type protein. A variant of fHbp may comprise no more than one amino acid change compared to the wild type protein. A variant of

fHbp may comprise no more than three amino acid changes compared to the wild type protein. A variant of fHbp may comprise no more than four amino acid changes compared to the wild type protein. A variant of fHbp may comprise no more than five amino acid changes compared to the wild type protein. A variant of fHbp may comprise no more than six amino acid changes compared to the wild type protein. In one embodiment, a variant of fHbp is provided which comprises six amino acid mutations compared to the wild type protein.

Amino acid substitutions may be conservative substitutions. For example, a mutated residue may comprise substantially similar properties as the wild-type substituted residue. For example, a substituted residue may comprise substantially similar or equal charge or hydrophobicity as the wild-type substituted residue. For example, a substituted residue may comprise substantially similar molecular weight or steric bulk as the wild-type substituted residue.

In one embodiment a variant fHbp may have at least 75% identity with wild-type. In another embodiment a variant fHbp may have at least 80% identity with wild-type. In another embodiment a variant fHbp may have at least 85% identity with wild-type. In another embodiment a variant fHbp may have at least 90% identity with wild-type. In another embodiment a variant fHbp may have at least 95% identity with wild-type. In another embodiment a variant fHbp may have at least 98% identity with wild-type. In another embodiment a variant fHbp may have at least 99% identity with wild-type. In another embodiment a variant fHbp may have at least 99.5% identity with wild-type. The above percentage variation is not intended to include percentage identity variation with addition of the exogenous peptide loop(s) (i.e. it is the percentage identity of the fHbp component alone relative to the wild-type), and does not include deletion of fHbp sequence at the site where loops from other proteins are inserted.

The modified fHbp may be modified such that it is not capable of binding factor H, or at least has reduced factor H binding activity. The modified fHbp may be non-functional relative to the function of wild-type fHbp. In one embodiment, the modified fHbp has an impaired capacity to bind CFH with a KD >2 orders of magnitude compared with the wild-type protein. Non-functional fHbps may be provided by mutation of the fHbp sequence. In one embodiment, non-functional fHbps may be provided by one or more of the exogenous peptide loops preventing the binding site of factor H.

The amino acid residue mutation(s) may prevent or reduce complement factor H binding of the modified fHbp. In another embodiment, the amino acid residue mutation(s) may not substantially affect the fHbp function. In one embodiment, the amino acid residue mutation(s) in the fHbp, or variants thereof, may be selected from the group consisting of the amino acid at position 85, 133, 134, 135, 136, 204, 206, 211, 212, 213, 222, 225, 227, 231, and 252 on v1.1 fHbp or corresponding position in other fHbps.

In one embodiment, the amino acid residue mutation(s) may comprise or consist of a substitution to alanine instead of the wild type residue. In one embodiment, the amino acid residue change(s) may comprise or consist of a substitution to any other amino acid instead of the wild type residue.

Advantageously, providing a non-functional fHbp (i.e. non- or less- binding of factor H) can eliminate or reduce any adverse effects of factor H recruitment on the success of the vaccine.

In one embodiment, the amino acid residue mutation(s) may enhance the stability of the modified fHbp in particular, in an embodiment wherein fHbp V2 is provided, the fHbp V2 may be stabilised by mutations in the fHbp V2 sequence. Details of the mutations for V2 stability may be found in WO2014030003, which is herein incorporated by reference. For example, the amino acid substitution for stabilisation may be at one or more of the amino

acids at position 35, 36, 42, 43, 46, 107, 112, 114, 137 and 138 in fHbp V2. The substitution for stabilisation may be at one or more of Ser35, Leu36, Asp42, Glu43, Arg46, Asp107, Val112, Leu114, Ser137, and Gly138.

In one embodiment, the exogenous peptide loop(s) is immunogenic. The exogenous peptide loop(s) may be derived from an outer membrane/surface exposed protein.

The exogenous peptide loop(s) may be prokaryotic in origin. The exogenous peptide loop(s) may be derived from a protein on the bacterium, such as an outer membrane protein (OMP) of a pathogen. The OMP may be an integral OMP or a lipoprotein. The exogenous peptide loop(s) may be derived from a meningococcal protein, such as a meningococcal outer membrane protein. The exogenous peptide loop(s) may be derived from an outer membrane protein of another pathogen such as *N. gonorrhoeae*.

The exogenous peptide loop may comprise a fragment of a transmembrane beta barrel protein. The exogenous peptide loop may comprise a fragment of a beta barrel porin protein. The exogenous peptide loop may comprise a fragment of PorA. In another embodiment, the exogenous peptide loop may comprise a fragment of FetA.

The exogenous peptide loop(s), such as PorA fragments, may be 16 amino acids in length. In one embodiment, the exogenous peptide loop(s), such as PorA fragments, may be between 8 and 20 amino acids in length. In another embodiment, the exogenous peptide loop(s), such as PorA fragments, may be between 8 and 16 amino acids in length. In another embodiment, the exogenous peptide loop(s), such as PorA fragments, may be between 10 and 16 amino acids in length. In another embodiment, the exogenous peptide loop(s), such as PorA fragments, may be between 12 and 16 amino acids in length. In another embodiment, the exogenous peptide loop(s), such as PorA fragments, may be between 14 and 18 amino acids in length. In another embodiment, the

exogenous peptide loop(s), such as PorA fragment, may be any length sufficient to provide an immunogenic epitope. In another embodiment, the exogenous peptide loop(s), such as PorA fragments, may be any length sufficient to provide an immunogenic epitope and maintain native conformation relative to the fragment in wild-type.

The exogenous peptide loop(s) may be selected from any one of the PorA loops 1 to 7, or fragments thereof; and/or combinations thereof. The exogenous peptide loop(s) may be selected from any one of the PorA loops of loop 1 (from between beta-strands 1 and 2), loop 4 (from between beta-strands 7 and 8), loop 5 (from between beta-strands 9 and 10) and loop 7 (from between beta-strands 11 and 12; or fragments thereof; and/or combinations thereof.

The exogenous peptide loop may comprise any one peptide selected from PorA loop 1 (between beta-strands 1 and 2); loop 4 (between beta-barrels 7 and 8); and loop 5 (between beta-strands 9 and 10); or fragments thereof; and/or combinations thereof.

The exogenous peptide loop may comprise PorA loop 1 (between beta-barrels 1 and 2), or a fragment thereof. The exogenous peptide loop may comprise PorA loop 4 (between beta-strands 7 and 8), or a fragment thereof. The exogenous peptide loop may comprise PorA loop 5 (between beta-strands 9 and 10), or a fragment thereof.

The skilled person will understand that variant sequences of PorA loops may be provided with minor mutations relative to wild-type and may still function as an epitope. Therefore, the exogenous peptide loop(s) may comprise PorA loop variants. Variants may include one or more amino acid additions, deletions or substitutions relative to the wild-type sequence. In another embodiment, variants may include no more than one amino acid addition, deletion or substitution relative to the wild-type sequence. In another embodiment, variants may include no more than 2, 3, 4 or 5 amino acid additions, deletions or

substitutions relative to the wild-type sequence. The substitutions may be conservative substitutions. For example, providing an alternative amino acid residue having substantially similar properties, such as charge, hydrophobicity, steric size or molecular weight. Variants may include sequences having at least 85% sequence identity with wild-type PorA loop sequence. In another embodiment, variants may include sequences having at least 90%, 95%, 98%, 99%, or 99.5% sequence identity with wild-type PorA loop sequence.

In one embodiment, the modified fHbp may comprise two or more exogenous peptide loops. In one embodiment, the modified fHbp may comprise three or more exogenous peptide loops. In one embodiment, the modified fHbp may comprise between 1 and 7 exogenous peptide loops. In one embodiment, the modified fHbp may comprise between 1 and 5 exogenous peptide loops. In one embodiment, the modified fHbp may comprise between 1 and 3 exogenous peptide loops. In one embodiment, the modified fHbp may comprise between 2 and 7 exogenous peptide loops. In one embodiment, the modified fHbp may comprise between 3 and 7 exogenous peptide loops. In one embodiment, the modified fHbp may comprise between 2 and 5 exogenous peptide loops. In one embodiment, the modified fHbp may comprise between 3 and 5 exogenous peptide loops. The modified fHbp, or variants thereof, may be modified with an exogenous peptide loop in at least one position. The modified fHbp, or variant thereof, may be modified with an exogenous peptide loop in at least two positions. The modified fHbp, or variant thereof, may be modified with an exogenous peptide loop in at least three positions. The modified fHbp, or variant thereof, may be modified with an exogenous peptide loop in at least four positions. The modified fHbp, or variant thereof, may be modified with an exogenous peptide loop in at least five positions. The modified fHbp, or variant thereof, may be modified with an exogenous peptide loop in at least six positions. The modified fHbp, or variant thereof, may be modified with an exogenous peptide loop in at least seven positions.

A peptide loop may be provided (for example using fHbp as a scaffold) between two beta sheets of the factor H binding protein. The peptide loop may be inserted into fHbp, or a variant thereof, at one or more of amino acid positions selected from positions where exogenous peptide loops, such as PorA loops, can be inserted (range is inclusive of all residues in loop) between amino acids 49-54, 83-88, 114-124, 199-206, 227-233, and 240-246 of v1.1 fHbp or corresponding positions in other fHbps.

The at least one exogenous peptide loop may not be provided as an N- or C-terminal fusion.

Sequences of fHbp into which the exogenous peptide loop(s) can be inserted may be at any of those positions underlined with regards to fHbp V1.1 primary amino acid sequence below. In an embodiment using an alternative variant fHBP, the insert sites may be at equivalent positions.

Position 1 in fHbp (P1), residues 83-88
P2, residues 199-206
P3, residues 227-233
P4, residues 49-54
P5, residues 114-124
P7, residues 240-246

```
1   CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA
                                                        P4
51  QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK
     P4                                    P1
101 QSHSALTAFQ TEQIQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA
                          P5
151 TYRGTAFGSD DAGGKLTYTI DFAAKQGNGK IEHLKSPELN VDLAAADIKP
                                                        P2
201 DGKRHAVISG SVLYNQAEKG SYSLGIFGGK AQEVAGSAEV KTVNGIRHIG
      P2                          P3            P7
```

251 LAAKQ (SEQ ID NO: 14)

In one embodiment, the insert site of an exogenous peptide loop may be at position 1 in fHbp (P1), residues 83-88 (Sequence EVDGQL (SEQ ID NO: 15)). In another embodiment, the insert site of an exogenous peptide loop may be at position P2, residues 199-206 (Sequence KPDGKRHA (SEQ ID NO: 16)). In another embodiment, the insert site of an exogenous peptide loop may be at position P3, residues 227-233 (Sequence FGGKAQE (SEQ ID NO: 17)). In another embodiment, the insert site of an exogenous peptide loop may be at position P4, residues 49-54 (Sequence AAQGAE (SEQ ID NO: 18)). In another embodiment, the insert site of an exogenous peptide loop may be at position P5, residues 114-124 (Sequence IQDSEHSGKM (SEQ ID NO: 19)). In another embodiment, the insert site of an exogenous peptide loop may be at position P7, residues 240-246 (Sequence KTVNGI (SEQ ID NO: 20)).

The exogenous peptide loop insert site at any given position 1-7 may be between any of the residues identified at positions 1 to 7 of fHbp. Alternatively, The exogenous peptide loop insert site at any given position 1-7 may be before the first residue or after the last residue identified at positions 1 to 7 of fHbp. For example if the exogenous peptide loop is inserted at position 4, the insert may be *AAQGAE (SEQ ID NO: 21), A*AQGAE (SEQ ID NO: 22), AA*QGAE (SEQ ID NO: 23), AAQ*GAE (SEQ ID NO: 24), AAQG*AE (SEQ ID NO: 25), AAQGA*E (SEQ ID NO: 26), or AAQGAE* (SEQ ID NO: 27), where * denotes the insert site.

In another embodiment, the skilled person will understand that the exogenous peptide loop insertion site may be variable such that between 1 and 5 residues in the region of the insertion site may be removed from fHbp (e.g. replaced by the loop) without significantly affecting the fHbp structure. In one embodiment, one or more of the amino acid residues at the identified positions are replaced/substituted by an exogenous peptide loop. In an alternative embodiment, two, three, four, five or more of the amino acid residues at the

identified positions are replaced/substituted by an exogenous peptide loop. In another embodiment, the exogenous peptide loop insertion site may be variable such that between 1 and 3 residues in the region of the insertion site may be removed from fHbp (e.g. replaced by the loop) without significantly affecting the fHbp structure. In another embodiment, the exogenous peptide loop insertion site may be variable such that 1 or 2 residues in the region of the insertion site may be removed from fHbp (e.g. replaced by the loop) without significantly affecting the fHbp structure. In another embodiment, the exogenous peptide loop insertion site may be variable such that 1 residue in the region of the insertion site may be removed from fHbp (e.g. replaced by the loop) without significantly affecting the fHbp structure. For example, where an insertion site is amino acid residue 86 at one end of the loop and residue 87 at the other end of the loop, a variant can include a 5, 4, 3, 2, or 1 residue replacement with the loop in the region of the stated insertion site. In an alternative embodiment, six or more of the amino acid residues at the identified positions are replaced/substituted by an exogenous peptide loop. In an alternative embodiment, seven or more (where applicable) of the amino acid residues at the identified positions are replaced/substituted by an exogenous peptide loop. In an alternative embodiment, eight or more (where applicable) of the amino acid residues at the identified positions are replaced/substituted by an exogenous peptide loop. In an alternative embodiment, nine or more (where applicable) of the amino acid residues at the identified positions are replaced/substituted by an exogenous peptide loop. The entire amino acid residues of any of insert positions 1 to 7 may be substituted with an exogenous peptide loop.

For example if the exogenous peptide loop is inserted at position 4 and substitutes one or more residues, the insert may be A*QGAE (SEQ ID NO: 28), AA*GAE (SEQ ID NO: 29), AA*AE (SEQ ID NO: 30), AA*E (SEQ ID NO: 31), AA*, A*GAE (SEQ ID NO: 32), A*AE (SEQ ID NO: 33), AA*E (SEQ ID NO: 34), A*E, A*, *AQGAE (SEQ ID NO: 35), *QGAE (SEQ ID NO: 36), *GAE (SEQ ID NO: 37), *AE, *E, AAQ*AE (SEQ ID NO: 38), AAQ*E (SEQ

ID NO: 39), AAQ* (SEQ ID NO: 40), AAQG*E (SEQ ID NO: 41), AAQG* (SEQ ID NO: 42), AAQGA* (SEQ ID NO: 43), where * denotes the insert site, and one or more residues are removed from the original sequence.

The skilled person will understand that equivalent combinations of insertion sites and/or substitutions with the exogenous peptide loop may be made with alternative sequences of the other identified insert positions 1 to 7.

In one embodiment, the region of the insertion site may be shifted +/- 5 residues up or downstream of any the positions 1 to 7. Alternatively, the region of the insertion site may be shifted +/- 4 residues up or downstream of any the positions 1 to 7. Alternatively, the region of the insertion site may be shifted +/- 3 residues up or downstream of any the positions 1 to 7. Alternatively, the region of the insertion site may be shifted +/- 2 residues up or downstream of any the positions 1 to 7. Alternatively, the region of the insertion site may be shifted +/- 1 residue up or downstream of any the positions 1 to 7.

Additionally or alternatively, the peptide loop(s) may be provided in a position that sterically prevents fHbp:CFH interaction. These include an exogenous peptide loop inserted into any one or more site between residues 114-124,199-206, or 240-246 (e.g. Positions 2, 5 and 7), underlined on V1 primary sequence below:

1 CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA
51 QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK
101 QSHSALTAFQ TEQIQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA
151 TYRGTAFGSD DAGGKLTYTI DFAAKQGNGK IEHLKSPELN VDLAAADIKP
201 DGKRHAVISG SVLYNQAEKG SYSLGIFGGK AQEVAGSAEV KTVNGIRHIG
251 LAAKQ (SEQ ID NO: 44)

In one embodiment of the invention, the modified fHbp is immunogenic. The modified fHbp may be a recombinant protein. The modified fHbp may be a fusion protein, such as a recombinant fusion protein. The modified fHbp may be

an isolated modified fHbp molecule. The modified fHbp molecule of the invention may be described as a single protein, multi-valent vaccine. The modified fHbp could be included in an OMV vaccine.

In embodiments where more than one exogenous peptide loop is inserted into fHbp, or variants thereof, the exogenous peptide loops may be the same, e.g. the same sequence, or substantially similar. For example, some epitopes such as PorA epitopes, may not elicit sufficient functional responses when displayed singly on fHbp. In this instance, the present invention may be used to provide the same epitope at multiple sites on the same modified fHbp molecule, thereby enhancing the immunogenic recognition of the epitope.

Alternatively, the exogenous peptide loops may be different relative to each other. For example, where the exogenous peptide loops are derived from a single protein, such as PorA, the different exogenous peptide loops may be from distinct regions of the protein, such as PorA. In one embodiment, the different exogenous peptide loops may be derived from overlapping and distinct regions of the protein, such as PorA.

In embodiments where more than one exogenous peptide loop is inserted into fHbp, or variants thereof, the exogenous peptide loops may be derived from different species or strains. For example, when a multivalent vaccine is desired for multiple different antigens including different organisms.

The PorA peptide loop sequence may be selected from any of the sequences provided in Table 1 (e.g. any of SEQ ID NOs: 45 to 79). Combinations of different PorA sequences of Table 1 may be provided (one loop per site) in any of insertion sites P1 to P7 described herein. Additionally or alternatively, two or more of the same PorA sequences of Table 1 may be provided (one loop per site) in any of insertion sites P1 to P7 described herein.

Table 1: sequences of PorA VR2 loops, any of which may be inserted into any variant of fHbp to make a chimeric fHbp-PorA protein.

PorA VR2 Loop	Primary sequence
P1.1	YVAVENGVAKKVA (SEQ ID NO: 45)
P1.2	HFVQQTPKSQPTLVP (SEQ ID NO: 46)
P1.2_2	HFVQQTPQSQPTLVP (SEQ ID NO: 47)
P1.3	TLANGANNTIIRVP (SEQ ID NO: 48)
P1.3_5	TLAKGANNTIIRVP (SEQ ID NO: 49)
P1.4	HVVVNNKVATHVP (SEQ ID NO: 50)
P1.9	YVDEQSKYHA (SEQ ID NO: 51)
P1.10	HFVQNKQNQRPTLVP (SEQ ID NO: 52)
P1.10_1	HFVQNKQNQPPTLVP (SEQ ID NO: 53)
P1.10_2	HFVQDKKGQPPTLVP (SEQ ID NO: 54)
P1.10_8	HFVQNKQNQQNQPPTLVP (SEQ ID NO: 55)
P1.10_4	HFVQNKQNKQNQPPTLVP (SEQ ID NO: 56)
P1.10_7	HFVQNKQNKPPTLVP (SEQ ID NO: 57)
P1.13	YWTTVNTGSATTTTTFVP (SEQ ID NO: 58)
P1.13_1	YWTTVNTGSATTTTFVP

	(SEQ ID NO: 59)
P1.13_2	YWTTVNTGSATTTFVP (SEQ ID NO: 60)
P1.13_4	YYTTVTQGSATTTTFVP (SEQ ID NO: 61)
P1.14	YVDEKKMVHA (SEQ ID NO: 62)
P1.14_6	YVDEKQVSHA (SEQ ID NO: 63)
P1.14_26	YVDEKKVVHA (SEQ ID NO: 64)
P1.15	HYTRQNNADVFVP (SEQ ID NO: 65)
P1.15_1	HYTRQNNTDVFVP (SEQ ID NO: 66)
P1.15_11	HYTRQNNIDVFVP (SEQ ID NO: 67)
P1.16	YYTKDTNNNLTLVP (SEQ ID NO: 68)
P1.16_3	YYTKDKNDNLTLVP (SEQ ID NO: 69)
P1.16_4	YYTKDKNDKLTLVP (SEQ ID NO: 70)
P1.16_26	YYTNTNNNLTLVP (SEQ ID NO: 71)
P1.23	HWNTVYNTNGTTTTFVP (SEQ ID NO: 72)
P1.23_2	HWNTVYNTNGTTTTTFVP (SEQ ID NO: 73)
P1.25	TYTVDSSGVVTPVP (SEQ ID NO: 74)
P1.26	HFVADSQGKITRVP (SEQ ID NO: 75)

P1.28	YYYTTATNSSTSTTFVP (SEQ ID NO: 76)
P1.30	HYTTVYNATTTTTTFVP (SEQ ID NO: 77)
P1.30_2	HYTTVYNATTTTTTTFVP (SEQ ID NO: 78)
P1.34	YVDDQGKVKGP (SEQ ID NO: 79)

The skilled person will understand that variants involving one or two or more amino acid substitutions, additions or deletions may be provided for the PorA sequences of Table 1 without substantially removing the immunogenic function. Substitutions may be to similar amino acid residues, for example having similar MW, charge, hydrophobicity or moieties, or synthetic analogues. The skilled person will further understand that variants may be truncations of the PorA sequences of Table 1, wherein the truncated variants provide sufficient amino acid residues to form a recognisable epitope. In one embodiment the PorA sequence has at least 80% identity to any one of the sequences in Table 1. In another embodiment the PorA sequence has at least 85% identity to any one of the sequences in Table 1. In another embodiment the PorA sequence has at least 90% identity to any one of the sequences in Table 1. In another embodiment the PorA sequence has at least 95% identity to any one of the sequences in Table 1. In another embodiment the PorA sequence has at least 98% identity to any one of the sequences in Table 1.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTAFQ TEQIQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA TYRGTAFGSD DAGGKLTYTI DFAAKQGNGK IEHLKSPELN VDLAAADIKP DGKRHAVISG SVLYNQAEKG SYSLGIFGGK AQEVAGSAEV KTVNGIRHIG LAAKQ (SEQ ID NO: 80, fHbp V1.1 GI:316985482), wherein the sequence of

any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTALQ TEQVQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA TYRGTAFGSD DASGKLTYTI DFAAKQGHGK IEHLKSPELN VDLAASDIKP DKKRHAVISG SVLYNQAEKG SYSLGIFGGQ AQEVAGSAEV ETANGIRHIG LAAKQ (SEQ ID NO: 81, fHbp V1.4 GI:989557230), wherein the sequence of any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGKLIT LESGEFQVYK QSHSALTALQ TEQVQDSEDS GKMVAKRQFR IGDIAGEHTS FDKLPKGGSA TYRGTAFGSD DAGGKLTYTI DFAAKQGHGK IEHLKSPELN VELATAYIKP DEKRHAVISG SVLYNQDEKG SYSLGIFGGQ AQEVAGSAEV ETANGIHHIG LAAKQ (SEQ ID NO: 82, fHbp V1.13 GI:752774533), wherein the sequence of any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTALQ TEQEQDPEHS GKMVAKRRFK IGDIAGEHTS FDKLPKDVMA TYRGTAFGSD DAGGKLTYTI DFAAKQGHGK IEHLKSPELN VELATAYIKP DEKHHAVISG SVLYNQDEKG SYSLGIFGGQ AQEVAGSAEV ETANGIHHIG LAAKQ (SEQ ID NO: 83, fHbp V1.14 GI:630057376), wherein the sequence of

any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGSGG GGVAADIGAG LADALTAPLD HKDKGLKSLT LEDSISQNGT LTLSAQGAER TFKAGDKDNS LNTGKLKNDK ISRFDFIRQI EVDGQLITLE SGEFQVYKQS HSALTALQTE QVQDSEHSGK MVAKRQFRIG DIVGEHTSFG KLPKDVMATY RGTAFGSDDA GGKLTYTIDF AAKQGHGKIE HLKSPELNVD LAAADIKPDE KHHAVISGSV LYNQAEKGSY SLGIFGGQAQ EVAGSAEVET ANGIRHIGLA AKQ (SEQ ID NO: 84, fHbp V1.15 GI:504394462), wherein the sequence of any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGSGG GGVTADIGTG LADALTAPLD HKDKGLKSLT LEDSISQNGT LTLSAQGAEK TYGNGDSLNT GKLKNDKVSR FDFIRQIEVD GQLITLESGE FQVYKQSHSA LTALQTEQEQ DPEHSEKMVA KRRFRIGDIA GEHTSFDKLP KDVMATYRGT AFGSDDAGGK LTYTIDFAAK QGHGKIEHLK SPELNVDLAV AYIKPDEKHH AVISGSVLYN QDEKGSYSLG IFGEKAQEVA GSAEVETANG IHHIGLAAKQ (SEQ ID NO: 85, fHbpV 1.55 GI:40353481), wherein the sequence of any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPDGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELAAAELKAD EKSHAVILGD TRYGSEEKGT YHLALFGDRA QEIAGSATVK IGEKVHEIGI AGKQ (SEQ ID NO: 86, fHbp V2.16 GI:488155511), wherein the sequence of any

PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGGEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 87, fHbp V2.19 GI:488148626), wherein the sequence of any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD PNGRLHYSID FTKKQGYGRI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGGEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 88, fHbp V2.22 GI:120865922), wherein the sequence of any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TTPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQTIT LASGEFQIYK QNHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPDGKAE YHGKAFSSDD PNGRLHYSID FTKKQGYGRI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGGEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 89, fHbp 2.25 GI:488158712), wherein the sequence of any

PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGSGSGGG GVAADIGTGL ADALTAPLDH KDKGLKSLTL EDSISQNGTL TLSAQGAEKT FKVGDKDNSL NTGKLKNDKI SRFDFVQKIE VDGQTITLAS GEFQIYKQDH SAVVALQIEK INNPDKIDSL INQRSFLVSG LGGEHTAFNQ LPSGKAEYHG KAFSSDDAGG KLTYTIDFAA KQGHGKIEHL KTPEQNVELA SAELKADEKS HAVILGDTRY GSEEKGTYHL ALFGDRAQEI AGSATVKIRE KVHEIGIAGK Q (SEQ ID NO: 90, fHbp V3.45 GI:284466869), wherein the sequence of any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

In one embodiment, the fHbp which is to be further modified with an exogenous peptide loop may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LKSLTLEDSI SQNGTLTLSA QGAEKTFKVG DKDNSLNTGK LKNDKISRFD FVQKIEVDGQ TITLASGEFQ IYKQNHSAVV ALQIEKINNP DKIDSLINQR SFLVSGLGGE HTAFNQLPGG KAEYHGKAFS SDDAGGKLTY TIDFAAKQGH GKIEHLKTPE QNVELAAAEL KADEKSHAVI LGDTRYGSEE KGTYHLALFG DRAQEIAGSA TVKIGEKVHE ISIAGKQ (SEQ ID NO: 91, fHbp V3.47 GI:284466897), wherein the sequence of any PorA VR2 loop in Table 1 may replace any amino acid or groups of amino acids highlighted by a box.

The modified fHbp may comprise the sequence of any one of SEQ ID NOs: 92 to 109.

The modified fHbp may comprise the sequence of SEQ ID NO: 92 to 109, wherein the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any VR2 loop sequence provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDYYTKDT NNNLTLVPQL ITLESGEFQV YKQSHSALTA FQTEQIQDSE HSGKMVAKRQ FRIGDIAGEH TSFDKLPEGG RATYRGTAFG SDDAGGKLTY TIDFAAKQGN GKIEHLKSPE LNVDLAAADI KPDGKRHAVI SGSVLYNQAE KGSYSLGIFG GKAQEVAGSA EVKTVNGIRH IGLAAKQ (SEQ ID NO: 92, fHbp V1.1 GI:316985482, PorA VR2 P1.16 in P1), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:
CSSGSGSGGG GVAADIGTGL ADALTAPLDH KDKGLKSLTL EDSISQNGTL TLSAQGAEKT FKVGDKDNSL NTGKLKNDKI SRFDFVQKIE VDYYTKDTNN NLTLVPQTIT LASGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGSEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 93, fHbp V3.45 GI:284466869, PorA VR2 P1.16 in P1), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDYYTKD TNNNLTLVPQ LITLESGEFQ IYKQDHSAVV ALQIEKINNP DKIDSLINQR SFLVSGLGGE HTAFNQLPSG KAEYHGKAFS SDDAGGKLTY TIDFAAKQGH GKIEHLKTPE QNVELASAEL KADEKSHAVI LGDTRYGGEE KGTYHLALFG DRAQEIAGSA TVKIREKVHE IGIAGKQ (SEQ ID NO: 94, fHbp V2.19 GI:488148626, PorA VR2 P1.16 in P1), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK

QSHSALTAFQ TEQIQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA TYRGTAFGSD DAGGKLTYTI DFAAKQGNGK IEHLKSPELN VDLAAADIKP DYYTKDTNNN LTLVPKRHAV ISGSVLYNQA EKGSYSLGIF GGKAQEVAGS AEVKTVNGIR HIGLAAKQ (SEQ ID NO: 95, fHbp V1.1 GI:316985482, PorA VR2 P1.16 in P2), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:
CSSGSGSGGG GVAADIGTGL ADALTAPLDH KDKGLKSLTL EDSISQNGTL TLSAQGAEKT FKVGDKDNSL NTGKLKNDKI SRFDFVQKIE VDGQTITLAS GEFQIYKQDH SAVVALQIEK INNPDKIDSL INQRSFLVSG LGGEHTAFNQ LPSGKAEYHG KAFSSDDAGG KLTYTIDFAA KQGHGKIEHL KTPEQNVELA SAELKADYYT KDTNNNLTLV PKSHAVILGD TRYGSEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 96, fHbp V3.45 GI:284466869, PorA VR2 P1.16 in P2), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELASAELKAD YYTKDTNNNL TLVPKSHAVI LGDTRYGGEE KGTYHLALFG DRAQEIAGSA TVKIREKVHE IGIAGKQ (SEQ ID NO: 97, fHbp V2.19 GI:488148626, PorA VR2 P1.16 in P2), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:
CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTAFQ TEQIQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA TYRGTAFGSD DAGGKLTYTI DFAAKQGNGK IEHLKSPELN VDLAAADIKP DGKRHAVISG SVLYNQAEKG SYSLGIFGYY TKDTNNNLTL VPKAQEVAGS AEVKTVNGIR HIGLAAKQ (SEQ ID NO: 98, fHbp V1.1 GI:316985482, PorA VR2

P1.16 in P3), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGSGSGGG GVAADIGTGL ADALTAPLDH KDKGLKSLTL EDSISQNGTL TLSAQGAEKT FKVGDKDNSL NTGKLKNDKI SRFDFVQKIE VDGQTITLAS GEFQIYKQDH SAVVALQIEK INNPDKIDSL INQRSFLVSG LGGEHTAFNQ LPSGKAEYHG KAFSSDDAGG KLTYTIDFAA KQGHGKIEHL KTPEQNVELA SAELKADEKS HAVILGDTRY GSEEKGTYHL ALFGYYTKDT NNNLTLVPRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 99, fHbp V3.45 GI:284466869, PorA VR2 P1.16 in P3), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGGEEKGT YHLALFGYYT KDTNNNLTLV PRAQEIAGSA TVKIREKVHE IGIAGKQ (SEQ ID NO: 100, fHbp V2.19 GI:488148626, PorA VR2 P1.16 in P3), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QYYTKDTNNN LTLVPAEKTY GNGDSLNTGK LKNDKVSRFD FIRQIEVDGQ LITLESGEFQ VYKQSHSALT AFQTEQIQDS EHSGKMVAKR QFRIGDIAGE HTSFDKLPEG GRATYRGTAF GSDDAGGKLT YTIDFAAKQG NGKIEHLKSP ELNVDLAAAD IKPDGKRHAV ISGSVLYNQA EKGSYSLGIF GGKAQEVAGS AEVKTVNGIR HIGLAAKQ (SEQ ID NO: 101, fHbp V1.1 GI:316985482, PorA VR2 P1.16 in P4), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGSGSGGG GVAADIGTGL ADALTAPLDH KDKGLKSLTL EDSISQNGTL TLSAQYYTKD TNNNLTLVPA EKTFKVGDKD NSLNTGKLKN DKISRFDFVQ KIEVDGQTIT LASGEFQIYK QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGSEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 102, fHbp V3.45 GI:284466869, PorA VR2 P1.16 in P4), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QYYTKDTNNN LTLVPAEKTY GNGDSLNTGK LKNDKVSRFD FIRQIEVDGQ LITLESGEFQ IYKQDHSAVV ALQIEKINNP DKIDSLINQR SFLVSGLGGE HTAFNQLPSG KAEYHGKAFS SDDAGGKLTY TIDFAAKQGH GKIEHLKTPE QNVELASAEL KADEKSHAVI LGDTRYGGEE KGTYHLALFG DRAQEIAGSA TVKIREKVHE IGIAGKQ (SEQ ID NO: 103, fHbp V2.19 GI:488148626, PorA VR2 P1.16 in P4), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTAFQ TEQIQDSYYT KDTNNNLTLV PHSGKMVAKR QFRIGDIAGE HTSFDKLPEG GRATYRGTAF GSDDAGGKLT YTIDFAAKQG NGKIEHLKSP ELNVDLAAAD IKPDGKRHAV ISGSVLYNQA EKGSYSLGIF GGKAQEVAGS AEVKTVNGIR HIGLAAKQ (SEQ ID NO: 104, fHbp V1.1 GI:316985482, PorA VR2 P1.16 in P5), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGSGSGGG GVAADIGTGL ADALTAPLDH KDKGLKSLTL EDSISQNGTL TLSAQGAEKT FKVGDKDNSL NTGKLKNDKI SRFDFVQKIE VDGQTITLAS

GEFQIYKQDH SAVVALQIEK INNPYYTKDT NNNLTLVPKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELASAELKAD EKSHAVILGD TRYGSEEKGT YHLALFGDRA QEIAGSATVK IREKVHEIGI AGKQ (SEQ ID NO: 105, fHbp V3.45 GI:284466869, PorA VR2 P1.16 in P5), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK QDHSAVVALQ IEKINNPYYT KDTNNNLTLV PKIDSLINQR SFLVSGLGGE HTAFNQLPSG KAEYHGKAFS SDDAGGKLTY TIDFAAKQGH GKIEHLKTPE QNVELASAEL KADEKSHAVI LGDTRYGGEE KGTYHLALFG DRAQEIAGSA TVKIREKVHE IGIAGKQ (SEQ ID NO: 106, fHbp V2.19 GI:488148626, PorA VR2 P1.16 in P5), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQVYK QSHSALTAFQ TEQIQDSEHS GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA TYRGTAFGSD DAGGKLTYTI DFAAKQGNGK IEHLKSPELN VDLAAADIKP DGKRHAVISG SVLYNQAEKG SYSLGIFGGK AQEVAGSAEV KTVYYTKDTN NNLTLVPGIR HIGLAAKQ (SEQ ID NO: 107, fHbp V1.1 GI:316985482, PorA VR2 P1.16 in P7), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGSGSGGG GVAADIGTGL ADALTAPLDH KDKGLKSLTL EDSISQNGTL TLSAQGAEKT FKVGDKDNSL NTGKLKNDKI SRFDFVQKIE VDGQTITLAS GEFQIYKQDH SAVVALQIEK INNPDKIDSL INQRSFLVSG LGGEHTAFNQ LPSGKAEYHG KAFSSDDAGG KLTYTIDFAA KQGHGKIEHL KTPEQNVELA SAELKADEKS HAVILGDTRY GSEEKGTYHL ALFGDRAQEI AGSATVKIRY

YTKDTNNNLT LVPKVHEIGI AGKQ (SEQ ID NO: 108, fHbp V3.45 GI:284466869, PorA VR2 P1.16 in P7), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

In one embodiment, the modified fHbp may comprise or consist of the sequence:

CSSGGGGVAA DIGAGLADAL TAPLDHKDKS LQSLTLDQSV RKNEKLKLAA
QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR QIEVDGQLIT LESGEFQIYK
QDHSAVVALQ IEKINNPDKI DSLINQRSFL VSGLGGEHTA FNQLPSGKAE
YHGKAFSSDD AGGKLTYTID FAAKQGHGKI EHLKTPEQNV ELASAELKAD
EKSHAVILGD TRYGGEEKGT YHLALFGDRA QEIAGSATVK IRYYTKDTNN
NLTLVPKVHE IGIAGKQ (SEQ ID NO: 109, fHbp V2.19 GI:488148626, PorA VR2 P1.16 in P7), or the same sequence whereby the sequence YYTKDTNNNLTLVP (SEQ ID NO: 68) is replaced by any PorA VR2 loop sequence, for example any PorA loop sequence as provided in Table 1.

The skilled person will understand that one, two, three or four or more amino acid substitutions, deletions or additions may be made to the modified fHbp of the invention herein without substantially removing its immunogenic function or affecting stability. Substitutions may be to similar amino acid residues, for example having similar MW, charge, hydrophobicity or moieties, or synthetic analogues. Such modifications are envisaged as part of the invention. In one embodiment the modified fHbp may have at least 75% identity with any one of the modified fHbp described herein. In one embodiment the modified fHbp may have at least 80% identity with any one of the modified fHbp described herein. In one embodiment the modified fHbp may have at least 85% identity with any one of the modified fHbp described herein. In one embodiment the modified fHbp may have at least 90% identity with any one of the modified fHbp described herein. In one embodiment the modified fHbp may have at least 95% identity with any one of the modified fHbp described herein. In one embodiment the modified fHbp may have at least 98% identity with any one of the modified fHbp described herein. In one embodiment the modified fHbp may have at least 99% identity with any one of the modified fHbp described herein.

In one embodiment the modified fHbp may have at least 99.5% identity with any one of the modified fHbp described herein.

According to another aspect of the invention, there is provided a nucleic acid encoding essentially or at least the modified fHbp according to the invention herein.

The nucleic acid may be in a vector, such as a viral vector.

According to another aspect of the invention, there is provided a composition comprising the modified fHbp according the invention herein.

The composition may comprise two or more different modified fHbp molecules (e.g. different forms/species thereof) according to the invention herein. For example, the composition may comprise two or more different variants of the modified fHbp according to the invention. For example, the composition may comprise fHbp variants v1 and v2. The composition may comprise fHbp variants v2 and v3. In another embodiment, the composition comprises at least fHbp variant v2.

According to another aspect of the invention, there is provided a composition comprising the nucleic acid according the invention herein.

The composition may comprise a pharmaceutically acceptable carrier. The composition may further comprise an adjuvant.

According to a further aspect of the invention, there is provided a modified fHbp, nucleic acid, or composition according to the invention, for use as a medicament.

According to a further aspect of the invention, there is provided a modified fHbp, nucleic acid, or composition according to the invention, for use in the treatment or prevention of a pathogenic infection or colonisation of a subject.

According to a further aspect of the invention, there is provided a method of treatment or prevention of a pathogenic infection or colonisation of a subject, comprising the administration of a modified fHbp, nucleic acid, or composition according to the invention to the subject.

According to a further aspect of the invention, there is provided a method of vaccination, comprising the administration of a modified fHbp, nucleic acid, or composition according to the invention to a subject.

The administration may be provided in a therapeutically effective amount. A skilled person will be capable of determining an appropriate dosage and repetitions for administration.

The subject may be mammalian, such as human.

The infection may be a bacterial infection. For example, the infection may be meningitis, such as *Neisseria meningitidis*, or *Neisseria gonorrhoeae*.

According to a further aspect of the invention, there is provided a single protein, multi-valent vaccine comprising the modified factor H binding protein (fHbp) according to the invention.

The vaccine may be used as a prophylactic or a therapeutic vaccine directed to *Nm*.

The use may be with a pharmaceutically acceptable carrier. Additionally or alternatively, the use may be with an adjuvant. Suitable pharmaceutically acceptable carriers and adjuvants are well known to the skilled person.

According to a further aspect of the invention, there is provided a combination of the modified fHbp according to the invention and at least one other prophylactically or therapeutically active molecule.

The at least one other prophylactically or therapeutically active molecule may comprise a vaccine or antigen different to the modified fHbp according to the invention herein. The combination may be used in a combination vaccine or therapy. For example, the combination may be used in a combination vaccine or therapy where another meningococcal antigen is provided.

In one embodiment, the at least one other prophylactically or therapeutically active molecule comprises a monovalent protein:capsule polysaccharide vaccine. The monovalent protein:capsule polysaccharide vaccine may comprise any of serogroup C or A capsule with bacterial toxoids, bi-valent vaccines (with serogroup C and A capsular polysaccharide conjugated to bacterial toxoids), quadri- (serogroups A, C, Y, W) or penta- (A, C, Y, W, X) valent conjugate vaccines.

Alternatively, the at least one other prophylactically or therapeutically active molecule may comprise a conjugate vaccine, wherein antigen(s) comprising the fHbp scaffold bearing exogenous peptide loops (such as PorA loops) may be incorporated as the protein carrier molecule in the conjugate vaccine. The conjugate vaccine may comprise any of serogroup capsular polysaccharides from A, C, Y, W, or X strains individually or in combination.

According to another aspect of the invention, there is provided the use of factor H binding protein (fHbp) as an epitope display scaffold.

The use as an epitope display scaffold may comprise the use of a factor H binding protein (fHbp) comprising any of the modifications described herein.

In addition to their potential use as vaccines, compositions or modified fHbps according to the invention may be useful as diagnostic reagents and as a measure of the immune competence of a vaccine.

The term "immunogenic" means that the molecule is capable of eliciting an immune response in a human or animal body. The immune response may be protective.

The immune response elicited by the modified fHbp of the invention may affect the ability of *Neisseria meningitidis (Nm)* to infect a subject immunised with the modified fHbp of the invention. Preferably, the ability of *Nm* to infect a subject immunised with the modified fHbp of the invention is impeded or prevented. The immune response elicited may recognise and destroy *Nm*. Alternatively or additionally, the immune response elicited may impede or prevent replication of *Nm*. Alternatively or additionally, the immune response elicited may impede or prevent *Nm* causing disease in the human or non-human animal.

The term "peptide loop" used herein is intended to refer to a single chain polypeptide sequence anchored at both ends (e.g. anchored to a scaffold such as fHbp). The term "loop" does not infer or require any particular secondary structure adopted by the polypeptide.

The term "exogenous" used in the context of "exogenous peptide loop" is understood to mean that the peptide loop is derived from a different source relative to the fHbp protein (i.e. it is not fHbp or a fragment thereof). However, it may be from the same organism as the fHbp. For example a modified fHbp may include an *N. meningitidis* fHbp modified with (exogenous) peptide loop(s) derived from *N. meningitidis* PorA.

The term "fusion protein" used herein is understood to mean a polypeptide comprising a combination of sequences from different gene products or sources.

Term “fusion protein” may be used interchangeably with the term “chimeric molecule”.

Reference to sequence “identity” used herein may refer to the percentage identity between two aligned sequences using standard NCBI BLASTp parameters (http://blast.ncbi.nlm.nih.gov).

The term "isolated", when applied to the modified fHbp of the present invention means a protein: (i) encoded by nucleic acids using recombinant DNA methods or a viral vector; or (ii) synthesized by, for example, chemical synthetic methods; or (iii) separated from biological materials, and then purified. An isolated polypeptide of the invention includes a protein expressed from a nucleotide sequence encoding the protein, or from a recombinant vector containing a nucleotide sequence encoding the protein.

The term "protective" means prevention of a disease, a reduced risk of disease infection, transmission and/or progression, reduced severity of disease, a cure of a condition or disease, an alleviation of symptoms, or a reduction in severity of a disease or disease symptoms.

The term “prophylaxis” means prevention of or protective treatment for a disease. The prophylaxis may include a reduced risk of infection, transmission and/or progression, or reduced severity of disease.

The term “treatment”, means a cure of a condition or disease, an alleviation of symptoms, or a reduction in severity of a disease or disease symptoms.

The skilled person will understand that optional features of one embodiment or aspect of the invention may be applicable, where appropriate, to other embodiments or aspects of the invention.

Where any or all of the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as

specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components.

A reference herein to a patent document or any other matter identified as prior art, is not to be taken as an admission that the document or other matter was known or that the information it contains was part of the common general knowledge as at the priority date of any of the claims.

Embodiments of the invention will now be described in more detail, by way of example only, with reference to the accompanying drawings.

Figure 1 Design of chimeric fHbp:PorAs

(A) Schematic of the surface of N. meningitidis, showing the pre-dominant outer membrane features, lipo-oligosaccharide and type 4 pili, and the important antigens, fHbp and PorA. The immunogenic PorA VR2 loop is highlighted and fHbp is shown interacting with domains 6 and 7 of human CFH.

(B) Structure of V1 fHbp with CFH domains 6-7 showing the six positions (P1-5, and P7) used to generate chimeric fHbp:PorAs into which we have inserted PorA loops. N.B. position 5 is in the fHbp:CFH interface.

Figure 2: Use of fHbp as a molecular scaffold

A) Protein structure of fHbp V1.1 (grey, ribbon representation) with the six positions (P1-5, and P7) used to generate chimeric fHbp:PorAs. B) Secondary structure of fHbp V1.1 (grey, arrows represent β-sheets, rectangles represent α-helices). Locations of the VR2 P1.16 PorA insertion sites are indicated by solid black lines, numbers indicate the residue range that the PorA VR2 loops may be inserted (corresponds with residue numbers in 1D). C) Analysis of purified fHbp:PorAs with the PorA P1.16 VR2 loop in positions 1-5 or 7 of fHbp, the wild-type (WT V1.1) by SDS-PAGE and Western blot. Blots were probed with α-V1 fHbp pAb and an α-P1.16 mAb. D) Primary sequence (SEQ ID NO: 1) of V1.1 fHbp indicating the locations (underlined) of positions 1-5 and 7 into which loops from other proteins can be inserted.

Figure 3 Characterisation of chimeric fHbp:PorAs

(A) Structure of fHbp:PorAs overlaid with the P1.16 loop (black, PDBID: 2mpa) with the Fab of the α-P1.16 mAb and fHbp:PorAs with the loop in position 1, position 3 and position 7, demonstrating that the epitope is in a conformation recognised by a bactericidal antibody.

(B) Stability of fHbp N-terminal (NT) and C-terminal (CT) beta-barrels of fHbps by Differential Scanning Calorimetry analysis performed using a 20-120°C temperature gradient. Melting temperature is shown for the fHbp N-terminal (NT_{TM}) and C-terminal (CT_{TM}) barrels. Binding fHbp:PorAs to

Complement Factor H (CFH) and mAbs SPR analysis of fHbp and chimeric fHbp:PorAs coupled to a BIAcore CM5 chip. CFH (fH67) was flowed over at a dilution range of 0.5–32 nM, and the dissociation constant (K_D) calculated; dissociation constants (K_Ds) for fHbp:PorAs confirms lack of CFH binding of fHbp with a loop in position 5 which impinges on the fHbp:CFH interface (Fig. 2A). NB = Non-binding.

Figure 4 Repertoire of antigens selected for chimeric fHbp:PorAs

(A, B) Frequency of fHbp variants and PorA VR2 subtypes, respectively, in *N. meningitidis* disease isolates in the UK between 2010-2015 from the Meningitis Research Foundation Genome Library (http://www.meningitis.org/research/genome), shown as Pie Charts (above) and Tables (below) with the frequency of specific fHbps and PorAs.

N.B. V2 fHbp accounts for 38.9% of isolates.

Table 2. Exact sequence matches for all *N. meningitidis* UK isolates between 2009-2015:

Antigen	**Variant**	**% MenB coverage**
fHbp	1.4	21.5
	2.19	9.1
	3.45	4.8
PorA	P1.4	19.3
	P1.9	19.1
	P1.14	16.3
	P1.16	7.0
	P1.15	5.5
	P1.15_11	5.3
% coverage minus antigen overlap in ALL UK strains (isolated between 2009-2015)		70.6
% coverage minus antigen overlap in UK MenB strains (isolated between 2009-2015)		79.2

Exact sequence matches for:

- Pfizer vaccine, 3.02%
- Bexsero fHbp (V1.1) or PorA (P1.16), 15.86%
- Chimeric fHbp:PorAs, fHbp or PorA, 72%

(23.5% with fHbp AND PorA)

Figure 5 Recognition of *Neisseria meningitidis* fHbp (A) and PorA (B) antigens by mouse immune sera. Whole cell lysates from *Neisseria meningitidis* strains H44/76 (WT), H44/67 ΔfHbp and H44/67 ΔPorA, were separated by SDS-PAGE, transferred to a PVDF membrane and probed with mouse immune sera. Mouse immune sera were obtained by immunising BalbC mice three times with 20 μg of purified fHbp-PorA chimeras with VR2 loops in P1, P2, P4, P5 or P7.

Figure 6 Stabilisation of V2 fHbp: construction and immunogenicity of fHbp:PorAs

(A) Stabilisation of V2 fHbp V2.22 and V2.25 with six (M6) or two (M2) a.a. substitutions. DSC analysis was performed with 20 μM of protein, using a 20-120°C temperature gradient. Melting temperature is recorded for the fHbp N-terminal (NT_{TM}) and C-terminal barrels (CT_{TM}).

(B) Chimeric fHbp:PorAs PorA loops are recognised by corresponding mAbs. PorA VR2 loops from P1.2, P1.4, P1.9, P1.14 and P1.15 were inserted into position 1 of V2.25 fHbp. SDS-PAGE and Western blot analysis of purified wild type V2.25 fHbp and V3.45 fHbp-PorA chimeras. Western blots were probed with fHbp V2.25 pAbs and loop specific PorA mAbs (NIBSC). CFH binding was detected by far Western blot analysis with normal human sera and CFH pAbs.

Figure 7 Chimeric fHbp:PorAs elicit protective immunity. Mice were immunised with chimeric fHbp:PorA i.e. P(1)(1)(13), P(2)(1)(13), and P(3)(1)(13) on three occasions, and SBAs measured against the strains indicated; an SBA > 8 is considered protective. The lack of PorA-directed SBA (*i.e.* SBA 0, against the fHbp mutant) with VR2 loop in position 3 i.e. P(3)(1)(13) is likely because the loop does not protrude from fHbp barrel as far as in pos. 1.

Figure 8. Frequency of PorA VR2 (**A**) and fHbp variants (**B**) in *N. meningitidis* serogroup B strains (n=243) isolated in 2016 in the UK. Data downloaded from the Meningococcal Research Foundation, 27 June 2017. Other: remaining alleles that occur in <4 isolates. (**C**) Analysis of recombinant Chimeric antigens by SDS-PAGE and Western blot. Immunoblots are probed with α-PorA VR2 mAbs: P1.4, P1.9, P1.14 and P1.15. (**D**) Detection of PorA in a panel of *N. meningitidis* serogroup B isolates by mouse polyclonal antisera from Chimeric Antigens $fHbp^{V1.4}$:$PorA^{151/P1.1.10\_1}$, $fHbp^{V1.4}$:$PorA^{151/P1.14}$ and $fHbp^{V1.4}$:$PorA^{151/P1.15}$, $fHbp^{V3.45}$:$PorA^{158/P1.4}$ and $fHbp^{V3.45}$:$PorA^{158/P1.9}$.

Example 1

It has been shown that immunogenic peptides can be introduced into factor H binding protein (fHbp), and the peptides are presented to the immune system and are able to elicit protective responses (Fig. 5 and 7). Peptides have been used from the integral membrane protein PorA for proof-in principle of this approach. PorA is difficult to express because of the insolubility of its membrane spanning domains. The immunogenic portions of the molecule reside in extracellular loops which are exposed to the immune system. However effective immune responses are only generated against the loops in their right conformation; linear peptide sequences do not elicit functional immune responses. Through knowledge of the structure of fHbp, it is possible to introduce PorA loops into fHbp and generate relevant responses against PorA. This results in a chimeric molecule, based on fHbp and PorA sequences in specific sites to generate a chimeric molecule. This approach can be used for any other immunogenic integral outer membrane protein.

It has been shown that the likely reason for the exclusion of v2 fHbp from vaccines is the inherent instability of its N-terminal β-barrel: i) it was not possible to determine the atomic structure of this portion of v2 $fHbp^{10}$, ii) v2 fHbp is sensitive to protease digestion (mass spectrometry demonstrates that the cleaved sites reside in the N-terminal β-barrel, not shown), and iii) differential

scanning calorimetry confirms that the instability lies in this region of v2 fHbp[10].

Stable v2 fHbps have been successfully generated. Mutagenesis affecting the N-terminal barrel has been undertaken, substituting amino acids (a.a.s) singly or in combination. Substitution of six amino acids in M6 fHbp stabilises v2 fHbp (*i.e.* 6 changes in c 130 a.a.s of this β-barrel, < 0.5%) (see WO2014030003 for details of the mutations). This is evident from differential scanning calorimetry (DSC) and protease sensitivity (see WO2014030003 for details). The side chains of the altered residues promote interactions between the β-sheets of the N-terminal barrel, so are orientated towards the centre of the molecule; the changes do not affect the immunogenicity of the protein as expected (no difference in SBA, or α-fHbp IgG levels not shown).

Chimeric v1.1 fHbp has been generated incorporating the 13 amino acid VR2 from P1.16 PorA which elicits SBA in recipients of OMV vaccines[16]. While integral membrane proteins contain hydrophobic (thence insoluble) β-barrels, fHbp contains two barrels which can be expressed and purified to high levels. The VR2 sequence has been introduced into six different positions of fHbp (Fig. 2B); these sites were selected on the basis of similar spacing of flanking β-sheets in PorA[22] and fHbp to reduce the likelihood of the insertion disrupting the overall structure of fHbp (Fig. 2B for predicted effect of the insertions). The immunogenicity of three fHbps with insertion of VR2 into a different of fHbp (Fig. 2B) has been assessed. All proteins elicit antibody responses that recognise against fHbp and PorA (Fig. 5 and 7), and importantly both proteins tested so far (with the VR2 in site 1 or 2) elicit SBA against fHbp and PorA independently (SBA for *Nm* H44/76, 512; and for *Nm* H44/76α*fHbp*, 256 for both fHbps). This provides proof of principle for this approach.

fHbp as a scaffold for multi-valent vaccines

Non-functional fHbps as vaccines- The function of fHbp was not known when clinical trials of fHbp-containing vaccines began; fHbp displays high affinity interactions with fH (dissociation constant <5 nM) irrespective of variant group, with fH engaging a large area of fHbp[5]. This interaction could impair the use of fHbp as a vaccine by i) blocking immunogenic epitopes and preventing the generation of antibodies that could compete with fH, and ii) reducing complement activation (through fH recruitment) and thence B cell activation at the site of immune induction. The use of non-functional fHbps circumvents these problems. Key amino acids of v1, 2 and 3 fHbps have been identified that are necessary for fH interactions[10], and modification of single a.a.s of v1, v2 and v3 fHbps which prevent fH binding have been shown to retain or even enhance immunogenicity of this important vaccine antigen[10,23].

To generate and evaluate single protein, multi-valent vaccine candidates: Protective PorA epitopes from prevalent serosubtypes (which are defined by their PorA sequence) of *Nm*[15] have been introduced into v1, stable v2 and v3 proteins; their stability and recognition by PorA and fHbp mAbs has been determined. PorA sequences have been selected to cover the diversity of isolates in the UK but data from any collection of meningococcal strains can be used.

Methods of research

Generation and characterisation of vaccine candidates - Recombinant fHbps were constructed and expressed in *E. coli* using standard plasmid vectors; proteins were affinity purified using the polyHis tag in the protein, anion exchange and gel filtration[10] of chimeric v1, V2 and V3 fHbps as these are either in existing vaccines (v1.1 and 3.45) or because of experience with the protein (v2), or because of their prevalence in *Nm* strains. PorA loops have been introduced into fHbp by standard methods, and we have demonstrated that the fusion proteins bind mAbs against common serosubtypes of PorA. This strategy has been used to compare native and designed sequences, and perform fine

mapping of antigenic and fH-binding of the candidates. DSC has been carried out using a VP Capillary DSC (GEHealthcare) and SPR with a Biacore 3000 (GE Healthcare) or ProteOn XPR36 (BioRad) as previously[10].

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All references are herein incorporated by reference.

Example 2 – Chimeric Antigens containing an expanded range of PorA VR2 loops generate immune responses

To test the adaptability of the fHbp:PorA Chimeric antigens, several Chimeric antigens composed from different combinations of fHbp and PorA VR2 were generated. The comprehensive meningococcal genome data available for strains isolated in the UK (Meningitis Research Foundation Meningococcus Genome Library developed by Public health England, the Wellcome Trust Sanger Institute and the University of Oxford as a collaboration.) enables construction of Chimeric antigens that have exact sequence matches to the most common antigens in a given region. In 2016, the most prevalent PorA VR2s in serogroup B *N. meningitidis* isolates were P1.4 (15.2%), P1.14 (15.2%), P1.9 (12.8%), P1.16 (11.1%) and P1.15 (5.8%, **Figure 8B**). VR2 P1.10_1 was present in 1.6% serogroup B isolates. The most prevalent variant 1, variant 2 and variant 3 fHbps were V1.4, V2.19 and V3.45, present in 21.8%, 5.3% and 4.9% of serogroup B *N. meningitidis* isolates respectively (**Figure 8C**). Five different Chimeric antigens were constructed, in which a PorA VR2 was inserted position 151 (V1.4) or position 158 (V3.45, **Figure 8A**). Following Chimeric antigen expression and purification, Western blot analyses confirmed these Chimeric antigens all retained epitopes recognised by their cognate α-VR2 mAb and α-fHbp pAbs (**Figure 8D**). The thermal stability of wild type fHbps V1.1, V1.4 and V3.45 and the Chimeric antigens was determined by differential scanning calorimetry (DSC, **Table 3**).

To examine the ability of these fHbp:PorA Chimeric antigens to elicit immune responses, groups of CD1 mice were immunized with each Chimeric antigen/alum; antisera obtained post immunisation were pooled. To assess the resulting PorA immune responses, Western blot were conducted with pooled antisera and a panel of serogroup B *N. meningitidis* disease isolates. **Figure 8E** demonstrates that all Chimeric antigens elicited α-PorA antibodies that recognised their cognate PorA VR2. To evaluate α-PorA SBA responses, Serum Bactericidal Assays were performed with pooled Chimeric antigen/alum antisera and serogroup B *N. meningitidis* strains with mismatched fHbp variants, to negate fHbp cross-protection. Titres range between ≥20 to ≥1280 and are above the ≥8 threshold for an accepted correlate of protective immunity

against *N. meningitidis* (Andrews, N. et al. *Clin Diagn Lab Immunol* 10, 780-786 (2003)) (**Table 4**).

Table 3: Stability of wild type fHbp and Chimeric Antigens

	Cp (kcal mole^{-1} °C^{-1})	
Protein	**N-terminal T_m**	**C-Terminal T_m**
fHbp V1.1	69.8	87.9
fHbp V1.4	64.0	89.0
fHbp V3.45	41.0	83.0
fHbp$^{V1.4}$:PorA$^{151/P1.1.10_1}$	54.0	89.0
fHbp$^{V1.4}$:PorA$^{151/P1.14}$	55.0	88.0
fHbp$^{V1.4}$:PorA$^{151/P1.15}$	55.0	89.0
fHbp$^{V3.45}$:PorA$^{158/P1.4}$	40.0	81.0
fHbp$^{V3.45}$:PorA$^{158/P1.9}$	39.0	80.0

Melting temperature, T_m

Table 4: Serum bactericidal assay titres

Pooled antisera	**Serogroup B isolate**	**fHbp variant**	**PorA VR2**	**SBA titre**
fHbp$^{V3.45}$:PorA$^{158/P1.4}$	M10240123	V1.92*	P1.4	1/160
fHbp$^{V3.45}$:PorA$^{158/P1.9}$	M11240431	V2.19	P1.9	1/1280
fHbp$^{V1.4}$:PorA$^{151/P1.1.10_1}$	M11240189	V3.84	P1.10_1	1/20
fHbp$^{V1.4}$:PorA$^{151/P1.14}$	M15240853	V3.45	P1.14	1/640

α-PorA SBA titres generated using pooled Chimeric Antigen/alum antisera and serogroup B *N. meningitidis* isolates with mismatched fHbp variants. * fHbp truncated at residue 242.

fHbp$^{V1.4}$:PorA$^{151/P1.15}$ not tested, as it was needed to generate Δ*fHbp* strains, as the fHbp in strains with PorA VR2 P1.15 is not mismatched.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS

1. A modified factor H binding protein (fHbp), comprising wild-type fHbp or the wild-type gonococcal orthologue of fHbp (Ghfp), or a variant thereof having at least 75% identity with any of the sequences of SEQ ID NOs: 1-13, which is further modified with the addition of an exogenous peptide loop,

wherein the exogenous peptide loop is between 8 and 20 amino acids in length and wherein the exogenous peptide loop is inserted at an amino acid position that is corresponding to any one of the amino acid residue numbers 49-54, 83-88, 114-124, 199-206, 227-233, and 240-246 of SEQ ID NO: 1, or equivalent residues in any of SEQ ID NOs: 2 to 13.

2. The modified factor H binding protein according to claim 1, wherein the modified fHbp is modified such that it is not capable of binding factor H, or at least has reduced factor H binding activity.

3. The modified factor H binding protein according to claim 1 or claim 2, wherein the exogenous peptide loop(s) has a sequence of an integral outer membrane protein.

4. The modified factor H binding protein according to any one of claims 1 to 3, wherein the exogenous peptide loop(s) has a sequence of a prokaryotic polypeptide.

5. The modified factor H binding protein according to claim 4, wherein the exogenous peptide loop(s) is a meningococcal protein; or wherein the exogenous peptide loop(s) is a gonococcal protein.

6. The modified factor H binding protein according to any one of claims 1 to 5, wherein the exogenous peptide loop(s) comprises a fragment of PorA.

7. The modified factor H binding protein according to any one of claims 1 to 6, wherein the exogenous peptide loop(s) are selected from any one of the PorA loops 1 to 7 or variants thereof having no more than 1, 2, 3, 4 or 5 amino acid additions, deletions or substitutions; and combinations thereof; or wherein the exogenous peptide loop(s) are selected from any one of the PorA loops comprising a sequence according to any one of SEQ ID NOs: 45 to 79,

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or a variant thereof having no more than 1, 2, 3, 4 or 5 amino acid additions, deletions or substitutions.

8. The modified factor H binding protein according to any one of claims 1 to 7, wherein the modified fHbp comprises two or more exogenous peptide loops; or wherein the modified fHbp comprises between 1 and 7 exogenous peptide loops.

9. The modified factor H binding protein according to any one of claims 1 to 8, wherein the modified fHbp, or variant thereof, is modified with an exogenous peptide loop in at least two positions.

10. The modified factor H binding protein according to any one of claims 1 to 9, wherein the modified fHbp comprises the sequence of any one of SEQ ID NOs: 1 to 13; or a variant thereof having at least 75% identity with any of the sequences of SEQ ID NOs: 1-13, wherein the at least one exogenous peptide loop is an additional insert within the sequence of any one of SEQ ID NOs: 1 to 13 or the variant thereof having at least 75% identity with any of the sequences of SEQ ID NOs: 1-13.

11. An isolated nucleic acid encoding the modified fHbp according to any one of claims 1 to 10.

12. The isolated nucleic acid according to claim 11, wherein the nucleic acid is a vector, optionally a viral vector.

13. A composition comprising a therapeutically effective amount of the modified fHbp according to any one of claims 1 to 10 or the isolated nucleic acid according to claim 11 or claim 12, and a pharmaceutically acceptable carrier.

14. The composition according to claim 13, wherein the composition comprises two or more different modified fHbp molecules; and/or wherein the composition further comprises an adjuvant.

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15. The composition according to claim 13 or claim 14, wherein the composition further comprises at least one other prophylactically or therapeutically active molecule; and optionally

wherein the at least one other prophylactically or therapeutically active molecule comprises:

a protein:capsule polysaccharide vaccine; or

a conjugate vaccine, wherein antigen(s)comprising the fHbp scaffold bearing exogenous peptide loops is incorporated as the protein carrier molecule in the conjugate vaccine.

16. A modified fHbp according to any one of claims 1 to 10, an isolated nucleic acid according to claim 11 or claim 12, or a composition according to any one of claims 13 to 15, for use as a medicament.

17. A modified fHbp according to any one of claims 1 to 10, an isolated nucleic acid according to claim 11 or claim 12, or a composition according to any one of claims 13 to 15, for use in the treatment or prevention of a pathogenic infection or colonisation of a subject.

18. A method of treatment or prevention of a *Neisseria meningitidis* or *Neisseria gonorrhoeae* infection or colonisation of a subject, comprising the administration of a modified fHbp according to any one of claims 1 to 10, an isolated nucleic acid according to claim 11 or claim 12, or a composition according to any one of claims 13 to 15, to the subject.

19. A method of vaccination, comprising the administration of a modified fHbp according to any one of claims 1 to 10, an isolated nucleic acid according to claim 11 or claim 12, or a composition according to any one of claims 13 to 15, to a subject.

20. A combination of a therapeutically effective amount of the modified fHbp according to any one of claims 1 to 10, an isolated nucleic acid according to claim 11 or claim 12, or a composition according to any one of claims 13 to 15, and a therapeutically effective amount of a protein:capsule polysaccharide vaccine, for use as a vaccine.

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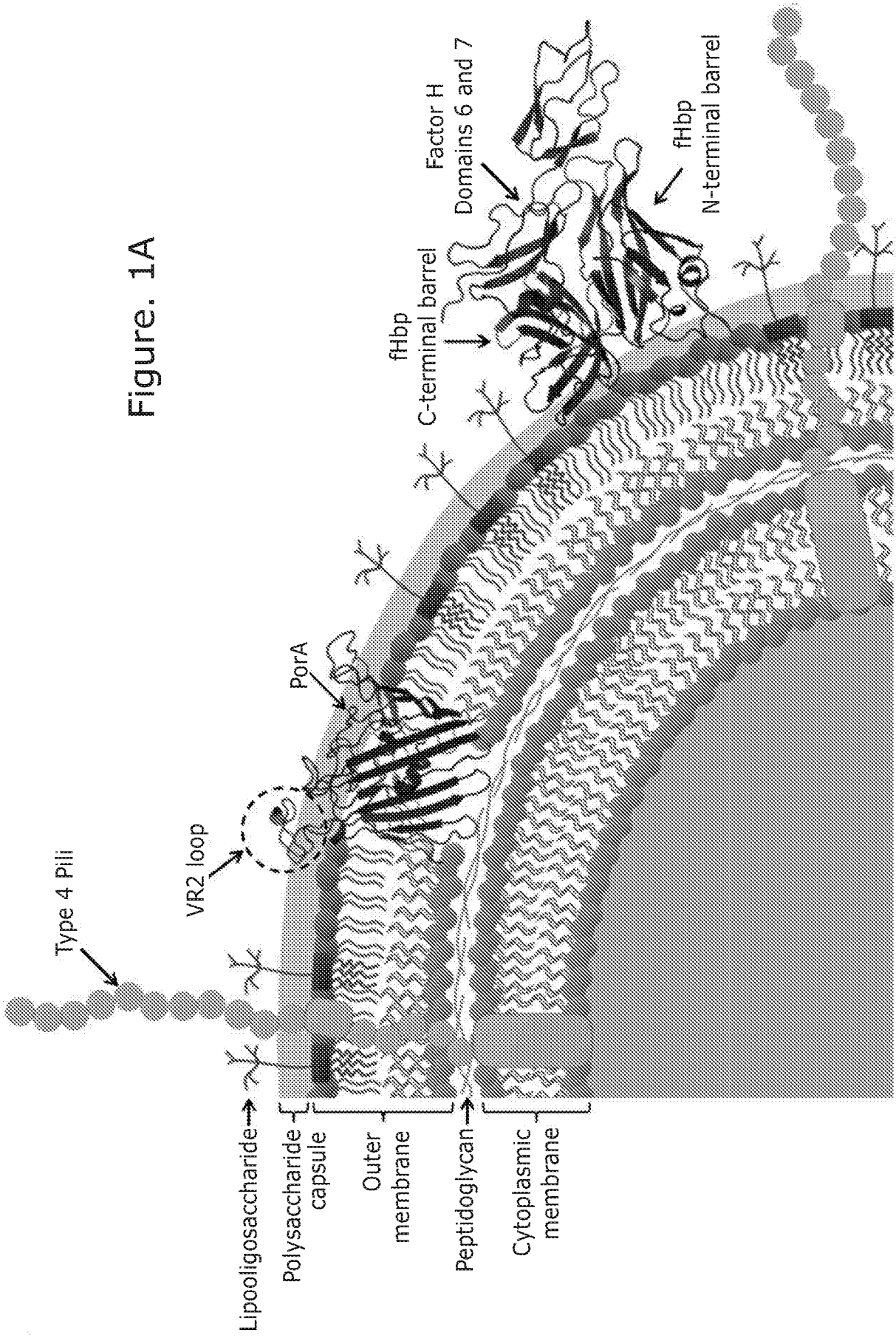
21. Use of the factor H binding protein (fHbp) according to any of claims 1 to 10 as an epitope display scaffold.

22. Use of a modified fHbp according to any one of claims 1 to 10, an isolated nucleic acid according to claim 11 or claim 12, or a composition according to any one of claims 13 to 15, in the manufacture of a medicament for the treatment or prevention of a *Neisseria meningitidis* or *Neisseria gonorrhoeae* infection or colonisation of a subject.

Figure. 1A


Type 4 Pili
VR2 loop
PorA
fHbp
C-terminal barrel
Factor H
Domains 6 and 7
fHbp
N-terminal barrel
Lipooligosaccharide
Polysaccharide capsule
Outer membrane
Peptidoglycan
Cytoplasmic membrane

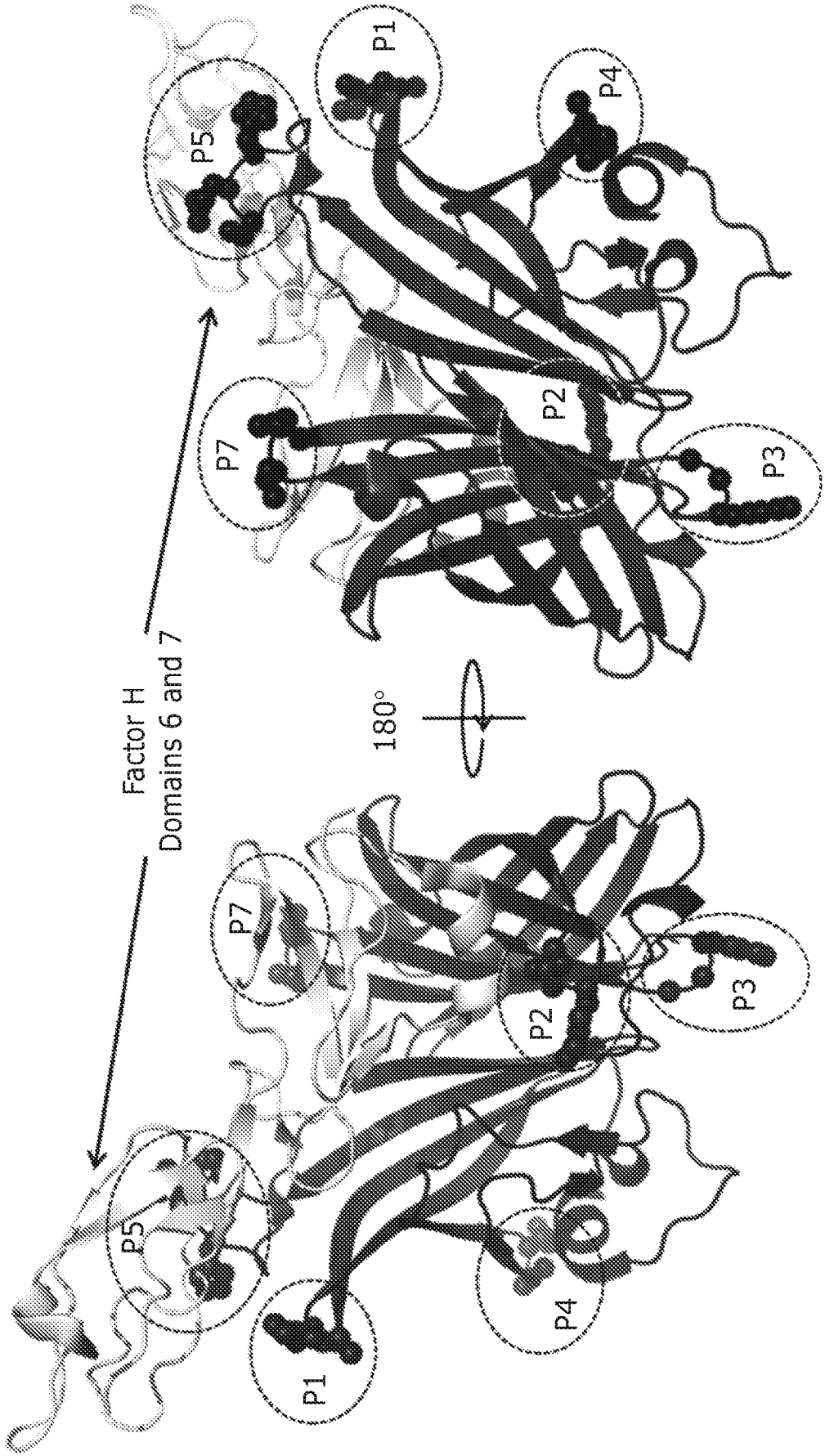


Figure 1B

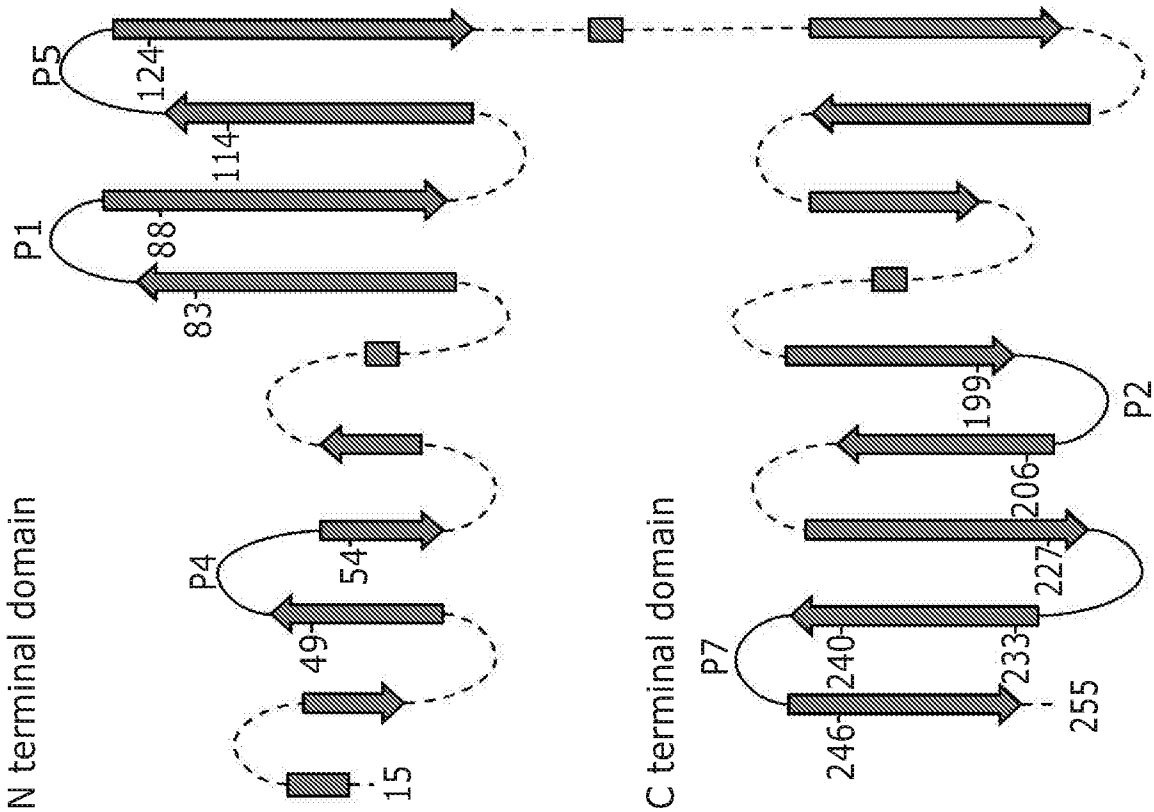


Figure 2B

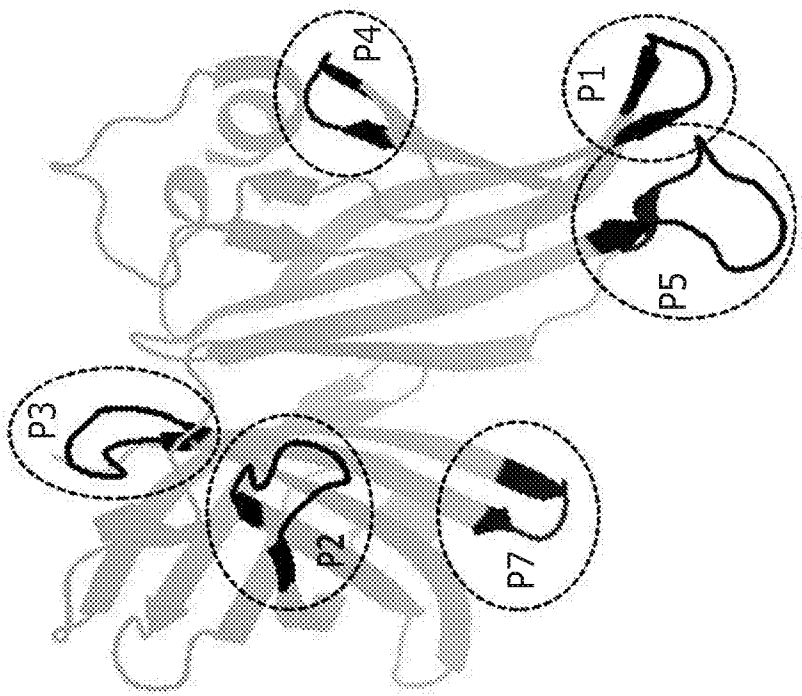


Figure 2A

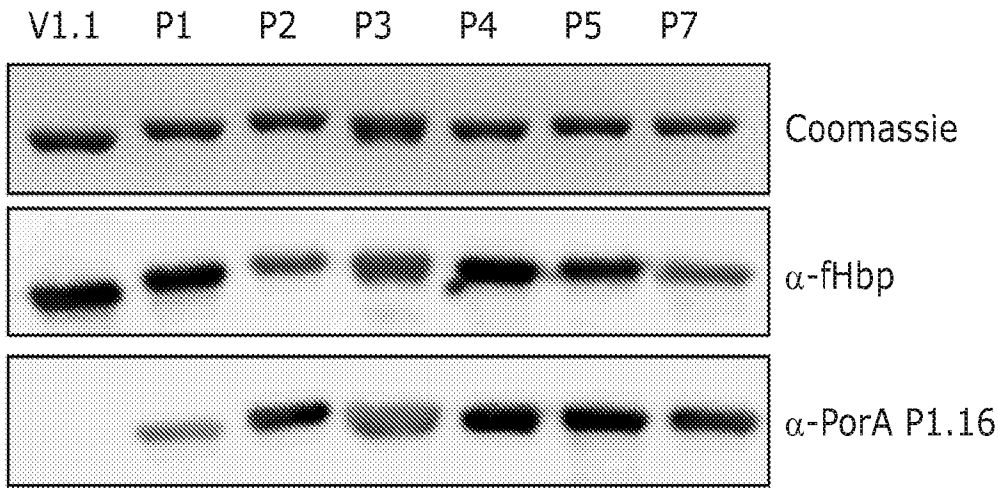


Figure 2C

```
1   CSSGGGGVAA DIGAGLADAL TAPLDHKDKG LQSLTLDQSV

41  RKNEKLKLAA QGAEKTYGNG DSLNTGKLKN DKVSRFDFIR
              ..P4...

81  QIEVDGQLIT LESGEFQVYK QSHSALTAFQ TEQIQDSEHS
      ..P1..                                ...P5..

121 GKMVAKRQFR IGDIAGEHTS FDKLPEGGRA TYRGTAFGSD
    ....

161 DAGGKLTYTI DFAAKQGNGK IEHLKSPELN VDLAAADIKP

201 DGKRHAVISG SVLYNQAEKG SYSLGIFGGK AQEVAGSAEV
    .P2...                          ...P3...

241 KTVNGIRHIG LAAKQ
    ..P7..
```

Figure 2D

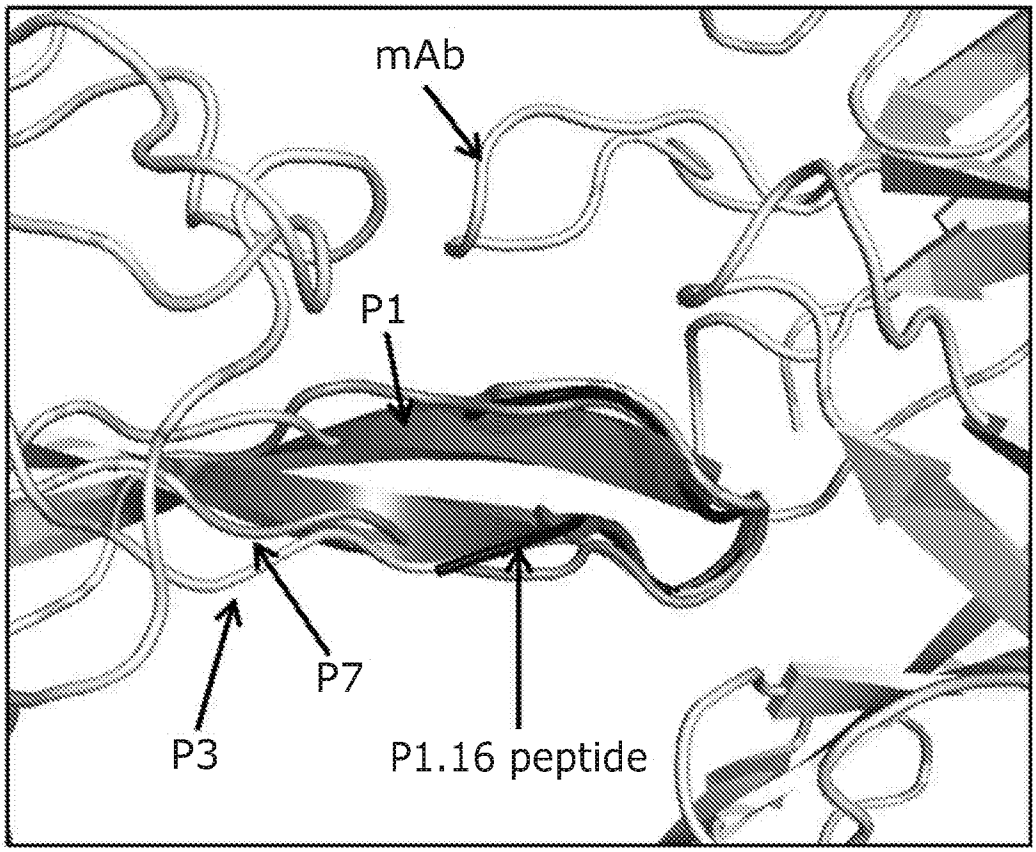
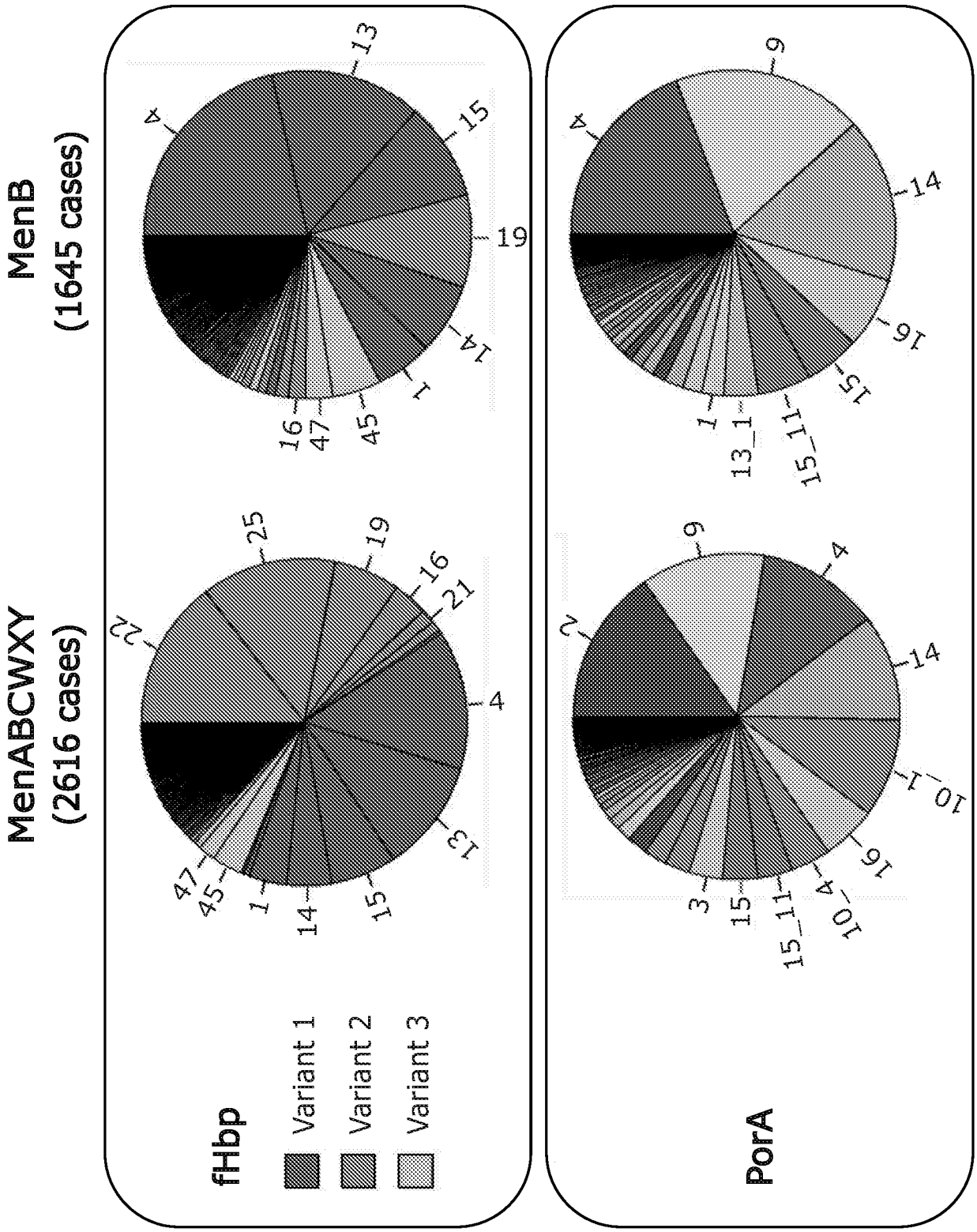


Figure 3A

Protein	Cp (kcal $mole^{-1} \circ C^{-1}$) NT	Cp (kcal $mole^{-1} \circ C^{-1}$) CT	Kd (nm)
V1.1	69.8	87.9	3.6
P1	60.5	87.3	2.3
P2	68.4	75.7	28
P3	61.7	72.4	2.7
P4	65	87.9	2.3
P5	68.8	88	NB
P7	69	76.9	5.5

Figure 3B


MenB
(1645 cases)
MenABCWXY
(2616 cases)
fHbp
Variant 1
Variant 2
Variant 3
PorA
Figure 4A
Figure 4B

	Variant	% MenABCWXY coverage (2009-2015 UK)	% MenB coverage (2009-2015 UK)
fHbp	1.4	13.8	21.5
	2.22	14.8	0.2
	2.19	6.5	9.1
	3.45	3.0	4.8
PorA	P1.2	15.4	1.3
	P1.9	12.3	19.1
	P1.4	12.1	19.3
	P1.14	10.5	16.3
	P1.10_1	9.7	1.3
	P1.16	5.4	7.0
	P1.15	3.4	5.5

Figure 4
Continued

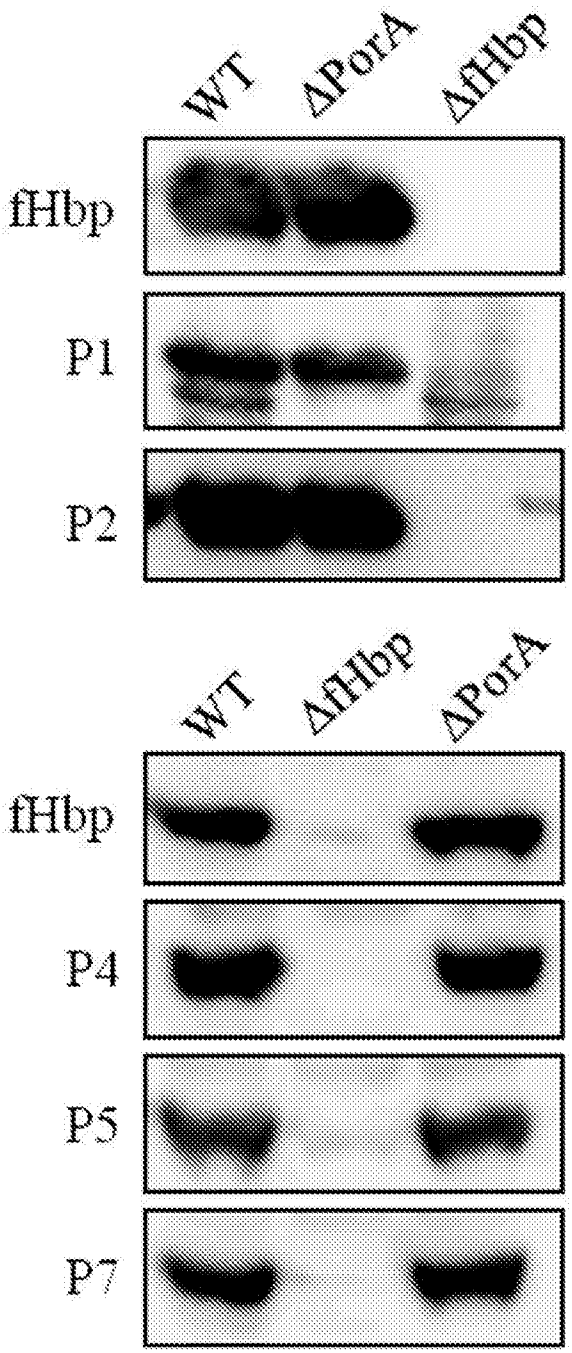


Figure 5A

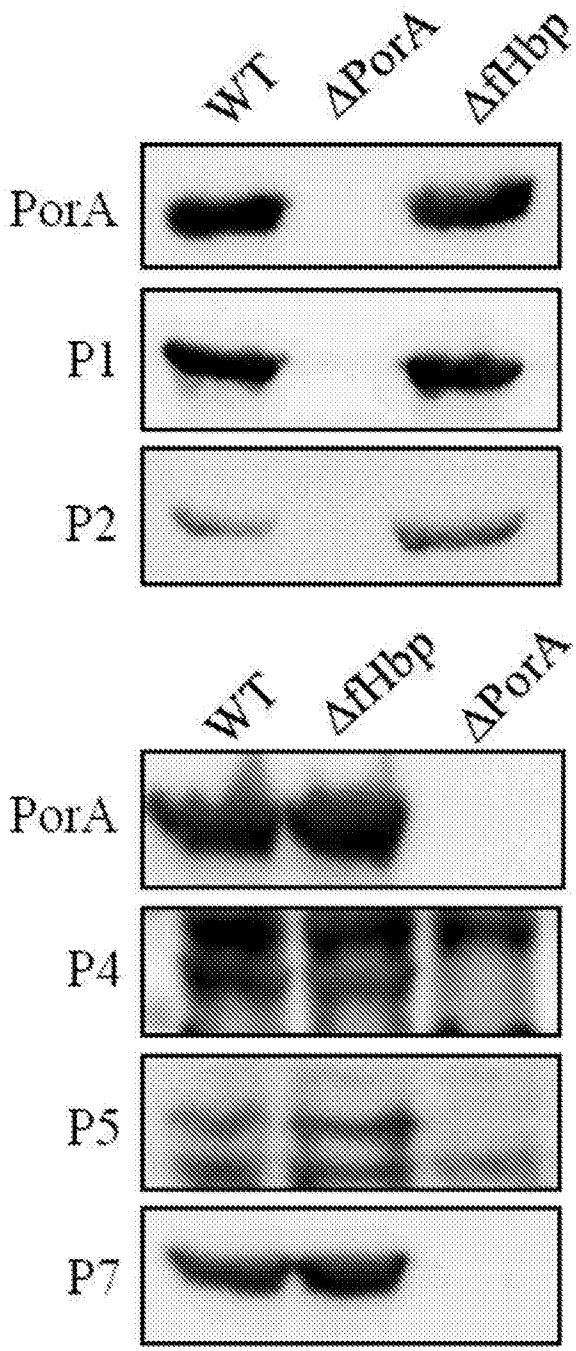
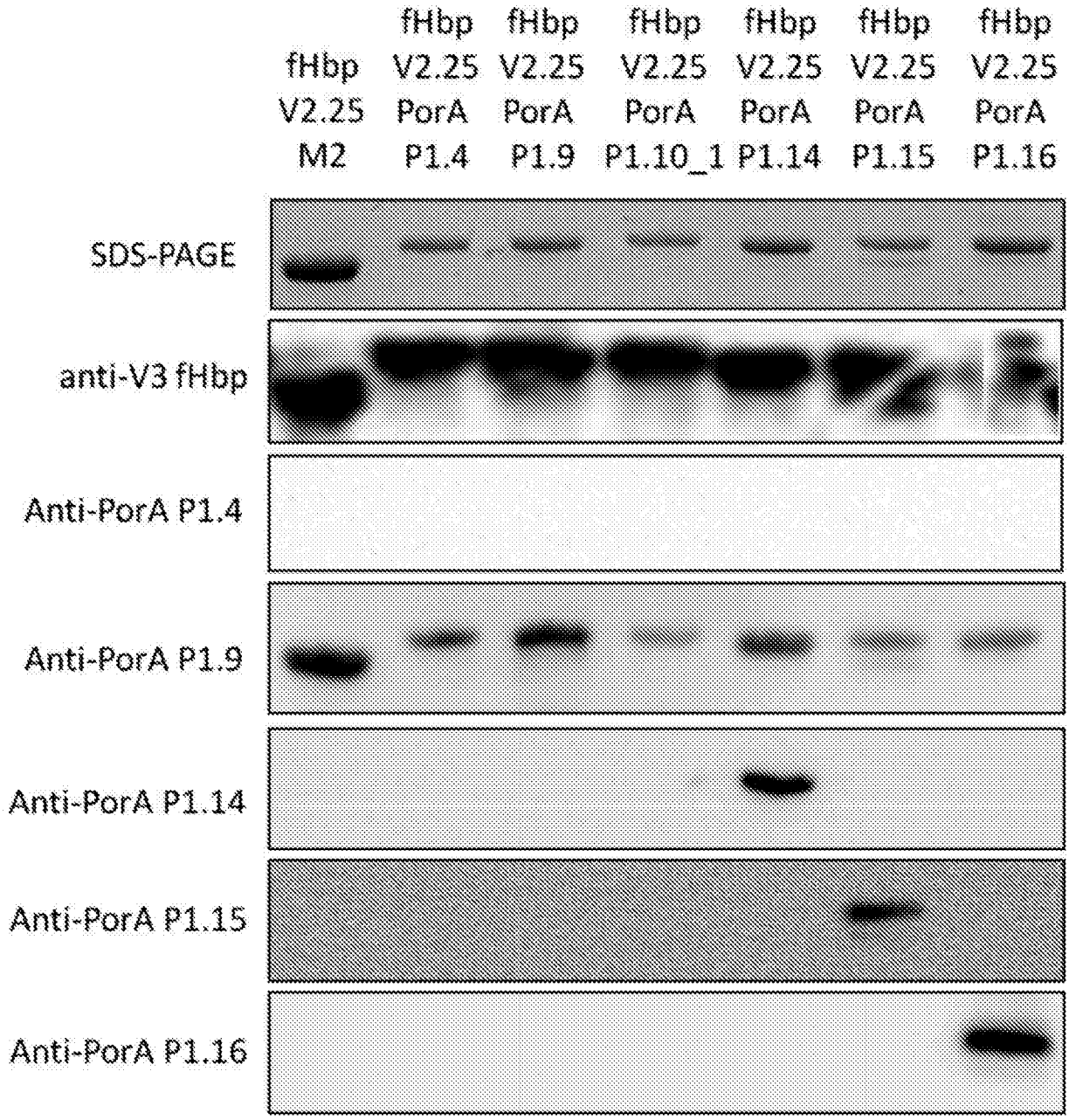


Figure 5B

Chimera	NT_{TM} (°C)	CT_{TM} (°C)
V1.1 WT	71	90
V2.25 WT	33?	87
V2.25 MT	67	87
V2.25 M6 PorA (P1) P1.16	40	86

Figure 6A



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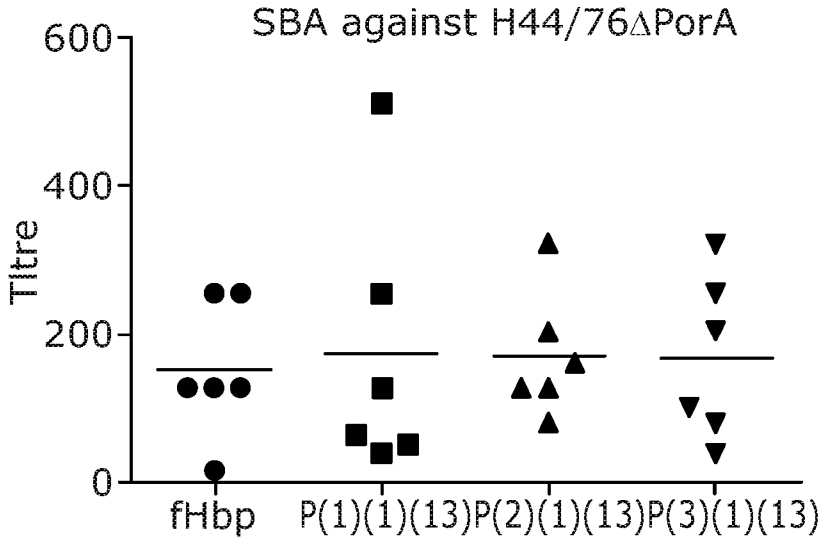
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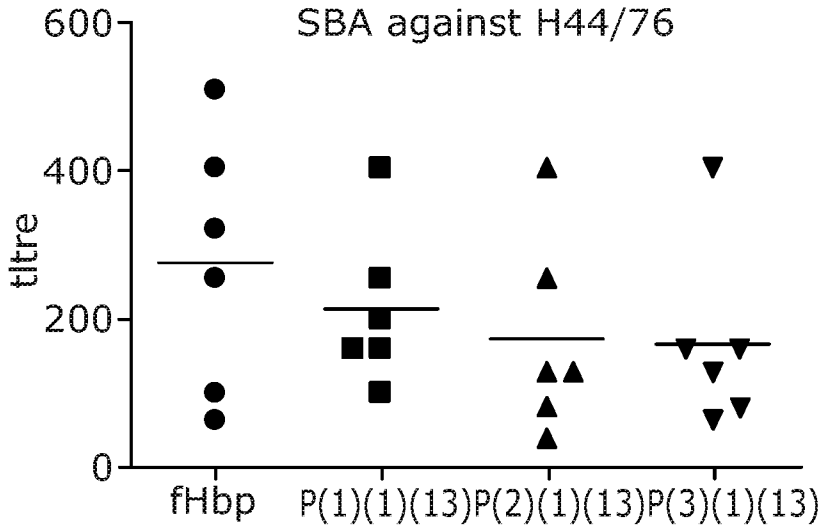
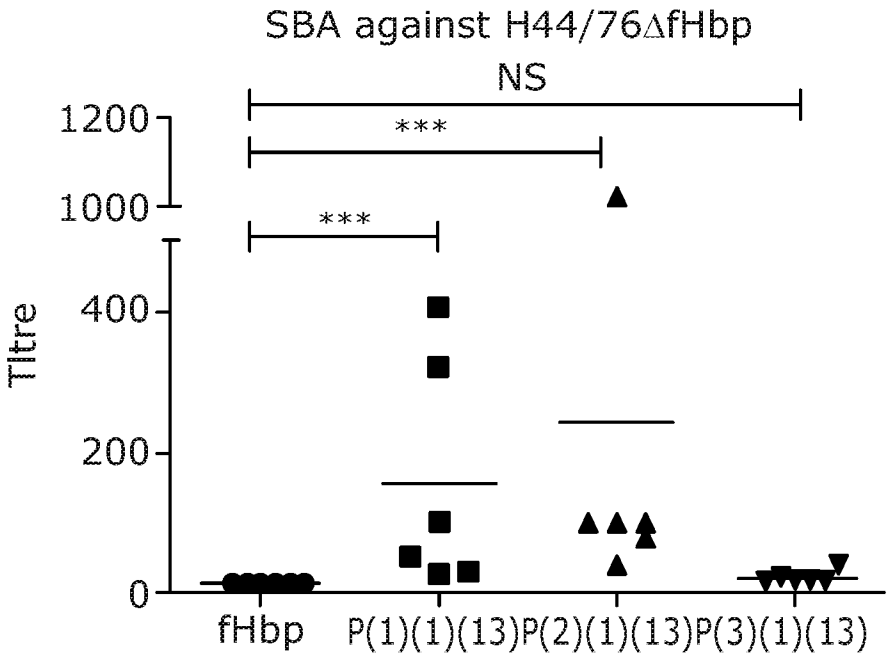
fHbp
P(1)(1)(13)
P(2)(1)(13)
P(3)(1)(13)


SBA against H44/76
600
400
200
0
titre
fHbp
P(1)(1)(13)
P(2)(1)(13)
P(3)(1)(13)


SBA against H44/76ΔfHbp
NS
***
***
1200
1000
400
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0
Titre
fHbp
P(1)(1)(13)
P(2)(1)(13)
P(3)(1)(13)

Figure 7

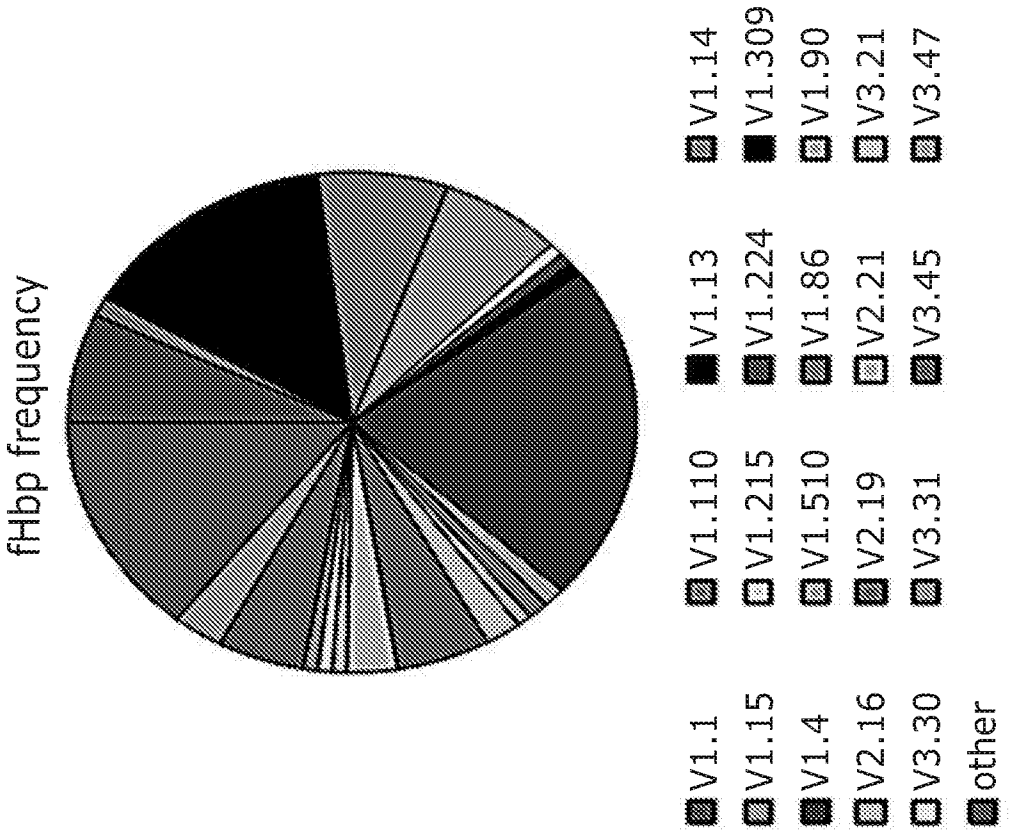


Figure 8B

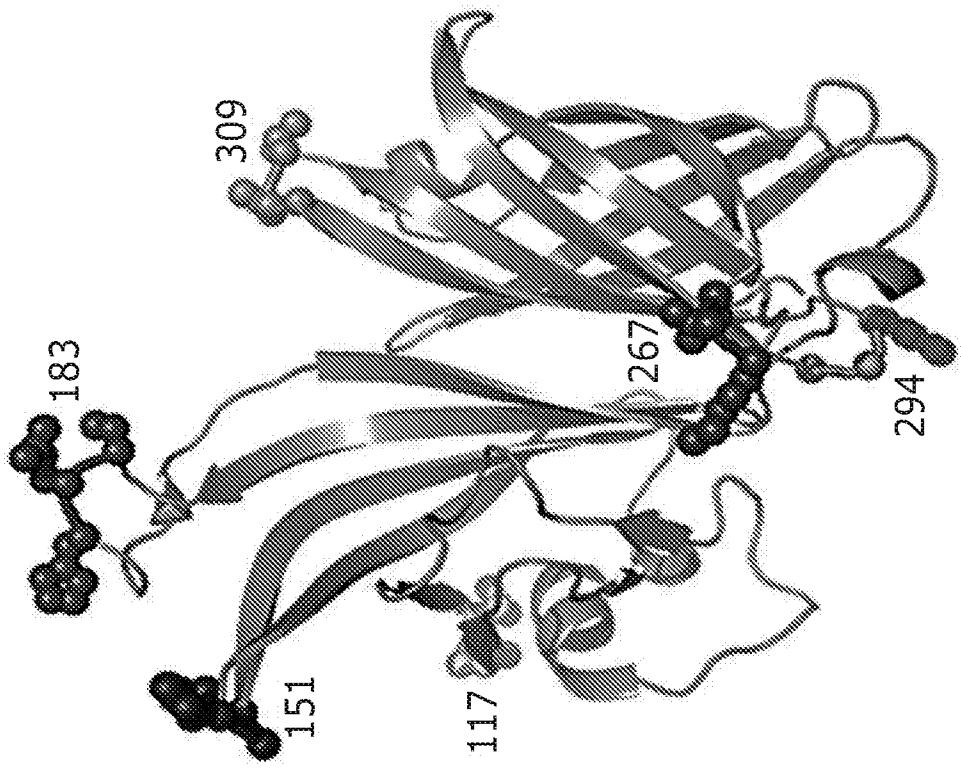


Figure 8A

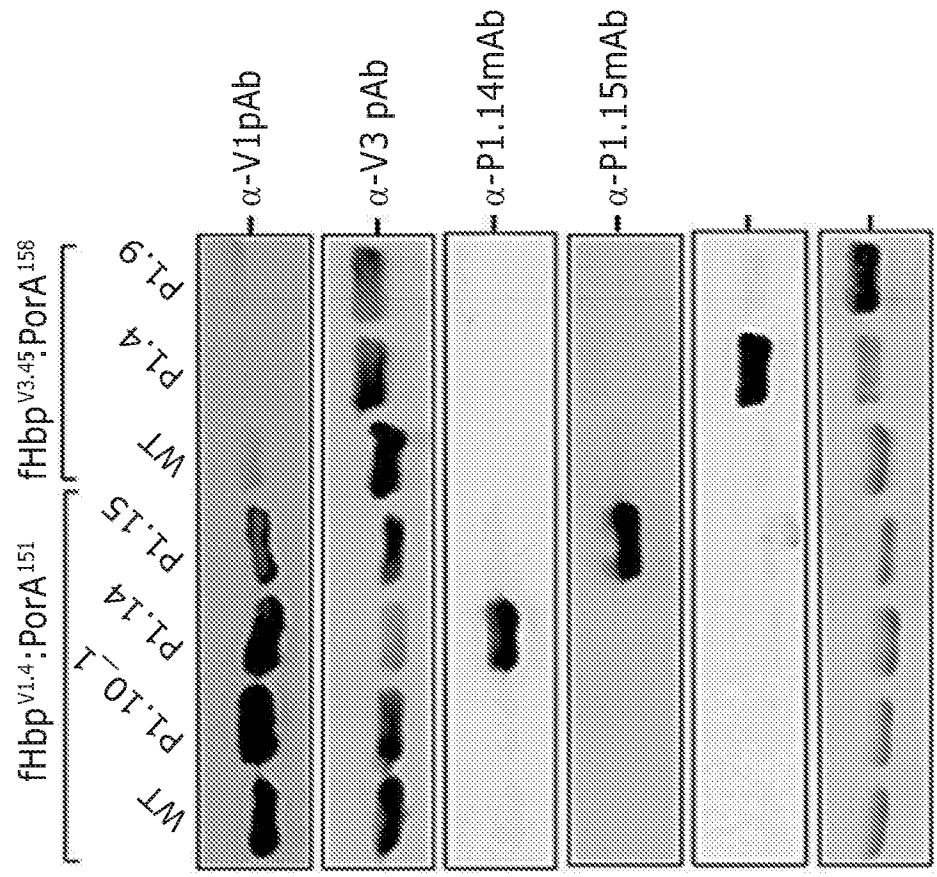


Figure 8D

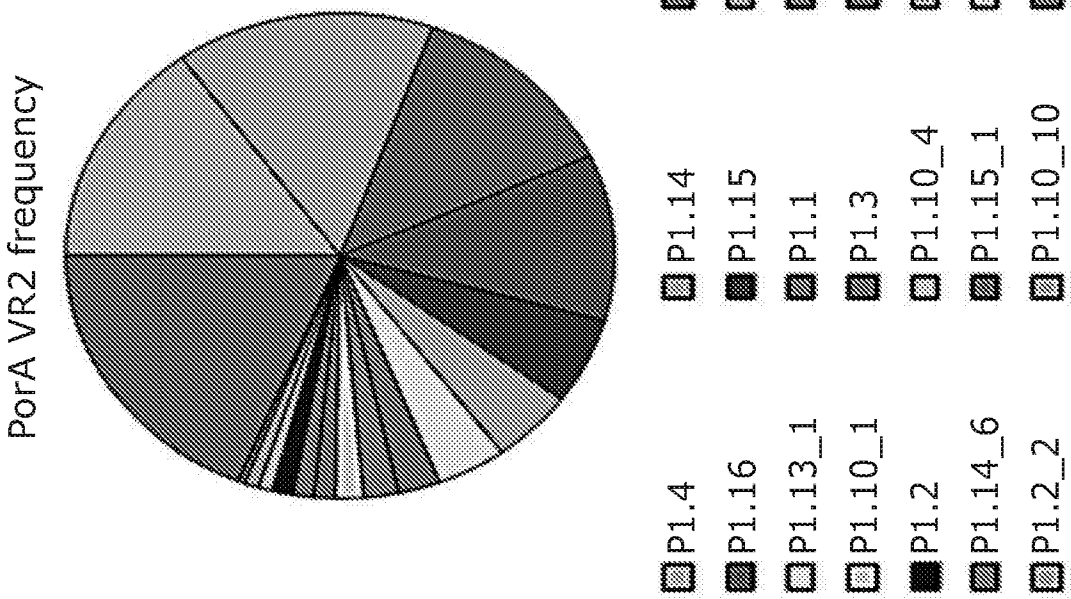
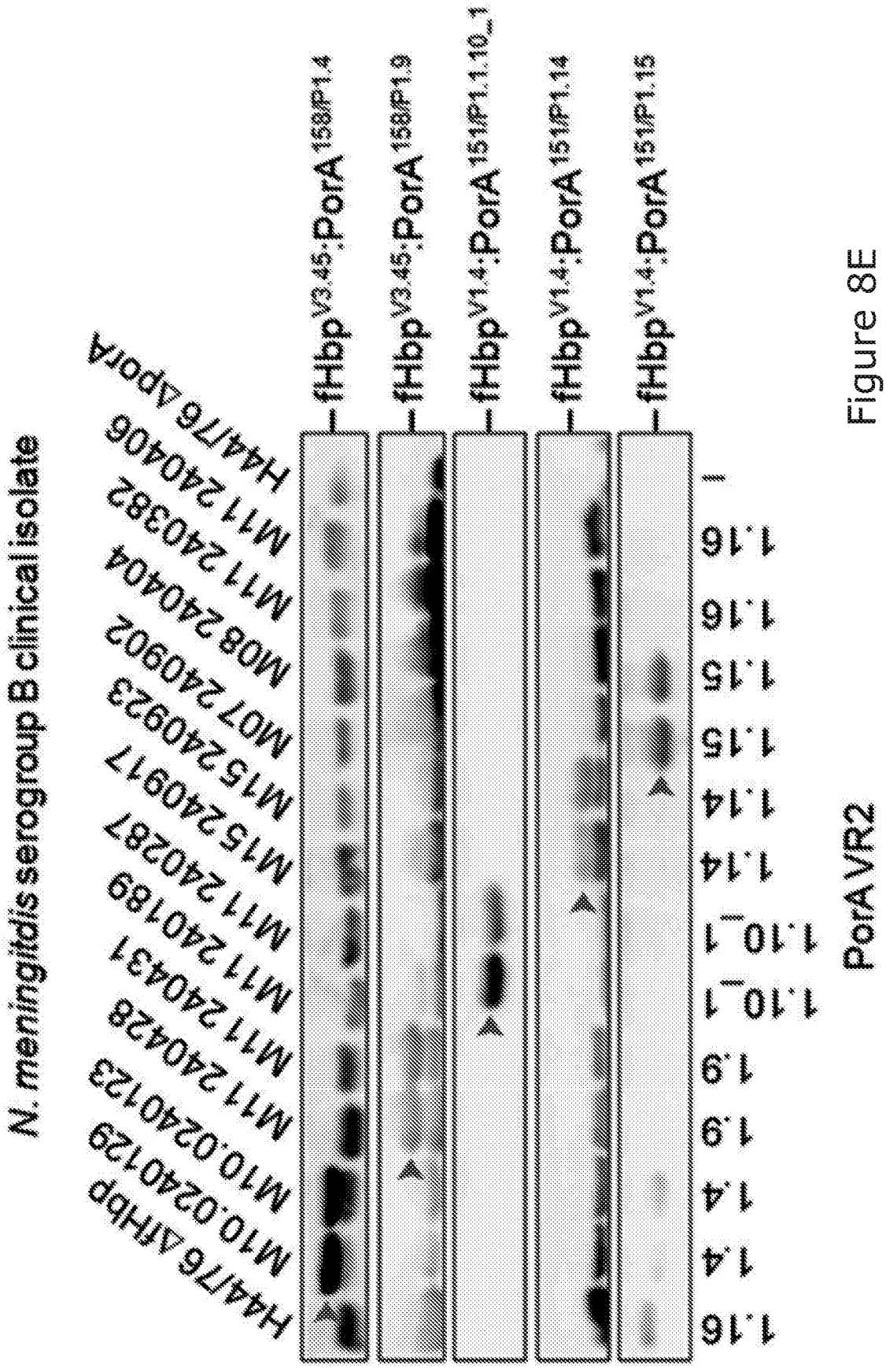


Figure 8C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fHbp V1.4:PorA 151/P1.15
PorA VR2
1.16
1.4
1.9
1.10_1
1.14
1.15
1.16
-
N. meningitidis serogroup B clinical isolate
H44/76 ΔfHbp
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M10.0240123
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M11 240189
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H44/76 ΔporA

Figure 8E

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<151> 2016-08-31

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            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80


Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95


Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu
            100                 105                 110


Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125
```

```
Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140

Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160

Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175

Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp
            180                 185                 190

Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile
        195                 200                 205

Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu
    210                 215                 220

Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val
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Lys Thr Val Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
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<213>  Neisseria meningitidis

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Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45
```

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Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Leu Gln Thr Glu
            100                 105                 110

Gln Val Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125

Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140

Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160

Asp Ala Ser Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175

Gly His Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp
            180                 185                 190

Leu Ala Ala Ser Asp Ile Lys Pro Asp Lys Lys Arg His Ala Val Ile
        195                 200                 205

Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu
    210                 215                 220

Gly Ile Phe Gly Gly Gln Ala Gln Glu Val Ala Gly Ser Ala Glu Val
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Glu Thr Ala Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
                245                 250                 255
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            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80


Gln Ile Glu Val Asp Gly Lys Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95


Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Leu Gln Thr Glu
            100                 105                 110


Gln Val Gln Asp Ser Glu Asp Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125


Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140


Pro Lys Gly Gly Ser Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160


Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175
```

```
Gly His Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Glu
            180                 185                 190


Leu Ala Thr Ala Tyr Ile Lys Pro Asp Glu Lys Arg His Ala Val Ile
        195                 200                 205


Ser Gly Ser Val Leu Tyr Asn Gln Asp Glu Lys Gly Ser Tyr Ser Leu
    210                 215                 220


Gly Ile Phe Gly Gly Gln Ala Gln Glu Val Ala Gly Ser Ala Glu Val
225                 230                 235                 240


Glu Thr Ala Asn Gly Ile His His Ile Gly Leu Ala Ala Lys Gln
                245                 250                 255


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            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80


Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95


Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Leu Gln Thr Glu
```

100 105 110

Gln Glu Gln Asp Pro Glu His Ser Gly Lys Met Val Ala Lys Arg Arg
115 120 125

Phe Lys Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
130 135 140

Pro Lys Asp Val Met Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145 150 155 160

Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
165 170 175

Gly His Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Glu
180 185 190

Leu Ala Thr Ala Tyr Ile Lys Pro Asp Glu Lys His His Ala Val Ile
195 200 205

Ser Gly Ser Val Leu Tyr Asn Gln Asp Glu Lys Gly Ser Tyr Ser Leu
210 215 220

Gly Ile Phe Gly Gly Gln Ala Gln Glu Val Ala Gly Ser Ala Glu Val
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Glu Thr Ala Asn Gly Ile His His Ile Gly Leu Ala Ala Lys Gln
245 250 255

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Ile Gly Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys
20 25 30

```
Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn
        35                  40                  45

Gly Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Arg Thr Phe Lys Ala
    50                  55                  60

Gly Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys
65                  70                  75                  80

Ile Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu
                85                  90                  95

Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser
            100                 105                 110

Ala Leu Thr Ala Leu Gln Thr Glu Gln Val Gln Asp Ser Glu His Ser
        115                 120                 125

Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile Val Gly
    130                 135                 140

Glu His Thr Ser Phe Gly Lys Leu Pro Lys Asp Val Met Ala Thr Tyr
145                 150                 155                 160

Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr
                165                 170                 175

Thr Ile Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu
            180                 185                 190

Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile Lys Pro
        195                 200                 205

Asp Glu Lys His His Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln
    210                 215                 220

Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Gln Ala Gln
225                 230                 235                 240
```

```
Glu Val Ala Gly Ser Ala Glu Val Glu Thr Ala Asn Gly Ile Arg His
                245                 250                 255


Ile Gly Leu Ala Ala Lys Gln
            260
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<213> Neisseria meningitidis

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1               5                   10                  15


Ile Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys
            20                  25                  30


Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn
        35                  40                  45


Gly Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn
    50                  55                  60


Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg
65                  70                  75                  80


Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu
                85                  90                  95


Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr
            100                 105                 110


Ala Leu Gln Thr Glu Gln Glu Gln Asp Pro Glu His Ser Glu Lys Met
        115                 120                 125


Val Ala Lys Arg Arg Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr
    130                 135                 140
```

```
Ser Phe Asp Lys Leu Pro Lys Asp Val Met Ala Thr Tyr Arg Gly Thr
145                 150                 155                 160


Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp
                165                 170                 175


Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Ser Pro
            180                 185                 190


Glu Leu Asn Val Asp Leu Ala Val Ala Tyr Ile Lys Pro Asp Glu Lys
        195                 200                 205


His His Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Asp Glu Lys
    210                 215                 220


Gly Ser Tyr Ser Leu Gly Ile Phe Gly Glu Lys Ala Gln Glu Val Ala
225                 230                 235                 240


Gly Ser Ala Glu Val Glu Thr Ala Asn Gly Ile His His Ile Gly Leu
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Ala Ala Lys Gln
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1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45
```

```
Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110

Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125

Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140

Pro Asp Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160

Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly
                165                 170                 175

His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190

Ala Ala Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
        195                 200                 205

Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr Tyr His Leu Ala
    210                 215                 220

Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
225                 230                 235                 240

Ile Gly Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
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Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80


Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95


Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110


Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125


Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140


Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160


Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly
                165                 170                 175


His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
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180 185 190

Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
195 200 205

Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala
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Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
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Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
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20 25 30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
35 40 45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
50 55 60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65 70 75 80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
85 90 95

Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
100 105 110

```
Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125


Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140


Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160


Pro Asn Gly Arg Leu His Tyr Ser Ile Asp Phe Thr Lys Lys Gln Gly
                165                 170                 175


Tyr Gly Arg Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190


Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
        195                 200                 205


Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala
    210                 215                 220


Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
225                 230                 235                 240


Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
                245                 250


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Ala Asp Ala Leu Thr Thr Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30
```

```
Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Thr Ile Thr Leu Ala Ser Gly Glu Phe
                85                  90                  95

Gln Ile Tyr Lys Gln Asn His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110

Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125

Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140

Pro Asp Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160

Pro Asn Gly Arg Leu His Tyr Ser Ile Asp Phe Thr Lys Lys Gln Gly
                165                 170                 175

Tyr Gly Arg Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190

Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
        195                 200                 205

Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala
    210                 215                 220

Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
225                 230                 235                 240
```

```
Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
                245                 250


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Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp
            20                  25                  30


Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly
        35                  40                  45


Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly
    50                  55                  60


Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile
65                  70                  75                  80


Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile
                85                  90                  95


Thr Leu Ala Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala
            100                 105                 110


Val Val Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp
        115                 120                 125


Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu
    130                 135                 140


His Thr Ala Phe Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly
145                 150                 155                 160
```

```
Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile
                165                 170                 175


Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr
            180                 185                 190


Pro Glu Gln Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu
        195                 200                 205


Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu
    210                 215                 220


Lys Gly Thr Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile
225                 230                 235                 240


Ala Gly Ser Ala Thr Val Lys Ile Arg Glu Lys Val His Glu Ile Gly
                245                 250                 255


Ile Ala Gly Lys Gln
            260


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Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
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Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Lys
            20                  25                  30


Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly Thr Leu Thr Leu
        35                  40                  45


Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly Asp Lys Asp Asn
    50                  55                  60


Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile Ser Arg Phe Asp
```

65 70 75 80

Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile Thr Leu Ala Ser
85 90 95

Gly Glu Phe Gln Ile Tyr Lys Gln Asn His Ser Ala Val Val Ala Leu
100 105 110

Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn
115 120 125

Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe
130 135 140

Asn Gln Leu Pro Gly Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser
145 150 155 160

Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala
165 170 175

Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn
180 185 190

Val Glu Leu Ala Ala Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala
195 200 205

Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr Tyr
210 215 220

His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala
225 230 235 240

Thr Val Lys Ile Gly Glu Lys Val His Glu Ile Ser Ile Ala Gly Lys
245 250 255

Gln

<210> 13

<211> 285
<212> PRT
<213> Neisseria meningitidis

<400> 13

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Met Thr Arg Ser Lys Pro Val Asn Arg Thr Thr Phe Cys Cys Leu Ser
1               5                  10                  15


Leu Thr Ala Gly Pro Asp Ser Asp Arg Leu Gln Gln Arg Arg Gly Gly
            20                  25                  30


Gly Gly Gly Val Ala Ala Asp Ile Gly Thr Gly Leu Ala Asp Ala Leu
        35                  40                  45


Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Lys Ser Leu Thr Leu
    50                  55                  60


Glu Ala Ser Ile Pro Gln Asn Gly Thr Leu Thr Leu Ser Ala Gln Gly
65                  70                  75                  80


Ala Glu Lys Thr Phe Lys Ala Gly Gly Lys Asp Asn Ser Leu Asn Thr
                85                  90                  95


Gly Lys Leu Lys Asn Asp Lys Ile Ser Arg Phe Asp Phe Val Gln Lys
            100                 105                 110


Ile Glu Val Asp Gly Gln Thr Ile Thr Leu Ala Ser Gly Glu Phe Gln
        115                 120                 125


Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Arg Ile Glu Lys
    130                 135                 140


Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe
145                 150                 155                 160


Leu Val Ser Asp Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu Pro
                165                 170                 175


Asp Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp Ala
            180                 185                 190
```

```
Asp Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly His
        195                 200                 205


Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu Ala
    210                 215                 220


Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu Gly
225                 230                 235                 240


Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr Arg Leu Ala Leu
                245                 250                 255


Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys Ile
            260                 265                 270


Gly Glu Lys Val His Glu Ile Gly Ile Ala Asp Lys Gln
        275                 280                 285


<210>  14
<211>  256
<212>  PRT
<213>  Neisseria meningitidis

<400>  14

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Pro Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu
    50                  55                  60


Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile
65                  70                  75                  80
```

```
Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu
                85                  90                  95

Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr
            100                 105                 110

Glu Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg
        115                 120                 125

Gln Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys
    130                 135                 140

Leu Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser
145                 150                 155                 160

Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys
                165                 170                 175

Gln Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val
            180                 185                 190

Asp Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val
        195                 200                 205

Ile Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser
    210                 215                 220

Leu Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu
225                 230                 235                 240

Val Lys Thr Val Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
                245                 250                 255
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<210> 15
<211> 6
<212> PRT
<213> Neisseria meningitidis

<400> 15

Glu Val Asp Gly Gln Leu
1 5

<210> 16
<211> 8
<212> PRT
<213> Neisseria meningitidis

<400> 16

Lys Pro Asp Gly Lys Arg His Ala
1 5

<210> 17
<211> 7
<212> PRT
<213> Neisseria meningitidis

<400> 17

Phe Gly Gly Lys Ala Gln Glu
1 5

<210> 18
<211> 6
<212> PRT
<213> Neisseria meningitidis

<400> 18

Ala Ala Gln Gly Ala Glu
1 5

<210> 19
<211> 10
<212> PRT
<213> Neisseria meningitidis

<400> 19

Ile Gln Asp Ser Glu His Ser Gly Lys Met
1 5 10

<210> 20
<211> 6
<212> PRT
<213> Neisseria meningitidis

<400> 20

Lys Thr Val Asn Gly Ile
1 5

<210> 21
<211> 7
<212> PRT
<213> Neisseria meningitidis

<220>
<221> Xaa
<222> (1)..(1)
<223> exogenous loop insert

<400> 21

Xaa Ala Ala Gln Gly Ala Glu
1 5

<210> 22
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (2)..(2)
<223> Exogenous loop insert

<400> 22

Ala Xaa Ala Gln Gly Ala Glu
1 5

<210> 23
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (3)..(3)
<223> Exogenous loop insert

<400> 23

Ala Ala Xaa Gln Gly Ala Glu
1 5

<210> 24
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (4)..(4)
<223> Exogenous loop insert

<400> 24

Ala Ala Gln Xaa Gly Ala Glu
1 5

<210> 25
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (5)..(5)
<223> Exogenous loop insert

<400> 25

Ala Ala Gln Gly Xaa Ala Glu
1 5

<210> 26
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (6)..(6)
<223> Exogenous loop insert

<400> 26

Ala Ala Gln Gly Ala Xaa Glu
1 5

<210> 27
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (7)..(7)
<223> Exogenous loop insert

<400> 27

Ala Ala Gln Gly Ala Glu Xaa
1 5

<210> 28
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (2)..(2)

<223> Exogenous loop insert

<400> 28

Ala Xaa Gln Gly Ala Glu
1   5

<210> 29
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (3)..(3)
<223> Exogenous loop insert

<400> 29

Ala Ala Xaa Gly Ala Glu
1   5

<210> 30
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (3)..(3)
<223> Exogenous loop insertion

<400> 30

Ala Ala Xaa Ala Glu
1   5

<210> 31
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa can be any naturally occurring amino acid

<400> 31

Ala Ala Xaa Glu
1

<210> 32
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypepitide

<220>
<221> Xaa
<222> (2)..(2)
<223> Exogenous loop insertion

<400> 32

Ala Xaa Gly Ala Glu
1   5

<210> 33
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (2)..(2)
<223> Exogenous loop insertion

<400> 33

Ala Xaa Ala Glu
1

<210> 34
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (3)..(3)
<223> Exogenous loop insertion

<400> 34

Ala Ala Xaa Glu
1

<210> 35
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (1)..(1)
<223> Exogenous loop insertion

<400> 35

Xaa Ala Gln Gly Ala Glu
1 5

<210> 36
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (1)..(1)
<223> Exogenous loop insertion

<400> 36

Xaa Gln Gly Ala Glu
1   5

<210> 37
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (1)..(1)
<223> Exogenous loop insertion

<400> 37

Xaa Gly Ala Glu
1

<210> 38
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (4)..(4)
<223> Exogenous loop insertion

<400> 38

Ala Ala Gln Xaa Ala Glu
1   5

<210> 39
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (4)..(4)
<223> Exogenous loop insertion

<400> 39

Ala Ala Gln Xaa Glu
1 5

<210> 40
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (4)..(4)
<223> Exogenous loop insertion

<400> 40

Ala Ala Gln Xaa
1

<210> 41
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (5)..(5)

<223> Exogenous loop insertion

<400> 41

Ala Ala Gln Gly Xaa Glu
1   5

<210> 42
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (5)..(5)
<223> Exogenous loop insertion

<400> 42

Ala Ala Gln Gly Xaa
1   5

<210> 43
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<220>
<221> Xaa
<222> (6)..(6)
<223> Exogenous loop insertion

<400> 43

Ala Ala Gln Gly Ala Xaa
1   5

<210> 44
<211> 255
<212> PRT
<213> Neisseria meningitidis

<400> 44

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Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                  10                  15

Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
            20                  25                  30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu
            100                 105                 110

Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125

Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140

Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160

Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175

Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp
            180                 185                 190

Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile
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195 200 205

Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu
210 215 220

Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val
225 230 235 240

Lys Thr Val Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
245 250 255

<210> 45
<211> 13
<212> PRT
<213> Neisseria meningitidis

<400> 45

Tyr Val Ala Val Glu Asn Gly Val Ala Lys Lys Val Ala
1 5 10

<210> 46
<211> 15
<212> PRT
<213> Neisseria meningitidis

<400> 46

His Phe Val Gln Gln Thr Pro Lys Ser Gln Pro Thr Leu Val Pro
1 5 10 15

<210> 47
<211> 15
<212> PRT
<213> Neisseria meningitidis

<400> 47

His Phe Val Gln Gln Thr Pro Gln Ser Gln Pro Thr Leu Val Pro
1 5 10 15

<210> 48
<211> 14
<212> PRT
<213> Neisseria meningitidis

<400> 48

Thr Leu Ala Asn Gly Ala Asn Asn Thr Ile Ile Arg Val Pro
1 5 10

<210> 49
<211> 14
<212> PRT
<213> Neisseria meningitidis

<400> 49

Thr Leu Ala Lys Gly Ala Asn Asn Thr Ile Ile Arg Val Pro
1 5 10

<210> 50
<211> 13
<212> PRT
<213> Neisseria meningitidis

<400> 50

His Val Val Val Asn Asn Lys Val Ala Thr His Val Pro
1 5 10

<210> 51
<211> 10
<212> PRT
<213> Neisseria meningitidis

<400> 51

Tyr Val Asp Glu Gln Ser Lys Tyr His Ala
1 5 10

<210> 52
<211> 15
<212> PRT
<213> Neisseria meningitidis

<400> 52

His Phe Val Gln Asn Lys Gln Asn Gln Arg Pro Thr Leu Val Pro
1 5 10 15

<210> 53

<211> 15
<212> PRT
<213> Neisseria meningitidis

<400> 53

His Phe Val Gln Asn Lys Gln Asn Gln Pro Pro Thr Leu Val Pro
1 5 10 15

<210> 54
<211> 15
<212> PRT
<213> Neisseria meningitidis

<400> 54

His Phe Val Gln Asp Lys Lys Gly Gln Pro Pro Thr Leu Val Pro
1 5 10 15

<210> 55
<211> 18
<212> PRT
<213> Neisseria meningitidis

<400> 55

His Phe Val Gln Asn Lys Gln Asn Gln Gln Asn Gln Pro Pro Thr Leu
1 5 10 15

Val Pro

<210> 56
<211> 18
<212> PRT
<213> Neisseria meningitidis

<400> 56

His Phe Val Gln Asn Lys Gln Asn Lys Gln Asn Gln Pro Pro Thr Leu
1 5 10 15

Val Pro

<210> 57

<211> 15
<212> PRT
<213> Neisseria meningitidis

<400> 57

His Phe Val Gln Asn Lys Gln Asn Lys Pro Pro Thr Leu Val Pro
1 5 10 15

<210> 58
<211> 18
<212> PRT
<213> Neisseria meningitidis

<400> 58

Tyr Trp Thr Thr Val Asn Thr Gly Ser Ala Thr Thr Thr Thr Thr Phe
1 5 10 15

Val Pro

<210> 59
<211> 17
<212> PRT
<213> Neisseria meningitidis

<400> 59

Tyr Trp Thr Thr Val Asn Thr Gly Ser Ala Thr Thr Thr Thr Phe Val
1 5 10 15

Pro

<210> 60
<211> 16
<212> PRT
<213> Neisseria meningitidis

<400> 60

Tyr Trp Thr Thr Val Asn Thr Gly Ser Ala Thr Thr Thr Phe Val Pro
1 5 10 15

<210> 61

<211> 17
<212> PRT
<213> Neisseria meningitidis

<400> 61

Tyr Tyr Thr Thr Val Thr Gln Gly Ser Ala Thr Thr Thr Thr Phe Val
1 5 10 15

Pro

<210> 62
<211> 10
<212> PRT
<213> Neisseria meningitidis

<400> 62

Tyr Val Asp Glu Lys Lys Met Val His Ala
1 5 10

<210> 63
<211> 10
<212> PRT
<213> Neisseria meningitidis

<400> 63

Tyr Val Asp Glu Lys Gln Val Ser His Ala
1 5 10

<210> 64
<211> 10
<212> PRT
<213> Neisseria meningitidis

<400> 64

Tyr Val Asp Glu Lys Lys Val Val His Ala
1 5 10

<210> 65
<211> 13
<212> PRT
<213> Neisseria meningitidis

<400> 65

His Tyr Thr Arg Gln Asn Asn Ala Asp Val Phe Val Pro
1 5 10

<210> 66
<211> 13
<212> PRT
<213> Neisseria meningitidis

<400> 66

His Tyr Thr Arg Gln Asn Asn Thr Asp Val Phe Val Pro
1 5 10

<210> 67
<211> 13
<212> PRT
<213> Neisseria meningitidis

<400> 67

His Tyr Thr Arg Gln Asn Asn Ile Asp Val Phe Val Pro
1 5 10

<210> 68
<211> 14
<212> PRT
<213> Neisseria meningitidis

<400> 68

Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr Leu Val Pro
1 5 10

<210> 69
<211> 14
<212> PRT
<213> Neisseria meningitidis

<400> 69

Tyr Tyr Thr Lys Asp Lys Asn Asp Asn Leu Thr Leu Val Pro
1 5 10

<210> 70
<211> 14

<212> PRT
<213> Neisseria meningitidis

<400> 70

Tyr Tyr Thr Lys Asp Lys Asn Asp Lys Leu Thr Leu Val Pro
1 5 10

<210> 71
<211> 13
<212> PRT
<213> Neisseria meningitidis

<400> 71

Tyr Tyr Thr Asn Thr Asn Asn Asn Leu Thr Leu Val Pro
1 5 10

<210> 72
<211> 17
<212> PRT
<213> Neisseria meningitidis

<400> 72

His Trp Asn Thr Val Tyr Asn Thr Asn Gly Thr Thr Thr Thr Phe Val
1 5 10 15

Pro

<210> 73
<211> 18
<212> PRT
<213> Neisseria meningitidis

<400> 73

His Trp Asn Thr Val Tyr Asn Thr Asn Gly Thr Thr Thr Thr Thr Phe
1 5 10 15

Val Pro

<210> 74
<211> 14

<212> PRT
<213> Neisseria meningitidis

<400> 74

Thr Tyr Thr Val Asp Ser Ser Gly Val Val Thr Pro Val Pro
1 5 10

<210> 75
<211> 14
<212> PRT
<213> Neisseria meningitidis

<400> 75

His Phe Val Ala Asp Ser Gln Gly Lys Ile Thr Arg Val Pro
1 5 10

<210> 76
<211> 17
<212> PRT
<213> Neisseria meningitidis

<400> 76

Tyr Tyr Tyr Thr Thr Ala Thr Asn Ser Ser Thr Ser Thr Thr Phe Val
1 5 10 15

Pro

<210> 77
<211> 17
<212> PRT
<213> Neisseria meningitidis

<400> 77

His Tyr Thr Thr Val Tyr Asn Ala Thr Thr Thr Thr Thr Thr Phe Val
1 5 10 15

Pro

<210> 78
<211> 18

<212> PRT
<213> Neisseria meningitidis

<400> 78

His Tyr Thr Thr Val Tyr Asn Ala Thr Thr Thr Thr Thr Thr Phe
1 5 10 15

Val Pro

<210> 79
<211> 11
<212> PRT
<213> Neisseria meningitidis

<400> 79

Tyr Val Asp Asp Gln Gly Lys Val Lys Gly Pro
1 5 10

<210> 80
<211> 255
<212> PRT
<213> Neisseria meningitidis

<400> 80

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1 5 10 15

Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
20 25 30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
35 40 45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
50 55 60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65 70 75 80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe

85 90 95

Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu
100 105 110

Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln
115 120 125

Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
130 135 140

Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145 150 155 160

Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
165 170 175

Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp
180 185 190

Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile
195 200 205

Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu
210 215 220

Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val
225 230 235 240

Lys Thr Val Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
245 250 255

<210> 81
<211> 255
<212> PRT
<213> Neisseria meningitidis

<400> 81

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1 5 10 15

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Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Leu Gln Thr Glu
            100                 105                 110

Gln Val Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125

Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140

Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160

Asp Ala Ser Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175

Gly His Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp
            180                 185                 190

Leu Ala Ala Ser Asp Ile Lys Pro Asp Lys Lys Arg His Ala Val Ile
        195                 200                 205

Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu
    210                 215                 220
```

```
Gly Ile Phe Gly Gly Gln Ala Gln Glu Val Ala Gly Ser Ala Glu Val
225                 230                 235                 240


Glu Thr Ala Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
                245                 250                 255


<210>  82
<211>  255
<212>  PRT
<213>  Neisseria meningitidis

<400>  82

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80


Gln Ile Glu Val Asp Gly Lys Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95


Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Leu Gln Thr Glu
            100                 105                 110


Gln Val Gln Asp Ser Glu Asp Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125


Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140
```

```
Pro Lys Gly Gly Ser Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160


Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175


Gly His Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Glu
            180                 185                 190


Leu Ala Thr Ala Tyr Ile Lys Pro Asp Glu Lys Arg His Ala Val Ile
        195                 200                 205


Ser Gly Ser Val Leu Tyr Asn Gln Asp Glu Lys Gly Ser Tyr Ser Leu
    210                 215                 220


Gly Ile Phe Gly Gly Gln Ala Gln Glu Val Ala Gly Ser Ala Glu Val
225                 230                 235                 240


Glu Thr Ala Asn Gly Ile His His Ile Gly Leu Ala Ala Lys Gln
                245                 250                 255


<210>  83
<211>  255
<212>  PRT
<213>  Neisseria meningitidis

<400>  83

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60
```

```
Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Leu Gln Thr Glu
            100                 105                 110

Gln Glu Gln Asp Pro Glu His Ser Gly Lys Met Val Ala Lys Arg Arg
        115                 120                 125

Phe Lys Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140

Pro Lys Asp Val Met Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160

Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175

Gly His Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Glu
            180                 185                 190

Leu Ala Thr Ala Tyr Ile Lys Pro Asp Glu Lys His His Ala Val Ile
        195                 200                 205

Ser Gly Ser Val Leu Tyr Asn Gln Asp Glu Lys Gly Ser Tyr Ser Leu
    210                 215                 220

Gly Ile Phe Gly Gly Gln Ala Gln Glu Val Ala Gly Ser Ala Glu Val
225                 230                 235                 240

Glu Thr Ala Asn Gly Ile His His Ile Gly Leu Ala Ala Lys Gln
                245                 250                 255
```

<210> 84
<211> 263
<212> PRT
<213> Neisseria meningitidis

<400> 84

```
Cys Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Val Ala Ala Asp
1               5                  10                  15


Ile Gly Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys
            20                  25                  30


Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn
        35                  40                  45


Gly Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Arg Thr Phe Lys Ala
    50                  55                  60


Gly Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys
65                  70                  75                  80


Ile Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu
                85                  90                  95


Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser
            100                 105                 110


Ala Leu Thr Ala Leu Gln Thr Glu Gln Val Gln Asp Ser Glu His Ser
        115                 120                 125


Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile Val Gly
    130                 135                 140


Glu His Thr Ser Phe Gly Lys Leu Pro Lys Asp Val Met Ala Thr Tyr
145                 150                 155                 160


Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr
                165                 170                 175


Thr Ile Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu
            180                 185                 190


Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile Lys Pro
```

195 200 205

Asp Glu Lys His His Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln
210 215 220

Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Gln Ala Gln
225 230 235 240

Glu Val Ala Gly Ser Ala Glu Val Glu Thr Ala Asn Gly Ile Arg His
245 250 255

Ile Gly Leu Ala Ala Lys Gln
260

<210> 85
<211> 260
<212> PRT
<213> Neisseria meningitidis

<400> 85

Cys Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Val Thr Ala Asp
1 5 10 15

Ile Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys
20 25 30

Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn
35 40 45

Gly Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn
50 55 60

Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg
65 70 75 80

Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu
85 90 95

Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr
100 105 110

```
Ala Leu Gln Thr Glu Gln Glu Gln Asp Pro Glu His Ser Glu Lys Met
        115                 120                 125


Val Ala Lys Arg Arg Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr
    130                 135                 140


Ser Phe Asp Lys Leu Pro Lys Asp Val Met Ala Thr Tyr Arg Gly Thr
145                 150                 155                 160


Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp
                165                 170                 175


Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Ser Pro
            180                 185                 190


Glu Leu Asn Val Asp Leu Ala Val Ala Tyr Ile Lys Pro Asp Glu Lys
        195                 200                 205


His His Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Asp Glu Lys
    210                 215                 220


Gly Ser Tyr Ser Leu Gly Ile Phe Gly Glu Lys Ala Gln Glu Val Ala
225                 230                 235                 240


Gly Ser Ala Glu Val Glu Thr Ala Asn Gly Ile His His Ile Gly Leu
                245                 250                 255


Ala Ala Lys Gln
            260


<210>  86
<211>  254
<212>  PRT
<213>  Neisseria meningitidis

<400>  86

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15
```

```
Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110

Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125

Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140

Pro Asp Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160

Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly
                165                 170                 175

His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190

Ala Ala Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
        195                 200                 205

Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr Tyr His Leu Ala
    210                 215                 220
```

```
Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
225                 230                 235                 240


Ile Gly Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
                245                 250


<210>  87
<211>  254
<212>  PRT
<213>  Neisseria meningitidis

<400>  87

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80


Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95


Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110


Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125


Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140
```

```
Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160


Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly
                165                 170                 175


His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190


Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
        195                 200                 205


Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala
    210                 215                 220


Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
225                 230                 235                 240


Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
                245                 250


<210>  88
<211>  254
<212>  PRT
<213>  Neisseria meningitidis

<400>  88

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
```

65 70 75 80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
85 90 95

Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
100 105 110

Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
115 120 125

Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
130 135 140

Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145 150 155 160

Pro Asn Gly Arg Leu His Tyr Ser Ile Asp Phe Thr Lys Lys Gln Gly
165 170 175

Tyr Gly Arg Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
180 185 190

Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
195 200 205

Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala
210 215 220

Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
225 230 235 240

Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
245 250

<210> 89
<211> 254
<212> PRT
<213> Neisseria meningitidis

<400> 89

```
Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                  10                  15

Ala Asp Ala Leu Thr Thr Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Thr Ile Thr Leu Ala Ser Gly Glu Phe
                85                  90                  95

Gln Ile Tyr Lys Gln Asn His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110

Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125

Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140

Pro Asp Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160

Pro Asn Gly Arg Leu His Tyr Ser Ile Asp Phe Thr Lys Lys Gln Gly
                165                 170                 175

Tyr Gly Arg Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190

Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
        195                 200                 205
```

Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala
210 215 220

Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
225 230 235 240

Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
245 250

<210> 90
<211> 261
<212> PRT
<213> Neisseria meningitidis

<400> 90

Cys Ser Ser Gly Ser Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile
1 5 10 15

Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp
20 25 30

Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly
35 40 45

Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly
50 55 60

Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile
65 70 75 80

Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile
85 90 95

Thr Leu Ala Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala
100 105 110

Val Val Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp
115 120 125

```
Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu
    130                 135                 140


His Thr Ala Phe Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly
145                 150                 155                 160


Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile
                165                 170                 175


Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr
            180                 185                 190


Pro Glu Gln Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu
        195                 200                 205


Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu
    210                 215                 220


Lys Gly Thr Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile
225                 230                 235                 240


Ala Gly Ser Ala Thr Val Lys Ile Arg Glu Lys Val His Glu Ile Gly
                245                 250                 255


Ile Ala Gly Lys Gln
            260


<210>  91
<211>  257
<212>  PRT
<213>  Neisseria meningitidis

<400>  91

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Lys
            20                  25                  30
```

```
Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly Thr Leu Thr Leu
        35                  40                  45

Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly Asp Lys Asp Asn
    50                  55                  60

Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile Ser Arg Phe Asp
65                  70                  75                  80

Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile Thr Leu Ala Ser
                85                  90                  95

Gly Glu Phe Gln Ile Tyr Lys Gln Asn His Ser Ala Val Val Ala Leu
            100                 105                 110

Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn
        115                 120                 125

Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe
    130                 135                 140

Asn Gln Leu Pro Gly Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser
145                 150                 155                 160

Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala
                165                 170                 175

Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn
            180                 185                 190

Val Glu Leu Ala Ala Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala
        195                 200                 205

Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr Tyr
    210                 215                 220

His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala
225                 230                 235                 240
```

Thr Val Lys Ile Gly Glu Lys Val His Glu Ile Ser Ile Ala Gly Lys
245 250 255

Gln

<210> 92
<211> 268
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 92

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1 5 10 15

Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
20 25 30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
35 40 45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
50 55 60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65 70 75 80

Gln Ile Glu Val Asp Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr
85 90 95

Leu Val Pro Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr
100 105 110

Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln
115 120 125

Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile
130 135 140

```
Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly
145                 150                 155                 160


Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly
                165                 170                 175


Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly
            180                 185                 190


Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala
        195                 200                 205


Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser
    210                 215                 220


Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe
225                 230                 235                 240


Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val
                245                 250                 255


Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
            260                 265


<210>  93
<211>  274
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Modified polypeptide

<400>  93

Cys Ser Ser Gly Ser Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile
1               5                   10                  15


Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp
            20                  25                  30
```

```
Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly
        35                  40                  45

Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly
    50                  55                  60

Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile
65                  70                  75                  80

Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val Asp Tyr Tyr Thr Lys
                85                  90                  95

Asp Thr Asn Asn Asn Leu Thr Leu Val Pro Gln Thr Ile Thr Leu Ala
            100                 105                 110

Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala
        115                 120                 125

Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile
    130                 135                 140

Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala
145                 150                 155                 160

Phe Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe
                165                 170                 175

Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala
            180                 185                 190

Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln
        195                 200                 205

Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His
    210                 215                 220

Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr
225                 230                 235                 240
```

Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser
245 250 255

Ala Thr Val Lys Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly
260 265 270

Lys Gln

<210> 94
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 94

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1 5 10 15

Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
20 25 30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
35 40 45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
50 55 60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65 70 75 80

Gln Ile Glu Val Asp Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr
85 90 95

Leu Val Pro Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Ile Tyr
100 105 110

Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu Lys Ile Asn
115 120 125

```
Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val
    130                 135                 140

Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu Pro Ser Gly
145                 150                 155                 160

Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly
                165                 170                 175

Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly His Gly Lys
            180                 185                 190

Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu Ala Ser Ala
        195                 200                 205

Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr
    210                 215                 220

Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala Leu Phe Gly
225                 230                 235                 240

Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys Ile Arg Glu
                245                 250                 255

Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
            260                 265
```

<210> 95
<211> 268
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 95

```
Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15
```

```
Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
            20                  25                  30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu
            100                 105                 110

Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125

Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140

Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160

Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175

Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp
            180                 185                 190

Leu Ala Ala Ala Asp Ile Lys Pro Asp Tyr Tyr Thr Lys Asp Thr Asn
        195                 200                 205

Asn Asn Leu Thr Leu Val Pro Lys Arg His Ala Val Ile Ser Gly Ser
    210                 215                 220
```

Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe
225 230 235 240

Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val
245 250 255

Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
260 265

<210> 96
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 96

Cys Ser Ser Gly Ser Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile
1 5 10 15

Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp
20 25 30

Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly
35 40 45

Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly
50 55 60

Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile
65 70 75 80

Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile
85 90 95

Thr Leu Ala Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala
100 105 110

Val Val Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp
115 120 125

```
Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu
    130                 135                 140

His Thr Ala Phe Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly
145                 150                 155                 160

Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile
                165                 170                 175

Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr
            180                 185                 190

Pro Glu Gln Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Tyr
        195                 200                 205

Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr Leu Val Pro Lys Ser His
    210                 215                 220

Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr
225                 230                 235                 240

Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser
                245                 250                 255

Ala Thr Val Lys Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly
            260                 265                 270

Lys Gln
```

<210> 97
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 97

```
Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15

Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110

Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125

Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140

Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160

Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly
                165                 170                 175

His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190

Ala Ser Ala Glu Leu Lys Ala Asp Tyr Tyr Thr Lys Asp Thr Asn Asn
        195                 200                 205
```

Asn Leu Thr Leu Val Pro Lys Ser His Ala Val Ile Leu Gly Asp Thr
210 215 220

Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala Leu Phe Gly
225 230 235 240

Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys Ile Arg Glu
245 250 255

Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
260 265

<210> 98
<211> 268
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 98

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1 5 10 15

Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
20 25 30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
35 40 45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
50 55 60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65 70 75 80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
85 90 95

Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu
100 105 110

```
Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125


Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140


Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160


Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175


Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp
            180                 185                 190


Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile
        195                 200                 205


Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu
    210                 215                 220


Gly Ile Phe Gly Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr Leu
225                 230                 235                 240


Val Pro Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val
                245                 250                 255


Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
            260                 265


<210>  99
<211>  274
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Modified polypeptide

<400>  99
```

```
Cys Ser Ser Gly Ser Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile
1               5                   10                  15


Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp
            20                  25                  30


Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly
        35                  40                  45


Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly
    50                  55                  60


Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile
65                  70                  75                  80


Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile
                85                  90                  95


Thr Leu Ala Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala
            100                 105                 110


Val Val Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp
        115                 120                 125


Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu
    130                 135                 140


His Thr Ala Phe Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly
145                 150                 155                 160


Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile
                165                 170                 175


Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr
            180                 185                 190


Pro Glu Gln Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu
        195                 200                 205
```

```
Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu
    210                 215                 220

Lys Gly Thr Tyr His Leu Ala Leu Phe Gly Tyr Tyr Thr Lys Asp Thr
225                 230                 235                 240

Asn Asn Asn Leu Thr Leu Val Pro Arg Ala Gln Glu Ile Ala Gly Ser
                245                 250                 255

Ala Thr Val Lys Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly
            260                 265                 270

Lys Gln
```

<210> 100
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 100

```
Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15

Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30

Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45

Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60

Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95
```

```
Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110

Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125

Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140

Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160

Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly
                165                 170                 175

His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190

Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
        195                 200                 205

Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala
    210                 215                 220

Leu Phe Gly Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr Leu Val
225                 230                 235                 240

Pro Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys Ile Arg Glu
                245                 250                 255

Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
            260                 265


<210>  101
<211>  268
<212>  PRT
<213>  Artificial Sequence

<220>
```

<223> Modified polypeptide

<400> 101

```
Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                  10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr Leu Val
    50                  55                  60


Pro Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys
65                  70                  75                  80


Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu
                85                  90                  95


Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr
            100                 105                 110


Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln
        115                 120                 125


Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile
    130                 135                 140


Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly
145                 150                 155                 160


Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly
                165                 170                 175


Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly
            180                 185                 190
```

Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala
195 200 205

Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser
210 215 220

Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe
225 230 235 240

Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val
245 250 255

Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
260 265

<210> 102
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 102

Cys Ser Ser Gly Ser Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile
1 5 10 15

Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp
20 25 30

Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly
35 40 45

Thr Leu Thr Leu Ser Ala Gln Tyr Tyr Thr Lys Asp Thr Asn Asn Asn
50 55 60

Leu Thr Leu Val Pro Ala Glu Lys Thr Phe Lys Val Gly Asp Lys Asp
65 70 75 80

Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile Ser Arg Phe
85 90 95

```
Asp Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile Thr Leu Ala
            100                 105                 110

Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala
        115                 120                 125

Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile
    130                 135                 140

Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala
145                 150                 155                 160

Phe Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe
                165                 170                 175

Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala
            180                 185                 190

Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln
        195                 200                 205

Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His
    210                 215                 220

Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr
225                 230                 235                 240

Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser
                245                 250                 255

Ala Thr Val Lys Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly
            260                 265                 270

Lys Gln
```

<210> 103
<211> 267

<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 103

```
Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                  10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr Leu Val
    50                  55                  60


Pro Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys
65                  70                  75                  80


Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu
                85                  90                  95


Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Ile Tyr
            100                 105                 110


Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu Lys Ile Asn
        115                 120                 125


Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val
    130                 135                 140


Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu Pro Ser Gly
145                 150                 155                 160


Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly
                165                 170                 175
```

```
Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly His Gly Lys
            180                 185                 190


Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu Ala Ser Ala
        195                 200                 205


Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr
    210                 215                 220


Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala Leu Phe Gly
225                 230                 235                 240


Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys Ile Arg Glu
                245                 250                 255


Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
            260                 265


<210>  104
<211>  268
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Modified polypeptide

<400>  104

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80
```

```
Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu
            100                 105                 110

Gln Ile Gln Asp Ser Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr
        115                 120                 125

Leu Val Pro His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile
    130                 135                 140

Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly
145                 150                 155                 160

Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly
                165                 170                 175

Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly
            180                 185                 190

Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala
        195                 200                 205

Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser
    210                 215                 220

Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe
225                 230                 235                 240

Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val
                245                 250                 255

Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
            260                 265
```

<210> 105
<211> 274

<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 105

```
Cys Ser Ser Gly Ser Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile
1               5                   10                  15


Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp
            20                  25                  30


Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly
        35                  40                  45


Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly
    50                  55                  60


Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile
65                  70                  75                  80


Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile
                85                  90                  95


Thr Leu Ala Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala
            100                 105                 110


Val Val Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Tyr Tyr Thr Lys
        115                 120                 125


Asp Thr Asn Asn Asn Leu Thr Leu Val Pro Lys Ile Asp Ser Leu Ile
    130                 135                 140


Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala
145                 150                 155                 160


Phe Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe
                165                 170                 175
```

```
Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala
            180                 185                 190


Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln
        195                 200                 205


Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His
    210                 215                 220


Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr
225                 230                 235                 240


Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser
                245                 250                 255


Ala Thr Val Lys Ile Arg Glu Lys Val His Glu Ile Gly Ile Ala Gly
            260                 265                 270


Lys Gln



<210>  106
<211>  267
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Modified polypeptide

<400>  106

Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60
```

```
Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80

Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95

Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110

Lys Ile Asn Asn Pro Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr
        115                 120                 125

Leu Val Pro Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val
    130                 135                 140

Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu Pro Ser Gly
145                 150                 155                 160

Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly
                165                 170                 175

Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly His Gly Lys
            180                 185                 190

Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu Ala Ser Ala
        195                 200                 205

Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr
    210                 215                 220

Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala Leu Phe Gly
225                 230                 235                 240

Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys Ile Arg Glu
                245                 250                 255

Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
            260                 265
```

<210> 107
<211> 268
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 107

```
Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                  10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80


Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95


Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu
            100                 105                 110


Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln
        115                 120                 125


Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu
    130                 135                 140


Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp
145                 150                 155                 160
```

```
Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln
                165                 170                 175


Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp
            180                 185                 190


Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile
        195                 200                 205


Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu
    210                 215                 220


Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val
225                 230                 235                 240


Lys Thr Val Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr Leu Val
                245                 250                 255


Pro Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln
            260                 265


<210>  108
<211>  274
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Modified polypeptide

<400>  108

Cys Ser Ser Gly Ser Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile
1               5                   10                  15


Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp
            20                  25                  30


Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser Ile Ser Gln Asn Gly
        35                  40                  45


Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Val Gly
    50                  55                  60
```

```
Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile
65                  70                  75                  80

Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile
                85                  90                  95

Thr Leu Ala Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala
            100                 105                 110

Val Val Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp
        115                 120                 125

Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu
    130                 135                 140

His Thr Ala Phe Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly
145                 150                 155                 160

Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile
                165                 170                 175

Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr
            180                 185                 190

Pro Glu Gln Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu
        195                 200                 205

Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu
    210                 215                 220

Lys Gly Thr Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile
225                 230                 235                 240

Ala Gly Ser Ala Thr Val Lys Ile Arg Tyr Tyr Thr Lys Asp Thr Asn
                245                 250                 255

Asn Asn Leu Thr Leu Val Pro Lys Val His Glu Ile Gly Ile Ala Gly
            260                 265                 270
```

Lys Gln

<210> 109
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Modified polypeptide

<400> 109

```
Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu
1               5                   10                  15


Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Ser Leu Gln
            20                  25                  30


Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu
        35                  40                  45


Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn
    50                  55                  60


Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg
65                  70                  75                  80


Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe
                85                  90                  95


Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu Gln Ile Glu
            100                 105                 110


Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn Gln Arg Ser
        115                 120                 125


Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu
    130                 135                 140
```

```
Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp
145                 150                 155                 160


Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly
                165                 170                 175


His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn Val Glu Leu
            180                 185                 190


Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu
        195                 200                 205


Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr His Leu Ala
    210                 215                 220


Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys
225                 230                 235                 240


Ile Arg Tyr Tyr Thr Lys Asp Thr Asn Asn Asn Leu Thr Leu Val Pro
                245                 250                 255


Lys Val His Glu Ile Gly Ile Ala Gly Lys Gln
            260                 265
```